Canada's Drug and Health Technology Agency

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

MIRIKIZUMAB (OMVOH)

(Eli Lilly Canada)

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

August 31, 2023

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0773
Brand name (generic)	Omvoh (mirikizumab)
Indication(s)	Ulcerative Colitis
Organization	IBD KOLs
Contact information[a]	Name: Drs. Brian Feagan and Vipul Jairath

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

Thank you for the opportunity to comment on the draft Mirikizumab review. We are academic gastroenterologists whose primary expertise is in the care of patients with inflammatory bowel disease. We have relevant experience in clinical epidemiology, trial design and therapeutics of IBD.

In general, we have found the draft review to be scientifically sound, accurate and informative. However, we do not agree with the stated conclusion, ***"At the sponsor submitted price for mirikizumab and publicly listed price for all other drug costs, mirikizumab was more costly than the least costly advanced therapy (tofacitinib) for adult patients with moderately to severely active UC. Direct comparative evidence to other advanced therapies was not identified, and indirect evidence is insufficient to conclude that mirikizumab is superior or inferior to other advanced therapies."***

Our conclusion is based upon the following two safety considerations.

First, as the CADH content experts know well, there has been substantial concern regarding the safety of the JAK inhibitors such as tofacitinib and upadacitinib for the treatment of chronic immune diseases. These drugs are broad spectrum immunosuppressives and have the expected "on target" side effects of dose-related serious infection and neoplasia which are identified in their product monographs. As de facto evidence of this property, it should be noted that the risk of varicella-zoster infection is four-fold greater in patients treated with tofacitinib than the general population and two-fold greater than patients treated with TNF antagonists. Varicella zoster is directly caused by viral re-activation as a consequence of systemic immunosuppression. This risk of infection has led the US FDA to take the unprecedented step of recommending that JAK inhibitors not be used as first line therapy for ulcerative colitis because safer alternatives such as vedolizumab and IL-12/23 antagonists are available.

In contrast, the risk of serious infection is not increased relative to placebo with mirikizumab and other IL-23 antagonists (guselkumab, risankizumab) that are used for the treatment of IBD and psoriasis. Notably, the TH17 response is grossly elevated in the relevant disease tissues and the treatment of this response with monoclonal antibodies to IL-23 restores immune homeostasis without systemic immune suppression. This is a fundamental and undisputable safety difference between JAK inhibitors and IL-23 antagonists that is highly relevant to patient care.

Second, mirikizumab is a monoclonal antibody that is highly specific for its target. In contrast, tofacitinib is a small molecule that has multiple "off target" side effects. Some of these are due to inhibition of JAK 2, in distinction to JAK1 and JAK 3. Development of hyperlipidemia, anemia, cytopenia, abnormal liver enzymes, and elevation of creatine kinase are common off target side effects with JAK inhibitors that require laboratory monitoring on a regular basis to ensure patient safety. Obviously, this is a burden to patients, health-care providers and an important cost to payors. No analogous situation is present for mirikizumab.

In summary, we believe there is strong indirect evidence, presented in the relevant product monographs, that for these two important safety issues tofacitinib cannot be considered clinically equivalent to

mirikizumab for the treatment of ulcerative colitis. As practitioners, we do not consider tofacitinib as the best choice of advanced therapy for most patients with ulcerative colitis primarily due to safety concerns.

Dr. Brian Feagan [redacted]

Dr. Vipul Jairath [redacted]

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?

As noted in the preceding section, the conclusion that mirikizumab and tofacitinib are therapeutically equivalent is not valid because of meaningful differences in safety that favour the former. This conclusion is clinically apparent even in the absence of a direct comparison of the two agents and supported by Health Canada's recommendations to practitioners described in the product monographs.

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.

Concluding that tofacitinib is a benchmark advanced therapy in ulcerative colitis and that reimbursement should be linked to the pricing of generic tofacitinib will restrict access to mirikizumab for patients. Endorsing a product that is less safe than other choices as the benchmark treatment is not, in our opinion, good public health policy

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.

The data supporting the conclusion that no safety differences exist between mirikizumab and tofacitinib is not supported by existing data. The most obvious evidence that supports this opinion is in the product monographs of the two drugs - tofacitinib has specific concerns detailed by Health Canada, most importantly risk of serious infection, which preclude its use as first line therapy for most patients with UC who have failed 5-ASA formulations or corticosteroids.

