CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

UPADACITINIB (Rinvoq)

(AbbVie)

Indication: Ulcerative colitis

August 18, 2023

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0730-000
Brand name (generic)	RINVOQ (upadacitinib)
Indication(s)	Ulcerative colitis
Organization	Atlantic Specialist Group
Contact information[a]	Name: Dr. Mark MacMillan

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

The Atlantic Specialist Group acknowledges the positive recommendation provided by CADTH for the reimbursement of upadacitinib for the treatment of adults with moderately to severely active ulcerative colitis (UC). Below are our recommendations and feedback:

Discussion points 1st bullet (page 6):

- Although we understand the reasoning behind deeming the NMA results as insufficient to recognize upadacitinib as superior to other therapies, we would like to note that in absence of head-to-head trials, the NMA results constitute the best available evidence for comparing the safety and efficacy of the different ulcerative colitis treatment options. As such, these results should be highlighted.

Reimbursement reason 6 (page 5) and discussion points 2nd bullet (page 6):

- The recommendation clearly raises long-term safety concerns with upadacitinib and other JAK inhibitors. However, considering upadacitinib's selectivity for JAK1, it should not be grouped with tofacitinib and should be regarded as distinct.

Table 3 (page 13-14):

- CADTH determines that upadacitinib is dominated by adalimumab; however, it overlooks the significance of patient preference and mode of administration in its evaluation. We strongly believe that these factors are highly important and should be considered.

Minor errors and typos:

- Page 11: "(Error! Reference source not found)" should be removed.
- Page 13-14: "Table 2" should be "Table 3".

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

The recommendation demonstrates that the committee has considered the stakeholder input that was provided to CADTH by the Atlantic Specialist Group.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
The reasons for the recommendation are clearly stated throughout.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
The implementation issues are clearly articulated and adequately addressed in the recommendation.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
The reimbursement conditions are clearly stated and the rational for the conditions are provided in this recommendation.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
Kataka Medical Communication helped us fill out the feedback form.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐

B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Mark Borgaonkar • Dr. Mark MacMillan • Dr. Remo Panaccione • Dr. Michael Stewart		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Jesse Siffledeen, MD FRCPC MSc*
Position	*Gastroenterologist, Covenant Health, Edmonton Ab.*
Date	*14-08-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☐	☐	☒	☐
Janssen	☐	☐	☒	☐
Takeda	☐	☐	☒	☐
Fresenius Kabi	☐	☒	☐	☐
BMS	☒	☐	☐	☐
Jamp	☐	☒	☐	☐
Lupin	☒	☐	☐	☐
Celltrion	☒	☐	☐	☐

Pendopharm	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Lilly	☒	☐	☐	☐
Pfizer	☐	☒	☐	☐

New or Updated Declaration for Clinician 2	
Name	*John Igoe*
Position	*Gastroenterologist, NB*
Date	*14-08-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☐	☐	☒	☐
Janssen	☒	☐	☐	☐
Takeda	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
Bio-JAMP	☒	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Christopher Ma*
Position	*Associate Professor, University of Calgary*
Date	*11-08-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☐	☐	☐	☒
Alimentiv Inc.	☐	☐	☐	☒
Amgen	☐	☐	☒	☐

AVIR Pharma Inc	☐	☒	☐	☐
BioJAMP	☐	☒	☐	☐
Bristol Myers Squibb	☐	☒	☐	☐
Celltrion	☐	☒	☐	☐
Ferring	☐	☐	☐	☒
Fresenius Kabi	☐	☐	☒	☐
Janssen	☐	☐	☒	☐
McKesson	☐	☒	☐	☐
Mylan	☐	☒	☐	☐
Pendopharm	☐	☒	☐	☐
Pfizer	☐	☐	☐	☒
Prometheus Biosciences Inc.	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Sanofi	☐	☐	☒	☐
Springer Publishing	☐	☐	☒	☐
Takeda	☐	☐	☒	☐
Tillotts Pharma	☐	☒	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Frank Hoentjen*
Position	*Associate Professor, University of Alberta*
Date	*11-08-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☐	☒	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Chadwick Williams*
Position	*Assistant Professor of Medicine, Dalhousie University*
Date	*15-08-2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Eli Lilly	☒	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0730
Name of the drug and Indication(s)	Upadacitinib (Rinvoq) for moderately to severely active ulcerative colitis (UC)
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0730-000
Brand name (generic)	Rinvoq® (upadacitinib)
Indication(s)	ulcerative colitis
Organization	Gastrointestinal Society
Contact information[a]	Name: Gail Attara

