

## Reimbursement Recommendation

# Risankizumab (Skyrizi)

**Indication:** For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor

**Sponsor:** AbbVie Corporation

**Final Recommendation:** Reimburse with conditions

# Summary

## What Is the Reimbursement Recommendation for Skyrizi?

Canada's Drug Agency (CDA-AMC) recommends that Skyrizi be reimbursed by public drug plans for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor if certain conditions are met.

## Which Patients Are Eligible for Coverage?

Skyrizi should be covered for a similar patient population and in a similar way to other advanced therapies for UC currently reimbursed by public drug plans for the treatment of moderately to severely active UC.

## What Are the Conditions for Reimbursement?

Skyrizi should only be reimbursed if it is prescribed by a physician experienced in the diagnosis and management of UC if it is not used in combination with other advanced therapies for UC and if the cost of Skyrizi is reduced so that it does not cost the drug programs more than the least costly relevant advanced therapy reimbursed in this patient population. A patient's disease must respond to treatment within the first 12 weeks of starting Skyrizi to continue receiving the drug.

## Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that more patients treated with Skyrizi showed clinical remission and endoscopic improvement than patients treated with placebo, both during the first 12 weeks of treatment and at longer-term follow-up.
- Skyrizi may meet some needs that are important to patients because it is an additional treatment option that induces and maintains disease remission.
- Based on the CDA-AMC assessment of the health economic evidence, Skyrizi does not represent good value to the health care system at the public list price. CDEC determined there is not enough evidence to justify a higher cost for Skyrizi than other advanced therapies reimbursed for the treatment of adults with moderately to severely active UC.
- Based on public list prices, Skyrizi is estimated to cost the public drug plans approximately \$13.8 million over the next 3 years. However, the actual budget impact is uncertain and is likely to be affected by the

# Summary

uptake of risankizumab, displacement of comparators, underlying growth in market size of patients receiving advanced therapies for UC, and the prices paid by the drug plans for other advanced therapies for UC.

## 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 the stool, frequent diarrhea, loss of appetite, a strong urge to use the bathroom without necessarily having a bowel movement, abdominal pain, and rectal bleeding. UC affects 414 per 100,000 people in Canada.

### Unmet Needs in UC

Patients may not have a response to, or may lose response to, currently available therapies for UC. More treatment options are needed to achieve and maintain disease remission.

### How Much Does Skyrizi Cost?

Treatment with Skyrizi is expected to cost approximately \$50,627 per patient in year 1 and \$29,958 per patient per year thereafter.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that risankizumab be reimbursed for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a JAK inhibitor only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

Two phase III, double-blind, placebo-controlled trials (INSPIRE induction trial: N = 977; COMMAND maintenance trial: N = 584) demonstrated that risankizumab, administered as a 1,200 mg IV infusion for induction and as either 180 mg or 360 mg subcutaneous (SC) injections for maintenance, provided added clinical benefit compared to placebo in adults with moderately to severely active UC who had inadequate response or were unable to tolerate conventional or advanced therapy. During the induction trial, risankizumab showed improvements in clinical response; clinical remission; endoscopic improvement; histologic-endoscopic mucosal improvement (HEMI); and histologic-endoscopic mucosal remission (HEMR). In the maintenance phase, benefits were observed in clinical remission per the adapted Mayo score, endoscopic improvement, HEMI, and HEMR. Greater proportions of patients in the risankizumab group had clinical remission compared with the placebo group, and the estimated [between-group] difference compared with placebo was 14.0% (95% confidence interval [CI], 10.0% to 18.0%) for the 1,200 mg IV dose at 12 weeks in the induction trial and 16.3% (95% CI, 7.4% to 25.3%) for the 180 mg SC dose and 14.2% (95% CI, 5.3% to 23.2%) for the 360 mg SC dose at 52 weeks in the maintenance trial. Greater proportions of patients in the risankizumab group also had clinical response, with an estimated between-group difference compared with placebo of 28.6% (95% CI, 22.3% to 34.8%) for the 1,200 mg IV dose at 12 weeks in the induction trial and 17.1% (95% CI, 7.5% to 26.6%) for the 180 mg SC dose and 11.5% (95% CI, 1.7% to 21.2%) for the 360 mg SC dose at 52 weeks in the maintenance trial. In addition, greater proportions of patients in the risankizumab group had endoscopic improvement at 12 weeks (between-group difference was 24.3% [95% CI, 19.3% to 29.4%] for the 1,200 mg IV dose induction trial) and at week 52 (between-group difference was 20.1% [95% CI, 10.6% to 29.6%] for the 180 mg SC dose and 17.4% [95% CI, 7.9% to 26.9%] for the 360 mg SC dose in the maintenance trial). For discontinuation of corticosteroid use in patients receiving corticosteroids at baseline (only measured in the COMMAND trial), the between-group difference was 28.4% (95% CI, 14.0% to 42.8%) for the 1,200 mg IV dose, 20.7% (95% CI, 4.9% to 36.6%) for the 180 mg SC dose, and the 360 mg SC dose, respectively. For health-related quality of life (HRQoL) assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), treatment with risankizumab was associated with improvements in HRQoL at 12 weeks (induction trial) and 52 weeks (maintenance trial) compared with placebo. The estimated between-group difference were 18.3 points (95% CI, 13.38 to 23.25 points) for the 1,200 mg IV dose at 12 weeks, 17.5 points (95% CI, 8.01 to 27.06 points) for the 180 mg SC dose, and 15.2 points (95% CI, 5.18 to 25.31 points) for the 360 mg SC dose at 52 weeks.

CDEC considered the results from 1 sponsor-submitted network meta-analysis (NMA) comparing the efficacy and safety of risankizumab to currently available therapies (adalimumab, infliximab, golimumab,

vedolizumab, tofacitinib, ustekinumab, ozanimod, upadacitinib, mirikizumab, and etrasimod). CDEC was unable to draw definitive conclusions from the NMA results due to methodological limitations in the analyses. Thus, the comparative efficacy and safety of risankizumab versus other relevant comparators remains uncertain.

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 risankizumab met some important needs identified by patients, such as sustained clinical remission, endoscopic improvement, clinical response, and improved HRQoL and it represents an additional advanced therapy option.

At the sponsor-submitted price for risankizumab and publicly listed price for comparators, risankizumab was more costly than most other reimbursed advanced therapies for adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or intolerance to conventional therapy, biologic treatment, or a JAK inhibitor. Because no definitive conclusion can be drawn regarding the relative efficacy and safety of risankizumab compared to other advanced therapies, the total drug cost of risankizumab 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                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Initiation</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                              |
| 1. Eligibility for reimbursement of risankizumab 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 INSPIRE induction and COMMAND maintenance trials demonstrated that induction and maintenance treatment with risankizumab resulted in a clinical benefit in patients with moderately to severely active UC who had an inadequate response or intolerance to conventional or advanced therapies. | The definitions of moderately to severely active UC should align with those used for other reimbursed advanced therapies.<br><br>Advanced therapies include biologic drugs, JAK inhibitors, and sphingosine 1-phosphate receptor modulators. |
| <b>Renewal</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                              |
| 2. The patient must have achieved a clinical response to risankizumab induction therapy 12 weeks after treatment initiation to continue to maintenance therapy. Clinical response targets should be based on the criteria used by each public drug plan 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 risankizumab therapy. The INSPIRE induction trial assessed the efficacy and safety of risankizumab after 12 weeks of induction treatment and the patients whose UC achieved clinical response and who entered the maintenance trial.                | —                                                                                                                                                                                                                                            |

| Reimbursement condition                                                                                                                                                                                              | Reason                                                                                                                                                                                                                                                                                                                                                                                           | Implementation guidance                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3. Assessment for drug renewal should be performed annually after the first assessment of treatment response. The patient's UC must maintain clinical response to therapy to continue receiving risankizumab.        | Patients whose UC no longer responds to risankizumab are no longer benefiting from treatment.                                                                                                                                                                                                                                                                                                    | —                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Prescribing</b>                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                          |
| 4. Risankizumab should be prescribed by clinicians with expertise in the diagnosis and management of UC.                                                                                                             | This is to ensure that risankizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.                                                                                                                                                                                                                                               | Induction reimbursement should be limited to a single induction treatment period of 12 weeks because there is no comparative evidence supporting an additional induction period.<br><br>Reimbursement should be restricted to the dosing regimen approved by Health Canada because there is no supporting evidence for dose escalation beyond the authorized dosage or for more frequent administration. |
| 5. Risankizumab should not be reimbursed when used in combination with other advanced therapies for UC, such as biologic drugs, sphingosine 1-phosphate receptor modulators, or JAK inhibitors.                      | There is no evidence to support the use of risankizumab in combination with a biologic therapy, sphingosine 1-phosphate receptor modulators, or JAK inhibitors for UC.                                                                                                                                                                                                                           | —                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Pricing</b>                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                          |
| 6. Risankizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly relevant advanced therapy reimbursed for the treatment of moderately to severely active UC. | The comparative efficacy and safety of risankizumab relative to other relevant advanced therapies available for moderately to severely active UC is inconclusive due to limitations with the sponsor's NMA.<br><br>As such, there is insufficient evidence to justify a cost premium for risankizumab over the least expensive advanced therapy reimbursed for moderately to severely active UC. | —                                                                                                                                                                                                                                                                                                                                                                                                        |

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 have UC with an inadequate response or loss of response to currently available advanced therapies, which requires alternative treatments. CDEC noted that there are currently several advanced therapies available for UC. Based on the submitted evidence, CDEC concluded that

risankizumab does not meet the unmet needs identified by patients compared to other advanced therapies; however, the evidence is supportive of risankizumab as an additional effective treatment option for patients with moderately to severely active UC, specifically in those with an inadequate response or loss of response to conventional or advanced therapy as per the patient populations in the INSPIRE and COMMAND trials.