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Thank you for listening to patients and providing a better reflection of patient input in this recommendation. This recommendation included a complete overview of patient experience with ulcerative colitis and currently available treatments, impacts of the disease to quality of life, and the vital role of having varied therapies due to the challenges most patients face with maintaining remission and achieving symptom relief.

We also appreciate that CDEC recognized the importance of leaving the determination of clinical response up to the treating physician, instead of requiring endoscopy within 8 weeks of treatment initiation. Endoscopies can be very invasive and costly in time and resources for patients and caregivers. Most need to take time off work and school to have the procedure and recover, and it can also incur out of pocket costs for preparation (which is a ghastly process!).

Thank you for helping individuals living with ulcerative colitis have access to new treatment options, such as Rinvoq®!

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Please note that there is a typo on page 7, under the subheading "Sources of Information Used by the Committee." We are listed as the "**Gastroenterological (GI) Society**." This should be corrected to the "**Gastrointestinal (GI) Society**)." This typo also occurred in the CADTH Final Recommendation for Skyrizi® (risankizumab), project number SR0767-000, page 9. We raised this as an error in the draft feedback process but, unfortunately, it was not adhered to. We kindly ask this time around to please correct this typo.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

The only concern we have is the feasibility of conducting yearly assessments to examine clinical response given the ongoing challenges with shortages of healthcare professionals. Patients often share with us the difficulties and months-long delays in scheduling an appointment with their family doctor and/or specialists. The draft feedback did not address or provide guidance on these current realities.

	Yes	☒

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No	☐

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Gail Attara*
Position	*President and Chief Executive Officer*
Date	*08-14-2023*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0730-000
Brand name (generic)	Rinvoq
Indication(s)	Upadacitinib
Organization	Crohn's and Colitis Canada
Contact information[a]	Name: Patrick Tohill

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We are surprised that the recommendation is restricted to those that have "demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, intolerance of, conventional and/or biologic therapy". This indication flies in the face of the recommendations of the clinician feedback that upatacitinib would be useful "as first-line therapy" and CADTH's own expert clinician who stated that "if the patients could access upadacitinib and without the need to have failed conventional therapies, immunomodulators, or previously available biologics, then access to upadacitinib would potentially cause a shift in the current treatment paradigm." It likewise fails to take into account the patient feedback we submitted that makes clear that patients would like to avoid steroid use if at all possible. For example, we stated that "Almost all patients surveyed agree that they only take systemic steroids if absolutely necessary (93%) with four in five in agreement that they wish they could eliminate systemic steroids from the list of medications they use. Half of respondents say that systemic steroids is/was a burden in their UC management."

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

While the recommendation report fairly summarized our input on disease experience, as stated above, our input on patient experiences with and concerns around systemic steroid use were ignored. As noted, 85% of patients have taken systemic steroids at least once with 30% reporting they had taken steroids within the past year. As noted in our feedback: "patients aren't particularly supportive of this treatment option. Almost all patients surveyed agree that they only take systemic steroids if absolutely necessary (93%) with four in five in agreement that they wish they could eliminate systemic steroids from the list of medications they use. Half of respondents say that systemic steroids is/was a burden in their UC management."

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. Declined to answer this question.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. Declined to answer this question.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Patrick Tohill*
Position	*Director, Advocacy and Government Affairs*
Date	*16-08-2023*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. Yes. The initial analysis of the data in the first survey cited in our feeback was conducted by Leger.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☐	☐	☐	☒
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0730
Brand name (generic)	RINVOQ (upadacitinib)
Indication(s)	For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional, and/or biologic therapy.
Organization	AbbVie Corporation
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

AbbVie agrees with the recommendation to reimburse RINVOQ (upadacitinib) for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional, and/or biologic therapy.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

While AbbVie agrees with the recommendation to reimburse RINVOQ (upadacitinib) for UC, we would ask the CDEC to kindly consider the following proposed changes:

1. RINVOQ is a unique reversible JAK inhibitor with market authorization for the use in patients who have failed conventional and/or biologics therapies in UC.