- Efficacy and safety:** CDEC highlighted that the evidence from the INSPIRE induction and COMMAND maintenance trials was of high certainty per the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) assessment. This showed that during the induction phase, there was evidence of moderate to high certainty favouring risankizumab regarding clinical response, clinical remission, endoscopic improvement, HEMI, and HEMR. Further, there was evidence of moderate certainty favouring risankizumab regarding IBDQ scores and evidence of low certainty for little to no difference in number of serious adverse events (SAEs). During the maintenance trial, there was evidence of high certainty favouring risankizumab for endoscopic improvement and HEMI. Further, there was evidence of moderate certainty favouring risankizumab for clinical response (180 mg SC only; the 360 mg SC dose showed likely little to no difference), clinical remission, HEMR, and IBDQ. Last, there was evidence of low certainty favouring risankizumab for discontinuation of corticosteroid use in patients receiving steroids at baseline and for little to no difference in SAEs. CDEC agreed with the clinical experts that there were no new safety signals identified, and the safety of risankizumab was consistent with the known safety profile of the drug class.
- Indirect evidence:** Direct evidence comparing risankizumab to other advanced therapies was not submitted. CDEC discussed the indirect evidence from the sponsor-submitted NMA that compared risankizumab to adalimumab, infliximab, golimumab, vedolizumab, tofacitinib, ustekinumab, ozanimod, upadacitinib, mirikizumab, and etrasimod. Except for a few isolated cases, the results of the NMA generally did not provide evidence favouring one treatment over another, with wide credible intervals crossing the null for most analyses. Furthermore, due to differences in study designs, inclusion criteria, patient populations, definitions of outcomes measures, and timing of assessment, there is uncertainty in the results because it is likely that the underlying assumption of exchangeability is violated.
- Induction and maintenance regimens:** CDEC discussed the length of induction therapy for risankizumab. In the INSPIRE induction trial, patients in the risankizumab group with UC 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, the proportion of patients with UC in clinical remission was 6 of 68 (8.8%) for the 1,200 mg IV dose of risankizumab, 9 of 71 (12.7%) for the 180 mg SC dose, and 11 of 70 (15.7%) for the 360 mg SC dose. CDEC recommended that, due to the absence of comparative evidence supporting an additional induction period, only one 12-week induction period should be reimbursed. CDEC also discussed that the 180 mg SC and 360 mg SC maintenance dose options evaluated in the COMMAND maintenance trial were both compared with placebo. CDEC concluded that there was no evidence of a dose-response relationship between the risankizumab 180 mg SC

and 360 mg SC groups. This information may prove useful for payers when assessing the total cost of treatment to ensure risankizumab is no more costly than the least costly relevant comparator (i.e., advanced therapy) reimbursed for adults with moderately to severely active UC.

## Background

UC is a chronic disease characterized by inflammation predominantly of the mucosal layer of the large intestine (colon), most often involving the rectum and frequently extending continuously into the proximal colon. The cause of UC remains uncertain, but a combination of genetic and environmental factors contributes to immune dysregulation and upregulation in response to micro-organisms in the GI tract. UC is characterized by blood and mucus in the stool, frequent diarrhea, bowel urgency, loss of appetite, and tenesmus (severe rectal cramp or spasm). Although UC principally affects the GI tract, extraintestinal manifestations may also occur, such as arthritis. Most patients have a mild to moderate disease course; however, approximately 10% to 15% of patients experience an aggressive course of UC. Relapse is common; the cumulative risk of relapse is 70% to 80% at 10 years. 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 bowel urgency, frequency, and incontinence.

The prevalence of UC in Canada in 2023 was estimated to be 414 per 100,000 people. It is estimated that 32% to 46% of people with UC in Canada have moderate disease and 13% to 14% have severe disease.

The general goal of pharmacotherapy is to accomplish complete remission, defined as both symptomatic and endoscopic remission, without corticosteroid therapy, and to preserve HRQoL and prevent disability. Guidelines generally recommend a standard step-up approach to the medical management of moderate to severe UC. It is further recommended that, for maintenance of remission, patients who responded to induction therapy should continue with that drug.

Risankizumab has been approved by Health Canada for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a JAK inhibitor. Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that binds to the p19 subunit of human IL-23 cytokine and inhibits IL-23 signalling, including the release of the proinflammatory cytokine, IL-17. The recommended dosage of risankizumab is 1,200 mg administered by IV infusion at week 0, week 4, and week 8, followed by 180 mg or 360 mg administered by SC injection at week 12 and every 8 weeks thereafter. It is recommended to use the lowest effective dosage needed to maintain therapeutic response.

## 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 (RCTs) in adult patients with moderately to severely active UC; 1 indirect treatment comparison; and 1 post hoc analysis of the pivotal INSPIRE and COMMAND trials included in the Studies Addressing Gaps in the Evidence From the Systematic Review section
- patients' perspectives gathered by 2 patient groups, the Gastrointestinal Society (GI Society) and Crohn's and Colitis Canada
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with UC
- input from 1 clinician group, the Canadian Inflammatory Bowel Disease Physicians Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Perspectives of Patients, Clinicians, and Drug Programs

### Patient Input

CDA-AMC received input from 2 patient groups, the GI Society and Crohn's and Colitis Canada. Both advocate for caregivers and patients with UC. The GI Society gathered information from online surveys, round tables, and a one-to-one conversation with a patient living with UC and receiving risankizumab. Crohn's and Colitis Canada gathered information from a survey, a Crohn's and Colitis Canada report (*Impact of Inflammatory Bowel Disease in Canada* [2023]), and interviews with patients who have had experience with risankizumab.

Respondents reported that sustained remission or treatment response is more important than relieving any 1 symptom, and the constant concern that there will be future flares, possibly worse than the last and at unpredictable times, can disastrously disrupt patients' lives. Patients also noted they need treatments that improve quality of life, and do not cause more symptoms, pain, frustration, or hardship. They also emphasized that improved outcomes included improved quality of life; having access to different treatment options; having access to a treatment that works, which results in less suffering and less unnecessary usage of health care resources (hospital stays, surgeries, and diagnostic procedures); having access to treatment with no side effects; reduction of symptoms; and ease of administration (e.g., fewer injections, self-injection, and oral treatment).

The GI Society interviewed a patient with UC who started receiving risankizumab through a clinical trial in December 2022. After 2 to 3 weeks, the patient noticed a significant improvement. The patient injections were every 8 weeks, and they felt by approximately week 6 that they needed the medication again.

## Clinician Input

### Input From Clinical Experts Consulted for This Review

According to the clinical experts consulted by CDA-AMC, more effective and safer treatments are welcomed because the currently available options are limited. The clinical experts noted that treating UC can be challenging, and the goal is to both control symptoms (e.g., frequency, urgency) and signs of UC (e.g., clinical and endoscopic remission) with advanced therapy as quickly as possible. There are many unmet needs in patients with UC because not all patients respond to the available treatments, and some patients may have UC that becomes refractory to current treatment options. In addition, new treatments are needed that have rapid onset, are better tolerated, have enhanced safety profiles, and can improve compliance. Historically, there have been few SC options for treatment of UC.

The clinical experts noted that risankizumab should be available as a first-line option for treatment of moderate to severe UC and that previous treatment failure should not be required. The only previous therapy that they would consider as a reasonable option would be corticosteroids, but these are not an option for long-term maintenance therapy.

The clinical experts noted that any patient with moderately to severely active UC would be a suitable candidate for treatment with risankizumab. Patients who are unable to complete a self-injection may require support administering the medication. Regarding diagnosis and staging of UC, both the diagnosis and treatment need to be made by a gastroenterologist. Misdiagnosis is unlikely because endoscopy would have been performed to establish diagnosis.

The clinical experts noted that the important outcomes can be categorized as follows:

- Improvement in symptoms, including decreasing stool frequency, bowel urgency, and bleeding. This has a direct impact on patients' HRQoL and important end points such as work or school participation, fatigue (able to sleep through the night), and overall function or activities of daily living.
- Sustained clinical remission, including no need for the addition of steroids (e.g., steroid sparing and steroid-free remission after induction with ongoing clinical remission).
- Endoscopic bowel healing, which is the best marker to ensure a very important adverse outcome is avoided, such as surgery or hospitalization.

In practice, the clinical experts noted that clinical scoring systems (e.g., Mayo scores, rectal bleeding score), endoscopic outcomes, and histopathological evaluation are used to evaluate response to treatment. In addition, biomarkers (e.g., fecal calprotectin) and corticosteroid-free remission are used to monitor ongoing treatment response and during maintenance therapy. From the patient's perspective, improvement in HRQoL is important to monitor.

The main issue with scoring systems is that there can be a level of subjectivity to them. Hard end points would include the Mayo endoscopic subscore and histopathological evaluation. Following the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE II) guidelines is imperative to ensure appropriate ongoing clinical management.

The clinical experts noted that treatment discontinuation can be organized into 3 main groups:

- primary nonresponse during induction with ongoing evidence of objective disease despite a robust attempt at induction (and possible reinduction) and no meaningful improvement with symptom persistence
- early symptomatic and objective disease improvement with subsequent relapse and persistent symptoms and disease activity that requires corticosteroid therapy either persistently or recurrently
- SAEs (e.g., anaphylactic reactions).

The clinical experts noted that, following a diagnosis and staging of UC by a gastroenterologist, treatment can be prescribed by a gastroenterologist or general internist with experience and expertise in treatment of inflammatory bowel disease. Treatment can occur in any clinical setting, but most patients will be initiated in the outpatient setting.

### Clinician Group Input

CDA-AMC received input from 1 clinician group, the Canadian Inflammatory Bowel Disease Physicians Group. Twenty-five clinicians who met through videoconference contributed to this submission.

Regarding the place in therapy, the clinician group believed that risankizumab should be used as the first choice in patients with moderately to severely active UC who did not respond to or are not candidates for other conventional therapy, or who had an inadequate response to 1 or more advanced therapies. They also noted that risankizumab is not generally recommended for patients with UC who have current or previous mildly to moderately active disease and whose remission can be adequately maintained with conventional treatments.

### Drug Program Input

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

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

| Implementation issues                                                                                                                                               | Response                                                                                                                                                                                     |
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| <b>Relevant comparators</b>                                                                                                                                         |                                                                                                                                                                                              |
| Given that risankizumab was compared to placebo (and not an active drug comparator) in the submitted studies, how do the efficacy outcomes for risankizumab compare | The clinical experts consulted for this review noted to CDEC that there is no strong evidence of a difference between the efficacy outcomes for risankizumab compared to other drugs for UC. |

| Implementation issues                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| to the outcomes for other drugs for UC, in particular, in comparison to drugs with the same mechanism of action (IL-23 inhibitors or IL-12/23 inhibitors)?                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Given that there are 3 other IL-23 inhibitors (mirikizumab, guselkumab, ustekinumab) with a similar mechanism of action, are there currently any unmet needs in the treatment of UC that risankizumab would address?                                                                                                                                                                                                                                                     | The clinical experts noted to CDEC that not all drugs in the same class have the same molecular composition and so the mode of action may be slightly different among them. The choice for use will be dependent on a case-by-case basis, including the patient's history with drugs of similar mechanisms of action.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Considerations for initiation of therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| The INSPIRE study included participants with intolerance or inadequate response to conventional therapy, tofacitinib (nonbiologic), or 1 or more biologic therapies. However, the efficacy results were more notable in patients who have not previously received advanced therapy. What place in therapy would risankizumab be used in patients with an inadequate response to other advanced therapies (i.e., those with experience with biologics or JAK inhibitors)? | The clinical experts noted to CDEC that, based on the available evidence from the studies and the indirect treatment comparison, the place in therapy of risankizumab would be similar to other advanced therapies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| The sponsor claims that risankizumab "is the first advanced therapy to demonstrate improvements in patient-reported outcomes such as tenesmus, fecal incontinence, sleep disturbance, and urgent bowel movements."<br><br>Would these patients be considered specifically for eligibility of risankizumab as opposed to other advanced therapies?                                                                                                                        | The clinical experts noted to CDEC that these patient-reported outcomes are expected to be improved with all advanced therapies and not just with risankizumab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Considerations for prescribing of therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Is there a possibility for the off-label use of a 24-week induction treatment in clinical practice? If appropriate, please comment on utility and efficacy of using an extended induction                                                                                                                                                                                                                                                                                | <p>The clinical experts noted to CDEC that it would depend on patient history (e.g., no prior treatment or an inadequate response, corticosteroid response), and the decision would be made on a case-by-case basis.</p> <p>In the INSPIRE trial, patients whose UC did not demonstrate clinical response with risankizumab 1,200 mg IV at week 12 continued treatment with risankizumab up to week 24. At week 24, the proportion of patients in clinical remission was 12.7% for those who received risankizumab 180 mg SC, 15.7% for those who received risankizumab 360 mg SC, and 8.8% for those who received risankizumab 1,200 mg IV.</p> <p>CDEC recommended that the induction reimbursement of risankizumab should be limited to a single induction treatment period of 12 weeks because no comparative evidence was available supporting an additional induction period.</p> |

CDEC = Canadian Drug Expert Committee; IL = interleukin; JAK = Janus kinase; SC = subcutaneous; UC = ulcerative colitis.

## Clinical Evidence

### Systematic Review

#### Description of Studies

The systematic review included 2 pivotal trials (INSPIRE and COMMAND). The INSPIRE trial was a phase III, randomized, placebo-controlled, double-blind, parallel-group induction study in adult patients with moderately to severely active UC who had an inadequate response or intolerance to conventional or other advanced therapies. Patients in the INSPIRE trial were randomized to receive 1,200 mg IV risankizumab (650 patients) or placebo (325 patients). Patients with an inadequate clinical response at week 12 were eligible to enter another blinded risankizumab treatment period (i.e., induction period 2 which lasted for an additional 12 weeks).

The COMMAND trial was a phase III, randomized, placebo-controlled, double-blind, parallel-group maintenance study in adult patients with UC who were previously enrolled in the INSPIRE induction trial and who had an adequate response to risankizumab. Patients were randomized to receive risankizumab 180 mg SC (179 patients), risankizumab 360 mg SC (186 patients), or placebo (183 patients). The placebo group included patients who discontinued risankizumab after the induction phase (risankizumab withdrawal).

Combined, the 2 studies lasted up to 81 weeks, including a screening period that lasted up to 35 days, a 12-week double-blind induction period, and a 52-week maintenance period. Randomization was stratified by a history of inadequate response to advanced therapy (yes, no), the last risankizumab induction dose (IV 600 mg, 1,200 mg, or 1,800 mg), and clinical remission status (per local evaluation) at the last visit of the induction trial (yes, no). Patients who experienced inadequate response were eligible for risankizumab rescue therapy starting at week 16 of the maintenance trial (1 dose of 1,200 mg IV or 1,800 mg IV followed by 360 mg SC every 8 weeks). The final patient follow-up occurred in April 2023.

The following efficacy outcomes were assessed as the most relevant to inform expert committee deliberations and were finalized in consultation with members of the expert committee: clinical remission per adapted Mayo score; clinical response per adapted Mayo score, endoscopic improvement, HEMI, HEMR, discontinuation of corticosteroid use in patients receiving corticosteroids at baseline (maintenance only), UC-related hospitalization, and the patient-reported outcome via IBDQ. Select notable harms outcomes that were considered important were the incidence of treatment-emergent adverse events (TEAEs), SAEs, and adverse events (AEs) of special interest. The adapted Mayo score consists of stool frequency, rectal bleeding, and endoscopic subscores, and is the most used method for measuring disease activity in UC. Each subscore is scored from 0 to 3 and the total score ranges from 0 to 9, with higher scores indicating greater UC severity. Clinical remission was determined using the adapted Mayo score (stool frequency score  $\leq 1$  and not greater than baseline, rectal bleeding score of 0, and endoscopic subscore  $\leq 1$  without friability). Clinical response on the adapted Mayo score was defined as a decrease of 30% or more and greater than or equal to 2 points from baseline and a decrease in rectal bleeding score of greater than or equal to 1 or an absolute rectal bleeding score of less than or equal to 1. Endoscopic improvement was defined as an endoscopic subscore or less than or equal to 1 without friability on the adapted Mayo score.

The baseline characteristics in both the risankizumab and placebo treatment arms in the INSPIRE trial were generally well balanced. The total study population had UC that was highly refractory. This is shown by the proportion of patients who had extensive UC or pancolitis at baseline in addition to the high proportion who had an inadequate response to advanced therapies (approximately 51%). Furthermore, this study population had a high proportion of patients with a baseline adapted Mayo score greater than 7 points and most patients had a baseline endoscopic subscore of the adapted Mayo score of 3 points.

Similarly, in the maintenance (COMMAND) trial, the study population also had UC that was highly refractory and had severe disease characteristics, which were indicated by the proportion of patients with extensive UC or pancolitis, longer mean disease duration, and the large proportion of patients who previously had an inadequate response to an advanced therapy (approximately 75%), including more than 2 advanced therapies (approximately 25%), and an inadequate response to JAK inhibitors (approximately 15%).

## Efficacy Results

In the induction (INSPIRE) trial, all efficacy outcomes were analyzed using data from all randomized patients who received at least 1 dose of study drug and were analyzed according to the treatment the patients were randomized to. Similarly, in the maintenance (COMMAND) trial, all efficacy outcomes were analyzed using data from all randomized patients who received at least 1 dose of study drug after receiving IV risankizumab for only 1 period of 12 weeks in the induction trial and were analyzed according to the treatment the patients were randomized to.

The primary end point of the INSPIRE trial was clinical remission at 12 weeks using the adapted Mayo score. The between-group difference was 14.0% (95% CI, 10.0% to 18.0%) for risankizumab compared to placebo. Similarly, in the COMMAND trial, the between-group difference at 52 weeks was 16.3% (95% CI, 7.4% to 25.3%) for risankizumab 180 mg SC and 14.2% (95% CI, 5.3% to 23.2%) for risankizumab 360 mg SC compared to placebo (risankizumab withdrawal).

The secondary outcomes were in line with the primary end point. In the INSPIRE trial, the between-group difference for clinical response was 28.6% (22.3% to 34.8%) for risankizumab compared to placebo. In the COMMAND trial, the between-group difference was 17.1% (95% CI, 7.5% to 26.6%) and 11.5% (95% CI, 1.7% to 21.2%) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

For endoscopic improvement, in the INSPIRE trial, the between-group difference was 24.3% (95% CI, 19.3% to 29.4%) for risankizumab compared to placebo. In the COMMAND trial, the between-group difference was 20.1% (95% CI, 10.6% to 29.6%) and 17.4% (95% CI, 7.9% to 26.9%) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

For HEMI, in the INSPIRE trial, the between-group difference was 16.6% (95% CI, 12.3% to 21.0%) for risankizumab compared to placebo. In the COMMAND trial, the between-group difference was 20.2% (95% CI, 11.2% to 29.2%) and 19.8% (95% CI, 10.8% to 28.8%) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

For HEMR, in the INSPIRE trial, the between-group difference was 5.6% (95% CI, 3.5% to 7.7%) for risankizumab compared to placebo. In the COMMAND trial, the between-group difference was 4.0% (95% CI, -2.2% to 10.3%) and 6.1% (95% CI, -0.3% to 12.5%) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

For discontinuation of corticosteroid use in patients receiving corticosteroids at baseline, which was only measured in the COMMAND trial, the between-group difference was 28.4% (95% CI, 14.0% to 42.8%) and 20.7% (95% CI, 4.9% to 36.6%) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

Total IBDQ scores ranged between 32 and 224 points (higher scores represent better HRQoL). Using the IBDQ scale, the mean difference was 18.3 points (95% CI, 13.38 to 23.25 points) for risankizumab compared to placebo in the INSPIRE trial. In the COMMAND trial, the mean difference was 17.5 points (95% CI, 8.01 to 27.06 points) and 15.2 (95% CI, 5.18 to 25.31 points) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

In the INSPIRE trial, the between-group difference for UC-related hospitalization was -4.8% (95% CI, -7.3% to -2.2%) for risankizumab compared to placebo. In the COMMAND trial, the incidence rate difference was -2.5 per 100 patient-years (95% CI, -5.4 to 0.4 per 100 patient-years) and -1.8 per 100 patient-years (95% CI, -5.0 to 1.3 per 100 patient-years) for risankizumab 180 mg SC and risankizumab 360 mg SC, respectively, compared to placebo (risankizumab withdrawal).