On page 6 of the draft recommendation, under Discussion Points, it is stated that "*Upadacitinib is a Janus kinase (JAK) inhibitor like tofacitinib, a treatment option for UC that has largely been relegated to post-biologic use due to safety concerns.*" **AbbVie would ask that this statement be removed.** The statement is not in line with the input provided by the clinical expert consulted by CADTH. As per the clinical expert's input from pages 8 and 21 of the Clinical Review Report, they indicated that "*patients with moderately to severely active UC, **either biologic-naïve or biologic-exposed**, are suitable for treatment with upadacitinib.*" The clinical expert also indicated that "*upadacitinib is a selective JAK1 inhibitor and would occupy a place in therapy similar to biologics and other targeted small molecule drugs. Upadacitinib can be given after 5-ASA and used instead of immunomodulators. Due to its mechanism of action, **it is thought that the safety profile of upadacitinib may be favourable to that of tofacitinib**, which is a less selective JAK inhibitor.*" Lastly, the clinical expert indicated that "*it may not be appropriate to have the patients try and fail prednisone and immunomodulators **before initiating upadacitinib**, considering the side effects and risks associated with treatment with prednisone and immunomodulators. For patients who have already failed biologics or targeted small molecule drugs, **upadacitinib would likely be recommended before other medications which have known side effects, such as tofacitinib**.*" In addition, as referenced in the

CADTH Horizon Scan: An Overview of the Emerging Trends and Technologies in Ulcerative Colitis (July 2023), "*recent literature suggests that the cardiovascular risk with JAK inhibitors may not be significantly higher than that of other small-molecule drugs*."[1] It is inappropriate to link upadacitinib and tofacitinib together in a statement that generalizes their place in therapy as being relegated to post-biologic use due to safety concerns. In Canada, upadacitinib is approved by Health Canada for use among patients who have demonstrated prior treatment failure to at least one conventional **and/or** biologic therapy. The same population is eligible for the use of upadacitinib across numerous other countries, including Europe, the UK, and Australia. Upadacitinib is a reversible JAK inhibitor with a selectivity, efficacy, and safety profile unique to upadacitinib alone. The difference in efficacy profile in particular can be seen clearly in IBD, where upadacitinib is the only JAK inhibitor to have demonstrated efficacy in **both UC and Crohn's Disease (CD)** (tofacitinib and filgotinib have both failed to demonstrate efficacy in CD).

2. There remains a considerable probability that upadacitinib may be more efficacious than other comparative treatments.

On page 6 of the draft recommendation, under Discussion Points, it is stated that "*However, there was much uncertainty in the effect estimates from the NMA due to sparse networks, heterogeneity in patient characteristics and trial characteristics, wide credible intervals, and lack of direct evidence between upadacitinib and other active treatments.*" **We would ask that the following be added after the present statement: "*Despite these limitations, consistent trends favoring upadacitinib were observed across different adjustment methodologies.*"** While AbbVie appreciates the perspective offered, we wish to provide an alternative interpretation of the data, emphasizing the consistent trend towards upadacitinib's clinical differentiation. The results of the submitted ITC show upadacitinib as a preferred treatment option compared to existing options for induction, with similar results demonstrated for maintenance. Indeed, while there is uncertainty due to the lack of direct evidence and the sparse network, we note that all NMAs inherently contain a degree of uncertainty. However, it is important to consider the whole body of evidence available. Multiple sources, including 5 robust peer-reviewed published NMAs with phase 3 data available at the time of this review (Lasa et al. 2022, Burr et al. 2021, Attauabi et al. 2023, Panaccione et al. 2023 and Ahuja et al. 2023)[2-6] and expert opinion, consistently suggest that upadacitinib outperforms other treatments in UC management. These findings support the validity of our conclusions despite the inherent uncertainty in the methodology. While recognizing the inherent limitations and uncertainties of NMAs, we contend that the trend favoring upadacitinib over other active comparators is compelling. **AbbVie maintains that it is more appropriate to acknowledge the potential efficacy of upadacitinib, rather than stating that firm conclusions about its comparative efficacy cannot be established. As such, AbbVie is requesting that a statement be included to reflect upadacitinib's differentiated efficacy vs. other UC advanced therapies as demonstrated in various NMAs.**

3. The cost-effectiveness of upadacitinib for the treatment of UC has likely been underestimated by CADTH reviewers in their reanalysis.

On page 4 of the draft recommendation, under Rationale for the Recommendation, it is stated that "*…there is insufficient evidence to justify a cost premium over the least expensive biologic or targeted synthetic drug reimbursed for the treatment of moderately to severely active UC*." This is largely driven by previously mentioned Clinical Reviewer concerns with the NMA uncertainty, and the resultant assumption of equal probability of clinical effectiveness applied to upadacitinib and all relevant comparators in the CADTH reanalysis of the submitted economic model. **We would respectfully request CADTH adapt this language to "*it is uncertain what level of cost premium would be warranted over comparator therapies reimbursed for the treatment of moderately to severely active UC*."** AbbVie respectfully disagrees with CADTH's assertion regarding the assumption of uniform efficacy across treatments. The objective of conducting a comprehensive NMA, as we have done, is to meticulously analyze the heterogeneity across trials and estimate the potential variation in

efficacy and safety of different treatments. This process enables a deeper understanding of the relative effects of different treatments and it is, therefore, inappropriate to homogenize the outcomes by assuming equal efficacy and safety for all treatments. In line with CADTH guidelines, the submitted NMA incorporated a series of statistical adjustments to address inherent variability and uncertainty before utilizing these findings in the cost-effectiveness analysis. This methodological choice allowed for differentiated efficacy point estimates and corresponding variance estimates for each treatment. It is a well-established practice in probabilistic modelling to incorporate overlapping efficacy distributions and employ simulation techniques to represent the underlying uncertainty accurately.

4. The upadacitinib UC clinical trials criteria aligns to the latest STRIDE-II practice guidelines by incorporating more stringent endpoints such as mucosal healing.
AbbVie would like to highlight that the upadacitinib clinical trials incorporated some of the most recently recommended treatment goals, as outlined in the STRIDE-II guidelines, such as the long-term goal of mucosal healing. Upadacitinib's mucosal healing benefits and the importance of achieving these endpoints have been overlooked. **We would ask that the following be added under the Clinical Evidence section starting on page 10 of the draft recommendation: "*The criteria in the upadacitinib phase 3 RCTs required both endoscopic and histological remission, aligning to the latest STRIDE-II guidance, and were the most stringent treatment endpoints when compared with previous competitor UC studies.*"** As referenced in the CADTH Horizon Scan: An Overview of the Emerging Trends and Technologies in Ulcerative Colitis (July 2023), "*although histologic remission is not considered a formal UC treatment target in STRIDE-II, it is acknowledged as an adjunctive measure to endoscopic remission to represent a deeper level of healing and is the focus of many current studies.*[1] *Lastly, several studies have shown that a combined endpoint of histologic and endoscopic healing may better predict long-term outcomes than either treatment target alone*."[1] There has been an evolution in IBD practice guidelines, such as in STRIDE-II, with treatment goals expanding beyond simply controlling symptoms and now ambitiously including mucosal healing. The STRIDE-II guidelines recommend the long-term target of achieving endoscopic healing and histological healing for the possibility of achieving better UC patient outcomes. **Achieving mucosal healing can lead to reduced symptoms, hospitalizations, and rates of surgery while increasing the chance of durable long-term remission.** Previous UC studies used endoscopic measures only or endoscopic and histological evaluation with less stringent criteria. RINVOQ led to statistically significant endoscopic remission rates and mucosal healing vs. placebo at Weeks 8 and 52 addressing the patients' need for new effective treatments that achieve mucosal healing in addition to symptom relief.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

References:

1. CADTH Horizon Scan An Overview of Emerging Trends and Technologies in Ulcerative Colitis. Canadian Journal of Health Technologies. July 2023, Volume 3, Issue 7. https://canjhealthtechnol.ca/index.php/cjht/article/view/EH0117
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