## Harms

For the safety analyses in both trials, it included all randomized patients who received at least 1 dose of study drug, analyzed according to the treatment that they received. In the INSPIRE trial, the number of patients with at least 1 TEAE was similar in the risankizumab (42.4%) and placebo (49.4%) groups. The most common TEAE in the risankizumab group was COVID-19 (4.8%), and the most common TEAE in the placebo group was colitis ulcerative (refers to the worsening of the underlying disease) (10.2%). The proportion of patients with at least 1 SAE was higher in the placebo group (10.2%) than in the risankizumab group (2.3%). The most common serious TEAEs in the risankizumab group were anemia, colitis ulcerative, and pulmonary embolism (2 patients [0.3%] each). In the placebo group, the most common serious TEAEs were colitis ulcerative (4.9%), anemia (0.6%), and anal fistula (0.6%). A higher proportion of patients in the placebo group (3.7%) discontinued treatment due to a TEAE than in the risankizumab group (0.6%). One patient in the risankizumab group died of COVID-19. The most frequently occurring AEs of special interest in both arms were hypersensitivity (risankizumab: 3.8%; placebo: 2.2%) and hepatic events (risankizumab: 1.5%; placebo: 4.0%).

In the COMMAND trial, the number of patients with at least 1 TEAE was similar in the risankizumab 180 mg SC (72.5%), risankizumab 360 mg SC (70.8%), and placebo (76.5%) groups. In the COMMAND trial, the proportion of patients with at least 1 SAE was similar across groups (risankizumab 180 mg SC: 5.2%; risankizumab 360 mg SC: 5.1%; placebo: 8.2%). In the risankizumab 180 mg group, the only serious TEAE that occurred in more than 1 patient was appendicitis (2 patients; 1.0%). In the risankizumab 360 mg SC group, no serious TEAE occurred in more than 1 patient. In the placebo (risankizumab withdrawal) group,

the most common serious TEAE was colitis ulcerative (2.6%); no other serious TEAE occurred in more than 1 patient. The proportion of patients who discontinued treatment due to a TEAE was highest in patients receiving risankizumab 360 mg SC (2.6%) compared to those receiving risankizumab 180 mg SC (1.6%) or placebo (1.5%). Regarding AEs of special interest, the risankizumab 180 mg SC group had the highest proportion of patients with hypersensitivity (10.4%). The risankizumab 360 mg SC group had the highest proportion of patients with hepatic events (6.7%).

## Critical Appraisal

### *Internal Validity*

#### INSPIRE Trial

Randomization in the INSPIRE trial took place using a 2:1 (to receive 1,200 mg IV risankizumab or placebo) computer-generated, block randomization via interactive response technology. This is an adequate form of randomization and allocation concealment. Participants were stratified for major confounding factors (e.g., corticosteroid use, baseline Mayo score, and prior advanced therapy exposure). The baseline characteristics of the randomized groups were balanced reflecting a proper randomization procedure. The trial was double-blinded, placebo-controlled, and with a detailed protocol including what concomitant medications were allowed and what changes in dosing were allowed after randomization. This decreases the probability of any deviations from the intended interventions during the trial. Concomitant medications were balanced across the treatment groups and not expected to affect the efficacy results. The primary and secondary efficacy end points in the INSPIRE trial were tested using a graphical multiple-testing procedure to ensure control of family-wise type I error at a significance level alpha of 0.05 (2-sided), which was deemed adequate.

The sponsor considered the occurrence of appropriate intercurrent events that impact the interpretation of the effect of interest within the trial estimands. Data for patients who prematurely discontinued treatment continued to be collected (i.e., treatment policy), while initiation or escalation of UC-related corticosteroids and the occurrence of UC-related surgery was considered as a nonresponse for binary end points and return to baseline for continuous end points. This approach is considered adequate by regulatory authorities if the therapeutic intent is to induce remission in the short term.

Regarding missing outcome data, and at the request by the review team, the sponsor was unable to provide information about the occurrence of intercurrent events before study discontinuation or on the potential for sporadic missing data for reasons other than study discontinuation (e.g., missing visit). Therefore, it was not possible to perform a complete appraisal of the potential for bias due to missing data arising from reasons that are incompatible with the nonresponder imputation approach used by the sponsor for binary end points (and missing at random for continuous end points). There was a higher discontinuation rate in the placebo group (8.3%) than the risankizumab group (2%), which can introduce attrition bias when nonresponder imputation is used and the reasons for study discontinuation (and possibly missing data) are incompatible with lack of efficacy. More than half the patients in the placebo group who withdrew did so for reasons of lack of efficacy or AEs, suggesting that the assumption of nonresponse is acceptable to account for withdrawals. Sensitivity analyses were conducted for the primary end point, including a tipping point analysis which supported that the statistical significance of the results would be maintained across a range of assumptions

about the missing data. The outcome of UC-related hospitalization used an as-observed analysis; this approach considers that data are missing completely at random, which is unlikely to be reasonable and may introduce bias if there is an increased proportion of missing data (could not be assessed).

To minimize detection bias, the trial used central endoscopic review with blinded assessment of objective outcomes, but it is important to note that this is only 1 component of the adapted Mayo score. For subjective outcomes, such as patient-reported outcomes (e.g., other components of the adapted Mayo score, IBDQ) and safety outcomes, bias is unlikely because the trial was double-blinded. Selective outcome and analysis reporting bias was marginalized by the publication of a prespecified protocol in ClinicalTrials.gov (NCT03398148). Overall, the INSPIRE trial is at low risk of bias for most end points, although uncertainty remains about potential attrition bias, which could not be fully assessed due to insufficient reporting.

The collection of information on harms included worsening UC as well as UC-related symptoms. Given that these are likely to be increased in the placebo group, the interpretation of the difference between groups is challenging. Further, it is implausible that there were significantly more SAEs reported in the placebo group than in the active intervention group, which would infer that the placebo effect is associated with SAEs.

Regarding the subgroup analyses, randomization in the INSPIRE trial was stratified by the presence of baseline corticosteroid use (yes, no), baseline adapted Mayo score ( $\leq 7$ ,  $> 7$ ), and a history of intolerance or inadequate response to advanced therapies (0, 1,  $> 1$  treatment). All other subgroup analyses may have potentially broken randomization and therefore could have been affected by biases, including selection bias and confounding due to unadjusted differences in baseline characteristics. The purpose of these analyses was to demonstrate consistency; they cannot be used to draw credible conclusions about effect modification.

## COMMAND Trial

The trial protocol was publicly available (NCT03398135), and the randomization and allocation concealment methods were similar to the INSPIRE trial, but with a 1:1:1 (to receive risankizumab 180 mg SC, risankizumab 360 mg SC, or placebo) allocation ratio stratified by prior advanced therapy response and induction dose. The baseline characteristics suggested imbalances in some disease characteristics, although these did not appear to systematically favour any treatment group. Therefore, it is not expected that there would be an important impact on the results.

The trial was double-blinded; however, open-label rescue with risankizumab 1,200 mg IV was allowed after week 16. The unblinded therapy may have introduced performance bias in the collection of data related to harms. For efficacy end points, the need for rescue therapy resulted in an assumption of nonresponse, which is appropriate and would not introduce bias. Concomitant medications were balanced across the treatment groups and not expected to affect the efficacy results. In the COMMAND trial, the testing began with testing the primary end point at the prespecified significant level of 0.025 (2-sided) for each risankizumab dose group compared to placebo. This was deemed as an adequate approach.

The sponsor considered the occurrence of appropriate intercurrent events that impact the interpretation of the effect of interest within the trial estimands. Data for patients who prematurely discontinued the drug continued to be collected (i.e., treatment policy) while initiation or escalation of UC-related corticosteroids,

the occurrence or UC-related surgery, and the need for rescue treatment were considered as a nonresponse for binary end points and return to baseline for continuous end points. Because the intent of the COMMAND trial was to demonstrate maintenance of treatment efficacy in the long term, considering treatment discontinuations as a nonresponse may be the preferred approach. Nonetheless, a supplemental analysis using the nonresponder imputation approach for treatment discontinuations showed similar results to the primary analysis on the primary and all secondary end points.

It was not possible to perform a comprehensive appraisal of the risk of bias due to missing outcome data as a result of incomplete reporting in the COMMAND study report. The concern for potentially unreported missing data may be higher for the COMMAND trial compared to the INSPIRE trial because of the longer follow-up period in the COMMAND trial. There was a higher discontinuation rate in all groups in the COMMAND trial compared to the INSPIRE trial; 9.8% of patients in the placebo group discontinued and the risankizumab groups ranged from 7.8% to 12.4%. This can introduce attrition bias when nonresponder imputation is used and the reasons for study discontinuation are incompatible with lack of efficacy (if these patients' data are considered missing). Because it is unclear how many patients were already imputed as nonresponders before study discontinuation (due to intercurrent events, which appeared common; e.g., 19% to 43% of patients received rescue medication), the appraisal of potential for bias cannot be completed with certainty. When this information was requested by the review team, the sponsor was unable to provide it. Sensitivity analyses were conducted for the primary end point, including a tipping point analysis which supported that the statistical significance of the results would be maintained across a range of assumptions about the missing data. The outcome of UC-related hospitalization used an as-observed analysis which considers data to be missing completely at random, which is unlikely to be reasonable and may introduce bias if there is an increased proportion of missing data (could not be assessed).

In addition, the outcome of discontinuation of corticosteroid use at week 52 in patients receiving corticosteroids at baseline did not utilize the full cohort of randomized participants, and it is unclear if the baseline characteristics in these individuals are similar among the groups. Overall, it is considered that bias is possible in the harms data because of the open-label rescue treatment and in the corticosteroid discontinuation end point due to possible loss of randomization. The risk of bias due to missing outcome data could be increased because of attrition and lack of information to understand the proportion of data that may be missing. This concern was mitigated for the primary outcome via sensitivity analysis.

The collection of harms information included worsening UC as well as UC-related symptoms. Because these are likely to be increased in the placebo group, the interpretation of the difference between groups is challenging. Additionally, the comparison may not reflect a true placebo group because risankizumab rescue therapy was permitted, which was received by 43% of patients in the placebo group.

In the COMMAND trial, randomization was stratified by history of inadequate response to advanced therapy (yes, no), last risankizumab induction dose (IV 600 mg, 1,200 mg, or 1,800 mg), and clinical remission status (per local evaluation) at the last visit of the induction trial (yes, no). All other subgroup analyses may have potentially broken randomization and therefore could have been affected by biases, including selection bias and confounding due to unadjusted differences in baseline characteristics.

The placebo group in the COMMAND trial also received risankizumab during induction (risankizumab withdrawal). Therefore, there could have been a carry-over effect due to an inadequate washout.

### ***External Validity***

The populations of both trials had UC with a history of being highly refractory to previous treatments, and the clinical experts consulted by the review team confirmed that it was the expectation that in the newer UC trials more patients with inadequate response to prior therapy would be enrolled. In addition, the trials excluded patients with a history of prior IL-23 inhibitor use. Regarding co-interventions, initiating or increasing the dosage of co-medications was prohibited in the INSPIRE trial; in the COMMAND trial, patients undergoing corticosteroid therapy were required to taper by week 8. Regarding the comparator, no direct comparison to an active intervention was available (it was only compared to a placebo). Furthermore, the main primary and secondary outcomes used the Mayo scoring system although this is not commonly used in clinical practice to inform decision-making. These specific trial characteristics and results may affect generalizability and implementation in a real-world setting.

### ***GRADE Summary of Findings and Certainty of the Evidence***

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.

Outcomes for the INSPIRE trial included:

- clinical remission
- clinical response
- endoscopic improvement
- HEMI
- HEMR
- IBDQ
- SAEs.

Outcomes for the COMMAND trial included:

- clinical remission
- clinical response
- endoscopic improvement
- HEMI
- HEMR
- discontinuation of corticosteroid use in patients receiving corticosteroids at baseline
- IBDQ
- SAEs.

**Table 3: Summary of Findings for Risankizumab vs. Placebo for Patients With Ulcerative Colitis (INSPIRE Trial)**

| Outcome and follow-up                                                                                     | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                                      |                                                              | Certainty             | What happens                                                                                                 |
|-----------------------------------------------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|--------------------------------------|--------------------------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------|
|                                                                                                           |                       |                          | Placebo                   | Risankizumab 1,200 mg IV             | Absolute difference (95% CI)                                 |                       |                                                                                                              |
| Efficacy                                                                                                  |                       |                          |                           |                                      |                                                              |                       |                                                                                                              |
| Proportion of patients with clinical remission per the adapted Mayo score<br>Follow-up: 12 weeks          | 975 (1 RCT)           | NR                       | 62 per 1,000              | 203 per 1,000 (172 to 234 per 1,000) | 140 more per 1,000 (100 more to 180 more)                    | Moderate <sup>a</sup> | Risankizumab likely results in a clinically important improvement in clinical remission compared to placebo. |
| Proportion of patients with clinical response per the adapted Mayo score<br>Follow-up: 12 weeks           | 975 (1 RCT)           | NR                       | 357 per 1,000             | 643 per 1,000 (606 to 679 per 1,000) | 286 more per 1,000 (223 more to 348 more)                    | High <sup>b</sup>     | Risankizumab results in a clinically important improvement in clinical response compared to placebo.         |
| Proportion of patients with endoscopic improvement<br>Follow-up: 12 weeks                                 | 975 (1 RCT)           | NR                       | 121 per 1,000             | 365 per 1,000 (328 to 402 per 1,000) | 243 more per 1,000 (193 more to 294 more)                    | High <sup>c</sup>     | Risankizumab results in a clinically important improvement in endoscopic improvement compared to placebo.    |
| Proportion of patients with HEMI<br>Follow-up: 12 weeks                                                   | 975 (1 RCT)           | NR                       | 77 per 1,000              | 245 per 1,000 (212 to 278 per 1,000) | 166 more per 1,000 (123 more to 210 more)                    | High <sup>d</sup>     | Risankizumab results in an improvement in HEMI compared to placebo. The clinical importance is uncertain.    |
| Proportion of patients with HEMR<br>Follow-up: 12 weeks                                                   | 975 (1 RCT)           | NR                       | 6 per 1,000               | 63 per 1,000 (44 to 82 per 1,000)    | 56 more per 1,000 (35 more to 77 more)                       | High <sup>d</sup>     | Risankizumab results in an improvement in HEMI compared to placebo. The clinical importance is uncertain.    |
| Patient-reported outcomes                                                                                 |                       |                          |                           |                                      |                                                              |                       |                                                                                                              |
| Change from baseline in IBDQ total score, points (range: 32 [worst] to 224 [best])<br>Follow-up: 12 weeks | 975 (1 RCT)           | NR                       | 24.3                      | 42.6 points (39.72 to 45.57 points)  | Mean difference = 18.3 higher (13.38 higher to 23.25 higher) | Moderate <sup>e</sup> | Risankizumab likely results in a clinically important improvement in IBDQ scores compared to placebo.        |

| Outcome and follow-up                                                     | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                          |                                         | Certainty        | What happens                                                                                                           |
|---------------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|--------------------------|-----------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------|
|                                                                           |                       |                          | Placebo                   | Risankizumab 1,200 mg IV | Absolute difference (95% CI)            |                  |                                                                                                                        |
| Harms                                                                     |                       |                          |                           |                          |                                         |                  |                                                                                                                        |
| Proportion of patients with serious adverse events<br>Follow-up: 12 weeks | 975 (1 RCT)           | NR                       | 102 per 1,000             | 23 per 1,000 (NR to NR)  | 79 less per 1,000 (114 less to 44 less) | Low <sup>f</sup> | Risankizumab may result in little to no clinically important difference in serious adverse events compared to placebo. |

CI = confidence interval; HEMI = histologic, endoscopic, and mucosal improvement; IBDQ = Inflammatory Bowel Disease Questionnaire; NR = not reported; MID = minimal important difference; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), 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. The proportion of missing data was not reported and therefore cannot be fully appraised.

<sup>a</sup>An empirically derived MID of 11% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for imprecision (because the CIs show both potential benefit and little to no clinically important difference between risankizumab and placebo).

<sup>b</sup>An empirically derived MID of 14% was identified in the literature for the between-group difference for this outcome.

<sup>c</sup>An empirically derived MID of 12.5% was identified in the literature for the between-group difference for this outcome.

<sup>d</sup>An empirically derived MID was not identified for the between-group difference for this outcome; effects were appraised using the null.

<sup>e</sup>An empirically derived improvement of 15 points or greater than placebo was considered be the MID for this outcome as identified in the literature. Rated down 1 level for imprecision because the CIs show both potential benefit and little to no clinically important difference between risankizumab and placebo.

<sup>f</sup>An empirically derived MID of 6% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for imprecision (as the confidence intervals show both potential benefit and little to no clinically important difference between risankizumab and placebo). Rated down 1 level for serious indirectness because the collection of SAEs includes symptoms of worsening UC which complicates interpretation. The effect was judged as not different than placebo because a reduction in SAEs compared to placebo is implausible.

Sources: INSPIRE Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

**Table 4: Summary of Findings for Risankizumab 180 mg SC vs. Placebo (Risankizumab Withdrawal) for Patients With Ulcerative Colitis (COMMAND Trial)**

| Outcome and follow-up                                               | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                                      |                                          | Certainty             | What happens                                                                                                 |
|---------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|--------------------------------------|------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------|
|                                                                     |                       |                          | Placebo                   | Risankizumab 180 mg SC               | Absolute difference (95% CI)             |                       |                                                                                                              |
| Efficacy                                                            |                       |                          |                           |                                      |                                          |                       |                                                                                                              |
| Proportion of patients with clinical remission per the adapted Mayo | 362 (1 RCT)           | NR                       | 251 per 1,000             | 402 per 1,000 (330 to 474 per 1,000) | 163 more per 1,000 (74 more to 253 more) | Moderate <sup>a</sup> | Risankizumab likely results in a clinically important improvement in clinical remission compared to placebo. |

| Outcome and follow-up                                                                                                                      | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                                      |                                           | Certainty             | What happens                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|--------------------------------------|-------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                            |                       |                          | Placebo                   | Risankizumab 180 mg SC               | Absolute difference (95% CI)              |                       |                                                                                                                             |
| score<br>Follow-up: 52 weeks                                                                                                               |                       |                          |                           |                                      |                                           |                       |                                                                                                                             |
| Proportion of patients with clinical response per the adapted Mayo score<br>Follow-up: 52 weeks                                            | 362 (1 RCT)           | NR                       | 519 per 1,000             | 682 per 1,000 (613 to 750 per 1,000) | 171 more per 1,000 (75 more to 266 more)  | Moderate <sup>b</sup> | Risankizumab likely results in a clinically important improvement in clinical response compared to placebo.                 |
| Proportion of patients with endoscopic improvement<br>Follow-up: 52 weeks                                                                  | 362 (1 RCT)           | NR                       | 317 per 1,000             | 508 per 1,000 (435 to 581 per 1,000) | 201 more per 1,000 (106 more to 296 more) | Moderate <sup>c</sup> | Risankizumab likely results in a clinically improvement in endoscopic improvement compared to placebo.                      |
| Proportion of patients with HEMI<br>Follow-up: 52 weeks                                                                                    | 362 (1 RCT)           | NR                       | 235 per 1,000             | 428 per 1,000 (356 to 501 per 1,000) | 202 more per 1,000 (112 more to 292 more) | High <sup>d</sup>     | Risankizumab results in an improvement in HEMI compared to placebo. The clinical importance is uncertain.                   |
| Proportion of patients with HEMR<br>Follow-up: 52 weeks                                                                                    | 362 (1 RCT)           | NR                       | 98 per 1,000              | 129 per 1,000 (80 to 179 per 1,000)  | 40 more per 1,000 (22 less to 103 more)   | Moderate <sup>e</sup> | Risankizumab likely results in an improvement in HEMR compared to placebo. The clinical importance is uncertain.            |
| Proportion of patients with discontinuation of corticosteroid use in patients receiving corticosteroids at baseline<br>Follow-up: 52 weeks | 142 (1 RCT)           | NR                       | 368 per 1,000             | 649 per 1,000 (540 to 757 per 1,000) | 284 more per 1,000 (140 more to 428 more) | Low <sup>f</sup>      | Risankizumab may result in a clinically important improvement in discontinuation of corticosteroid use compared to placebo. |
| Patient-reported outcomes                                                                                                                  |                       |                          |                           |                                      |                                           |                       |                                                                                                                             |
| Change in baseline in IBDQ total score, points (range: 32                                                                                  | 362 (1 RCT)           | NR                       | 35.0                      | 52.6 (44.93 to 60.20)                | Mean difference = 17.5 higher (8.01       | Moderate <sup>g</sup> | Risankizumab likely results in a clinically important improvement                                                           |

| Outcome and follow-up                                                     | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                         |                                        | Certainty        | What happens                                                                                                           |
|---------------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|-------------------------|----------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------|
|                                                                           |                       |                          | Placebo                   | Risankizumab 180 mg SC  | Absolute difference (95% CI)           |                  |                                                                                                                        |
| [worst] to 224 [best]<br>Follow-up: 52 weeks                              |                       |                          |                           |                         | higher to 27.06 higher)                |                  | in IBDQ scores compared to placebo.                                                                                    |
| <b>Harms</b>                                                              |                       |                          |                           |                         |                                        |                  |                                                                                                                        |
| Proportion of patients with serious adverse events<br>Follow-up: 52 weeks | 389 (1 RCT)           | NR                       | 82 per 1,000              | 52 per 1,000 (NR to NR) | 30 less per 1,000 (79 less to 20 more) | Low <sup>h</sup> | Risankizumab may result in little to no clinically important difference in serious adverse events compared to placebo. |

CI = confidence interval; HEMI = histologic, endoscopic, and mucosal improvement; IBDQ = Inflammatory Bowel Disease Questionnaire; MID = minimal important difference; NR = not reported; RCT = randomized controlled trial; SC = subcutaneous.

Note: Study limitations (which refers to internal validity or risk of bias), 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. The proportion of missing data was not reported and therefore cannot be fully appraised.

<sup>a</sup>An empirically derived MID of 11% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for serious imprecision; the point estimate suggests clinically important benefit while the lower bound of the CI suggests little to no difference.

<sup>b</sup>An empirically derived MID of 14% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for serious imprecision; the CI includes the potential for benefit and little to no difference.

<sup>c</sup>An empirically derived MID of 12.5% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for imprecision because the CIs show both potential benefit and little to no difference between risankizumab and placebo.

<sup>d</sup>An empirically derived MID was not identified for the between-group difference for this outcome; effects were appraised using the null.

<sup>e</sup>An empirically derived MID was not identified for the between-group difference for this outcome; effects were appraised using the null. Rated down 1 level for imprecision because the CIs show both potential benefit and little to no difference between risankizumab and placebo.

<sup>f</sup>No threshold of clinical importance could be established from the literature. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 15% between the groups was identified by the clinical experts consulted by Canada's Drug Agency as a threshold of clinical importance for this outcome. Rated down 1 level for serious study limitations; the randomization was not stratified by baseline corticosteroid use; therefore, randomization in this population might not be upheld. Rated down 1 level for imprecision because the CIs show both potential benefit and equivalence between risankizumab and placebo.

<sup>g</sup>An empirically derived improvement of 15 points or greater than placebo was considered be the MID for this outcome. Rated down 1 level for imprecision because the CIs show both potential benefit and little to no clinically important difference between risankizumab and placebo.

<sup>h</sup>An empirically derived MID of 6% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for imprecision (because the CIs show both potential benefit and little to no clinically important difference between risankizumab and placebo). Rated down 1 level for serious indirectness because the collection of SAEs includes symptoms of worsening ulcerative colitis, which complicates interpretation.

Sources: COMMAND Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

**Table 5: Summary of Findings for Risankizumab 360 mg SC vs. Placebo (Risankizumab Withdrawal) for Patients With Ulcerative Colitis (COMMAND Trial)**

| Outcome and follow-up                                                                                      | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                                      |                                           | Certainty             | What happens                                                                                                                |
|------------------------------------------------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|--------------------------------------|-------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------|
|                                                                                                            |                       |                          | Placebo                   | Risankizumab 360 mg SC               | Absolute difference (95% CI)              |                       |                                                                                                                             |
| Efficacy                                                                                                   |                       |                          |                           |                                      |                                           |                       |                                                                                                                             |
| Proportion of patients with clinical remission per the adapted Mayo score<br>Follow-up: 52 weeks           | 362 (1 RCT)           | NR                       | 251 per 1,000             | 376 per 1,000 (307 to 446 per 1,000) | 142 more per 1,000 (53 more to 232 more)  | Moderate <sup>a</sup> | Risankizumab likely results in a clinically important improvement in clinical remission compared to placebo.                |
| Proportion of patients with clinical response per the adapted Mayo score<br>Follow-up: 52 weeks            | 362 (1 RCT)           | NR                       | 519 per 1,000             | 623 per 1,000 (554 to 693 per 1,000) | 115 more per 1,000 (17 more to 212 more)  | Moderate <sup>b</sup> | Risankizumab likely results in little to no clinically important difference in clinical response compared to placebo.       |
| Proportion of patients with endoscopic improvement<br>Follow-up: 52 weeks                                  | 362 (1 RCT)           | NR                       | 317 per 1,000             | 483 per 1,000 (411 to 555 per 1,000) | 174 more per 1,000 (79 more to 269 more)  | Moderate <sup>c</sup> | Risankizumab likely results in a clinically important improvement in endoscopic improvement compared to placebo.            |
| Proportion of patients with HEMI<br>Follow-up: 52 weeks                                                    | 362 (1 RCT)           | NR                       | 235 per 1,000             | 422 per 1,000 (351 to 494 per 1,000) | 198 more per 1,000 (108 more to 288 more) | High <sup>d</sup>     | Risankizumab results in an improvement in HEMI compared to placebo. The clinical importance is uncertain.                   |
| Proportion of patients with HEMR<br>Follow-up: 52 weeks                                                    | 362 (1 RCT)           | NR                       | 98 per 1,000              | 156 per 1,000 (104 to 209 per 1,000) | 61 more per 1,000 (3 less to 125 more)    | Moderate <sup>e</sup> | Risankizumab results in an improvement in HEMR compared to placebo. The clinical importance is uncertain.                   |
| Proportion of patients with discontinuation of corticosteroid use in patients receiving corticosteroids at | 142 (1 RCT)           | NR                       | 368 per 1,000             | 542 per 1,000 (415 to 669 per 1,000) | 207 more per 1,000 (49 more to 366 more)  | Low <sup>f</sup>      | Risankizumab may result in a clinically important improvement in discontinuation of corticosteroid use compared to placebo. |

| Outcome and follow-up                                                                                     | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) |                         |                                                                    | Certainty             | What happens                                                                                          |
|-----------------------------------------------------------------------------------------------------------|-----------------------|--------------------------|---------------------------|-------------------------|--------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------------------------------------|
|                                                                                                           |                       |                          | Placebo                   | Risankizumab 360 mg SC  | Absolute difference (95% CI)                                       |                       |                                                                                                       |
| baseline<br>Follow-up: 52 weeks                                                                           |                       |                          |                           |                         |                                                                    |                       |                                                                                                       |
| Patient-reported outcomes                                                                                 |                       |                          |                           |                         |                                                                    |                       |                                                                                                       |
| Change from baseline in IBDQ total score, points (range: 32 [worst] to 224 [best])<br>Follow-up: 52 weeks | 362 (1 RCT)           | NR                       | 35.0                      | 50.3 (42.20 to 58.36)   | Mean difference = 15.2 points higher (5.18 higher to 25.31 higher) | Moderate <sup>g</sup> | Risankizumab likely results in a clinically important improvement in IBDQ scores compared to placebo. |
| Harms                                                                                                     |                       |                          |                           |                         |                                                                    |                       |                                                                                                       |
| Proportion of patients with serious adverse events<br>Follow-up: 52 weeks                                 | 389 (1 RCT)           | NR                       | 82 per 1,000 (NR to NR)   | 51 per 1,000 (NR to NR) | 30 less per 1,000 (80 less to 19 more)                             | Low <sup>h</sup>      | Risankizumab may result in little to no difference in serious adverse events compared to placebo.     |

CI = confidence interval; HEMI = histologic, endoscopic, and mucosal improvement; IBDQ = Inflammatory Bowel Disease Questionnaire; MID = minimal important difference; NR = not reported; RCT = randomized controlled trial.

Note: Study limitations (which refers 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. The proportion of missing data was not reported and therefore cannot be fully appraised.

<sup>a</sup>An empirically derived MID of 11% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for serious imprecision; the point estimate suggests clinically important benefit while the lower bound of the CI suggests little to no difference.

<sup>b</sup>An empirically derived MID of 14% was identified in the literature for the between-group difference for this outcome. Rated down 1 level of serious imprecision; the CI includes the potential for benefit and little to no difference.

<sup>c</sup>An empirically derived MID of 12.5% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for imprecision because the CIs show both potential benefit and equivalence between risankizumab and placebo.

<sup>d</sup>An empirically derived MID was not identified for the between-group difference for this outcome; effects were appraised using the null.

<sup>e</sup>An empirically derived MID was not identified for the between-group difference for this outcome; effects were appraised using the null. Rated down 1 level for imprecision because the CIs show both potential benefit and little to no difference between risankizumab and placebo.

<sup>f</sup>No threshold of clinical importance could be established from the literature. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 15% between the groups was identified by the clinical expert consulted by Canada's Drug Agency as a threshold of clinical importance for this outcome. Rated down 1 level for serious study limitations; the randomization was not stratified by baseline corticosteroid use; therefore, randomization in this population might not be upheld. Rated down 1 level for imprecision because the CIs show both potential benefit and equivalence between risankizumab and placebo.

<sup>g</sup>An empirically derived improvement of 15 points or greater than placebo was considered be the MID for this outcome. Rated down 1 level for imprecision because the CIs show both potential benefit and little to no clinically important difference between risankizumab and placebo.

<sup>h</sup>An empirically derived MID of 6% was identified in the literature for the between-group difference for this outcome. Rated down 1 level for imprecision (because the CIs show both potential benefit and little to no clinically important difference between risankizumab and placebo). Rated down 1 level for serious indirectness because the collection of SAEs includes symptoms of worsening ulcerative colitis which complicates interpretation.

Sources: COMMAND Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

## Long-Term Extension Studies

The sponsor submitted an abstract for the COMMAND open-label extension. Because of the lack of access to the complete methods and results, the open-label extension summary is not reported in this section.

## Indirect Evidence

### Description of Studies

No direct comparison exists between risankizumab and other publicly listed or recommended advanced therapies in Canada for moderately to severely active UC. Due to the absence of head-to-head RCTs, an NMA was used to compare the efficacy and safety of risankizumab with other publicly listed or recommended advanced therapies in Canada for moderately to severely active UC, which include adalimumab, infliximab, golimumab, vedolizumab, tofacitinib, ustekinumab, ozanimod, upadacitinib, mirikizumab, and etrasimod. The NMA included 28 (21 for induction and 16 for maintenance) phase III or IV randomized, double-blinded trials. The NMA reported on clinical remission, clinical response, endoscopic improvement, AEs, SAEs, and serious infections.

### Induction

#### Efficacy

Results from the indirect comparison on induction period, risankizumab 1,200 mg IV was

\_\_\_\_\_ adalimumab (OR \_\_\_\_\_) for clinical response and to adalimumab (OR \_\_\_\_\_), golimumab (OR \_\_\_\_\_), mirikizumab (OR \_\_\_\_\_), tofacitinib (OR \_\_\_\_\_), and ustekinumab (OR \_\_\_\_\_) with \_\_\_\_\_ in the risankizumab group achieving endoscopic improvement in the patient population who did not previously receive advanced therapy (non-AT). Upadacitinib was \_\_\_\_\_ risankizumab 1,200 mg IV for clinical remission (OR \_\_\_\_\_), clinical response (OR \_\_\_\_\_) and endoscopic improvement (OR \_\_\_\_\_) in the inadequate response or intolerance to advanced therapy (AT-IR) population. There was no evidence of difference between risankizumab 1,200 mg IV and the other interventions in the efficacy NMAs during induction period.

#### Safety

Risankizumab 1,200 mg IV was \_\_\_\_\_ adalimumab (OR \_\_\_\_\_), etrasimod (OR \_\_\_\_\_), and tofacitinib (OR \_\_\_\_\_) with \_\_\_\_\_ in the risankizumab 1,200 mg IV group having serious AEs during induction. Etrasimod was \_\_\_\_\_ risankizumab 1,200 mg IV (OR \_\_\_\_\_) with regards to serious infections. There was no

evidence of difference between risankizumab 1,200 mg IV and the other interventions in the safety NMAs during induction.

## Maintenance

### *Efficacy*

For the maintenance phase, in the patient population that did not receive advanced therapy and had an inadequate response (non-AT-IR), upadacitinib 30 mg was [REDACTED] risankizumab 180 mg SC (OR [REDACTED]) and risankizumab 360 mg SC (OR [REDACTED]) with [REDACTED] in the risankizumab groups having a clinical response in the non-AT-IR population during maintenance. There was no evidence of a difference between risankizumab groups and the other interventions in the efficacy NMAs during maintenance.

For the maintenance phase, in AT-IR populations, risankizumab 180 mg SC was [REDACTED] compared to upadacitinib (upadacitinib 15 mg: OR [REDACTED]; upadacitinib 30 mg: OR [REDACTED]); vedolizumab 300 mg every 8 weeks: OR [REDACTED] for clinical remission, tofacitinib ([REDACTED]) and upadacitinib (upadacitinib 15 mg: OR [REDACTED]; upadacitinib 30 mg: OR [REDACTED]) for clinical response, and upadacitinib (upadacitinib 15 mg: OR [REDACTED]; upadacitinib 30 mg: OR [REDACTED]) and vedolizumab (OR [REDACTED]) for endoscopic remission. There was no evidence of a difference between risankizumab 180 mg and the other interventions in the efficacy NMAs during maintenance.

Risankizumab 360 mg SC was [REDACTED] compared to mirikizumab (OR [REDACTED]), upadacitinib (upadacitinib 15 mg: OR [REDACTED]; upadacitinib 30: OR [REDACTED]) and vedolizumab (vedolizumab 108 mg every 2 weeks: OR [REDACTED]; vedolizumab 300 mg every 4 weeks (OR [REDACTED]); vedolizumab 300 mg every 8 weeks (OR [REDACTED]) for clinical remission, tofacitinib (OR [REDACTED]) and upadacitinib (upadacitinib 15 mg: OR [REDACTED]; upadacitinib 30 mg: OR [REDACTED]) for clinical response, and etrasimod (OR [REDACTED]), upadacitinib (upadacitinib 15 mg: OR [REDACTED]; upadacitinib 30 mg: OR [REDACTED]) and vedolizumab (vedolizumab 300 mg every 4 weeks: OR [REDACTED] and vedolizumab 300 mg every 8 weeks: OR [REDACTED]) for endoscopic remission. There was no

evidence of a difference between risankizumab 360 mg SC and the other interventions in the efficacy NMAs during maintenance.

### **Safety**

Risankizumab 360 mg was [REDACTED] golimumab (OR [REDACTED] [REDACTED]) with [REDACTED] with AEs in the risankizumab group during maintenance. There was no evidence of a difference between risankizumab 180 mg SC or risankizumab 360 mg SC and the other interventions in the safety NMAs during maintenance.

### **Critical Appraisal of the NMA**

In the sponsor-submitted ITC, relevant RCTs were identified using a systematic review produced following accepted methodological guidance and based on an a priori protocol that outlined the inclusion and exclusion criteria. The search is 2 years old, and it is not known whether more recent studies are available or what impact that might have on the results. Selection, data extraction, and risk of bias assessments were conducted in duplicate by independent researchers, which is considered adequate. Risk of bias for the included studies was conducted using the Cochrane Risk of Bias tool. The overall bias of all included studies was deemed to be “low.” The assessments occurred at the study level and not the outcome level as suggested by Cochrane, and bias concerns may vary by effect estimate. The appraisal may not be universally applicable across all outcomes. There was no assessment of the risk of publication bias; therefore, its presence or absence cannot be confirmed.

The methods used for the NMA were considered to be appropriate, including the use of Bayesian framework, because its conduct adhered to relevant guidance. However, there were no sensitivity analyses to understand the potential impact of the chosen priors for between-study standard deviation. Overall, the patient populations, interventions, comparators, and outcomes (PICO) of the included studies were consistent with the overall review’s objective. The clinical experts consulted by the review team did not expect any major issues regarding the representativeness of the study populations enrolled in the RCTs that were included in the ITC in relation to the populations in Canada that may be eligible for treatment with risankizumab.

As is common in NMAs of treatments for UC, an overall concern was the heterogeneity in the patient populations, including their baseline characteristics, average disease severity (and how this was defined across trials), disease duration, and the extent of the disease. In addition, the length of the induction and maintenance periods were not uniform across the trials. There were some differences in the AT-IR definitions used across studies and, due to changes in the standard of care and available treatments over time, the number and type of prior treatments to which patients were exposed likely varies. There was heterogeneity in the use of concurrent immunomodulators and corticosteroids. Additionally, the timing of the outcome assessments varied substantially, and the definitions of the efficacy end points of interest were not always consistent. Some relevant evidence was excluded due to misalignment in the assessment time points; although this was necessary to reduce heterogeneity, the effect on the results is not known.

There were additional sources of heterogeneity in the maintenance phase. In treat-through studies, patients were randomized to treatment or placebo at baseline and outcomes were measured at the end of an induction phase and again at the end of a maintenance phase. In re-randomization studies (e.g., risankizumab studies), patients were randomized to induction treatment or placebo at baseline, with outcomes measured at the end of the induction phase; those who responded to induction were then re-randomized to maintenance treatment or placebo, with outcomes measured at the end of the maintenance phase strictly among those who responded to induction. Adjustments were applied to accommodate the inclusion of treat-through and re-randomized trial designs in the same NMA. This was necessary, and has been applied to other NMAs for UC, but it relies on assumptions that cannot be fully validated. Placebo was a common comparator in the NMAs, although the placebo groups across studies are likely not equivalent due to carry-over effects from different induction treatments. Differences in the corticosteroid tapering strategy (and whether this was included) may also differ across the studies. For both induction and maintenance phases, the information needed to comprehensively assess the level of heterogeneity was not always available for all studies. The notable clinical and methodological heterogeneity raises concern for intransitivity, which undermines the validity of the indirect comparisons because it indicates that the assumption of exchangeability may not hold.

Relevant efforts were made to reduce or account for heterogeneity across the NMAs, including stratification of the results by AT-IR status, attempts at baseline risk meta-regression, and sensitivity analyses. The stratification of analyses by AT-IR and non-AT-IR populations for efficacy analyses is appropriate but limits generalizability of the results of either analysis to the overall indicated population. The interpretation of these subgroups faces some limitations. The baseline characteristics within subgroups was not always fully known (i.e., the full population was used for comparison), challenging comprehensive assessments of comparability. It is not clear whether randomization was stratified by AT-IR status across all trials. Confounding is possible because the effect estimates might not be from fully randomized groups. None of the baseline risk adjusted models converged; therefore, it became impossible to apply this adjustment. Sensitivity analyses of some sources of heterogeneity were not possible.

The networks were sparsely populated, with several nodes centred around a single connection (placebo) in a star geometry, with only 1 to 2 trials compared with placebo per treatment and only a few head-to-head trials (i.e., within-study comparisons of different doses of the same treatment). This reduces the robustness of the NMA and makes most comparisons underpowered by the lack of direct evidence. Further, all evidence for risankizumab was in comparison with placebo, which increases the uncertainty in the estimates for each outcome, and the consistency assumption could not be assessed. The heterogeneity and network sparsity are reflected in imprecise credible intervals. Fixed effect models were chosen for a small number of outcomes based on model fit, when it was a better fit than the random effect model. However, given the expected heterogeneity, the fixed effect model has the potential to underestimate the uncertainty in the results (i.e., width of the credible intervals). There was poor model fit for the analysis of serious infections in the induction phase. Last, based on the ITC feasibility assessment, 1 study was not included in the NMA because the drug is not approved in Canada.

Six outcomes of interest to this review were reported: clinical remission, clinical response, endoscopic improvement, AEs, SAEs, and serious infections. Interpretation of harms outcomes was complicated by inclusion of UC worsening and related symptoms as harms for the placebo groups, and potential differences in how harms data were collected across studies. Some outcomes that are of importance to patients, such as corticosteroid-free clinical remission and HRQoL, were not included.

## Studies Addressing Gaps in the Evidence From the Systematic Review

### Description of Studies

This study by Panaccione et al. (2025) was a post hoc analysis of the pivotal INSPIRE and COMMAND trials. The objective of the study was to assess the efficacy and safety of risankizumab induction and maintenance therapy in patients with moderately to severely active UC based on a prior inadequate response or intolerance to advanced therapy (i.e., AT-IR status). There were 472 patients in the non-AT-IR group and 503 in the AT-IR group who were included in the efficacy analysis of the induction period; 137 patients in the non-AT-IR group and 411 patients in the AT-IR group were included in the efficacy analysis of the maintenance phase.

### Induction Efficacy Outcomes

During the induction period of treatment, clinical outcomes at week 12 showed that a higher proportion of patients had clinical response in the risankizumab 1,200 mg group than in the placebo group across both the AT-IR and non-AT-IR subgroups. In the AT-IR subgroup, clinical remission rates were 11.4% for risankizumab and 4.3% for placebo (difference = 7.2%), whereas in the non-AT-IR subgroup, clinical remission rates were higher at 29.7% and 8.4% (difference: 21.3%) for risankizumab and placebo, respectively. Clinical response rates followed a similar trend; clinical response rates were 55.2% in the AT-IR subgroup and 73.8% in the non-AT-IR subgroup for risankizumab compared to 31.2% and 40.6% for placebo (AT-IR: difference = 24.0%; non-AT-IR: difference = 33.2%).

Endoscopic outcomes were also higher in the risankizumab group. Endoscopic improvement at week 12 was observed in 25.9% of patients in the AT-IR subgroup and 47.6% of patients in the non-AT-IR subgroup receiving risankizumab compared to 10.1% and 14.2% in the placebo groups (AT-IR: difference = 15.8%; non-AT-IR: difference = 33.2%). Endoscopic remission rates were 4.8% (AT-IR) and 16.7% (non-AT-IR) for risankizumab versus 3.0% and 3.9% for placebo (AT-IR: difference = 1.8%; non-AT-IR: difference = 12.8%). Additionally, HEMI rates were 16.0% for patients in the AT-IR subgroup and 33.4% for patients in the non-AT-IR subgroup for risankizumab compared to 7.1% and 8.4% for placebo, respectively (AT-IR: difference = 8.9%; non-AT-IR: difference = 25.1%).

### Maintenance Efficacy Outcomes

During the maintenance period at week 52, the difference in clinical remission rates in the AT-IR subgroup versus placebo was 6.3% for risankizumab 360 mg and 13.4% for risankizumab 180 mg. In the non-AT-IR subgroup, remission rates versus placebo were 30.6% for risankizumab 360 mg and 19.8% for risankizumab 180 mg. Clinical response rates in the AT-IR subgroup versus placebo were 11.2% for risankizumab 360 mg and 17.8% for risankizumab 180 mg; in the non-AT-IR subgroup, they were 7.5% and 11.1%, respectively.

Endoscopic outcomes were also higher in the risankizumab groups. Endoscopic improvement in the AT-IR subgroup versus placebo was observed in 8.4% of patients in the risankizumab 360 mg group and 17.3% of patients in the risankizumab 180 mg group; in the non-AT-IR subgroup, endoscopic improvement was observed in 40.6% and 24.2% of patients in the risankizumab 360 mg and risankizumab 180 mg groups, respectively. Endoscopic remission rates in the AT-IR subgroup versus placebo were 2.1% for the risankizumab 360 mg group and 5.6% for the risankizumab 180 mg group; in the non-AT-IR subgroup, endoscopic remission rates were 31.6% for the risankizumab 360 mg group and 16.6% for the risankizumab 180 mg group. HEMI rates in the AT-IR subgroup versus placebo were 11.4% for the risankizumab 360 mg group and 17.1% for risankizumab 180 mg group; in the non-AT-IR subgroup, HEMI rates were 40.4% for the risankizumab 360 mg group and 25.9% for risankizumab 180 mg group.

### **Safety Outcomes**

In the induction study, the proportion of patients with any TEAE in the AT-IR subgroup was 44.1% and 53.5% in the risankizumab 1,200 mg and placebo groups, respectively. The proportion of patients with any TEAE in the non-AT-IR subgroup was 39.9% and 45.5% in the risankizumab 1,200 mg and placebo groups, respectively.

In the maintenance study, the proportion of patients with any TEAE in the AT-IR subgroup was 69.4%, 74.7%, and 76.5% in the risankizumab 360 mg, risankizumab 180 mg, and placebo groups, respectively. The proportion of patients with any TEAE in the non-AT-IR subgroup was 75.0%, 66.0%, and 76.6% in the risankizumab 360 mg, risankizumab 180 mg, and placebo groups, respectively.

### **Critical Appraisal of the Studies Addressing Gaps in the Evidence From the Systematic Review**

This was a post hoc analysis. There is no type I error control, which increases the risk of type I error. Conversely, subgroups might not be powered to find significant differences. There is a risk that randomization was broken for some of the subgroups (those not included as stratification factors); previous advanced therapies were stratification factors, but not always in the manner they were classified in this post hoc analysis. The analysis could not distinguish whether observed differences across groups would be due to AT-IR status or other differences between the groups. There were no tests for subgroup differences. Based on these reasons, CDA-AMC cannot draw credible conclusions about effect modification; but this can be used for hypothesis generation. In several cases, the analysis suggests consistency in the direction of effect with the overall population in the trials, although the magnitude of these effects differed.

## **Economic Evidence**

### **Economic Evaluation and Budget Impact**

- Risankizumab is available as 600 mg vials for IV infusion as well as 180 mg and 360 mg cartridges for SC injection. At the submitted price of \$4,593.14 per vial or cartridge, the annual cost of

risankizumab is expected to be \$50,627 per patient in the first year of treatment and \$29,958 in subsequent years, based on the Health Canada–recommended dosage for UC.

- Clinical efficacy in the economic analysis was derived from a sponsor-submitted NMA, with the efficacy of risankizumab informed by the INSPIRE and COMMAND trials. Indirect evidence submitted by the sponsor was affected by several methodological limitations identified by CDA-AMC, which included likely violations of the underlying assumptions, network sparsity, imprecision, and inconsistency of results across outcomes. As a result, the relative treatment effects of risankizumab versus relevant comparators are subject to uncertainty, and there is no conclusive evidence of which treatment may provide the preferred balance of benefits and harms.
- In the sponsor’s base case, risankizumab was dominated (less effective, more costly) by multiple comparators in both populations. This finding is uncertain due to limitations in the submitted NMA and thus it is uncertain if, and to what extent, risankizumab provides a net benefit relative to other therapies currently funded.
- Given the limitations of the sponsor-submitted indirect evidence, there is insufficient evidence to suggest risankizumab should be priced higher than other advanced therapies for the treatment of UC and further price reductions may be required to ensure cost-effectiveness.
- CDA-AMC estimates that the budget impact of reimbursing risankizumab for the treatment of the indicated population will be approximately \$13.8 million over the first 3 years of reimbursement compared to the amount currently spent on other advanced therapies funded for the treatment of UC, with an estimated expenditure of \$41.7 million on risankizumab over this period. The actual budget impact of reimbursing risankizumab will depend on the uptake of risankizumab, comparator displacement, underlying growth in market size of patients receiving AT for UC, and potentially confidential pricing of comparators.

## CDEC Information

### Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, 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:** August 27, 2025

**Regrets:** Three expert committee members did not attend.

**Conflicts of interest:** None



**Canada's Drug Agency**  
**L'Agence des médicaments du Canada**  
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

**ISSN:** 2563-6596

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