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

Appendix 2. Conflict of Interest Declarations for Clinician 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.
- For conflict of interest declarations:
  - Please 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.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
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: • Clinician 1. B. Feagan new • Clinician 2 V. Jairath (updated) • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Brian Feagan*
Position	*Professor of Medicine, Western University*
Date	*30-08-2023*
☒	**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	☒	☐	☒	☐
AgomAB Therapeutics	☒	☐	☐	☐
Allianthera	☒	☐	☐	☐
AnaptysBio	☐	☒	☐	☐
Applied Molecular Transport	☐	☐	☒	☐
Arena Pharma	☐	☒	☐	☐
Atomwise	☒	☐	☐	☐
BioJamp	☒	☐	☐	☐
Boehringer Ingelheim	☐	☐	☒	☐
Celsius Therapeutics	☐	☐	☒	☐
Celgene/BMS	☐	☐	☒	☐
Connect Biopharm	☐	☐	☒	☐
Eli Lilly	☐	☐	☒	☐
First Wave	☒	☐	☐	☐
Galapagos	☐	☐	☒	☐
Genentech/Roche	☐	☒	☐	☐
Gilead	☐	☐	☒	☐
Gossamer Pharma	☐	☐	☒	☐
GSK	☐	☐	☒	☐
Index Pharma	☐	☒	☐	☐
Imhotex	☐	☐	☒	☐
Immunic Therapeutics	☐	☒	☐	☐
Janssen	☐	☐	☒	☐
Japan Tabacco	☐	☒	☐	☐
Kaleido Biosciences	☒	☐	☐	☐
Landos Biopharma	☐	☒	☐	☐
Morphic Therapeutics	☒	☐	☐	☐
Origo Biopharma	☐	☒	☐	☐
Orphagen	☐	☒	☐	☐
Pandion Therapeutics	☒	☐	☐	☐
Pendopharm	☒	☐	☐	☐
Pfizer	☐	☐	☒	☐
Prometheus Therapeutics	☐	☐	☒	☐

Sanofi	☐	☒	☐	☐
Seres Therapeutics	☒	☐	☐	☐
Surrozen	☐	☒	☐	☐
Takeda	☐	☐	☒	☐
Teva	☐	☒	☐	☐
Tillotts	☐	☒	☐	☐
Ventyx Biosciences	☐	☒	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. Vipul Jairath*
Position	*Professor of Medicine, Western University*
Date	*30-08-2023*
☒	**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	☐	☐	☒	☐
Altrubio	☒	☐	☐	☐
Anokion	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Arena Pharma	☒	☐	☐	☐
Asahi Kasei Pharma	☒	☐	☐	☐
Astra Zeneca	☐	☒	☐	☐
BioJamp	☒	☐	☐	☐
BMS	☐	☐	☒	☐
Eli Lilly	☐	☐	☒	☐
Endpoint Health	☐	☒	☐	☐
Enthera	☒	☐	☐	☐
Ferring	☒	☐	☐	☐
Flagship Pioneering	☒	☐	☐	☐
Fresenius Kabi	☒	☐	☐	☐
Galapagos	☒	☐	☐	☐
GSK	☒	☐	☐	☐
Genentech	☒	☐	☐	☐

Gilead	☐	☒	☐	☐
Janssen	☐	☐	☒	☐
Merck	☒	☐	☐	☐
Mylan	☒	☐	☐	☐
Pandion	☒	☐	☐	☐
Pendopharm	☒	☐	☐	☐
Pfizer	☐	☐	☒	☐
Pioneering Medicine	☐	☒	☐	☐
Prometheus Therapeutics	☐	☐	☒	☐
Reistone Biopharma	☒	☐	☐	☐
Roche	☐	☒	☐	☐
Roivant	☒	☐	☐	☐
Sandoz	☒	☐	☐	☐
Second Genome	☐	☒	☐	☐
Sorriso	☐	☒	☒	☐
Takeda	☐	☐	☒	☐
Teva	☐	☒	☐	☐
Ventyx Biosciences	☐	☒	☐	☐

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0773
Name of the drug and Indication(s)	Mirikizumab (Omvoh) for ulcerative colitis
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	X
	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.

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0773-000
Brand name (generic)	Omvoh™ (mirikizumab)
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	☐

We are grateful that CDEC has issued a recommendation to reimburse Omvoh™ (mirikizumab) for the treatment of ulcerative colitis.

Thank you for continuing to listen to patients and considering our input into your decision-making processes. This recommendation highlighted our concerns with the unmet needs of patients with currently available treatments and the importance of having access to new therapies with different mechanisms of action. It also reflected the relevance of our survey data, and the 1-to-1 interviews we conducted with patients who participated in the clinical trials.

We are glad to see that there was agreement with the clinical expert on not requiring failure of other biologics to initiate therapy with mirikizumab. This is aligned with the recommendations of early use of biologics from the March 2023 *Insititut national d'excellence en santé et en services sociaux* (INESSS) state of knowledge findings and the American Gastroenterological Association (AGA) guidelines reported in the July 2023 CADTH Horizon Scan: An Overview of Emerging Trends and Technologies in Ulcerative Colitis.

We also appreciate that CDEC recognized the importance of leaving the determination of clinical response up to the treating physician, instead of requiring scoping, which is invasive and costly in time and resources for patients and caregivers. CDEC also acknowledged difficulties with timely access to care given the ongoing crises in healthcare by not enforcing a timeline for determination of clinical response after 24 weeks, and by expanding prescribing to physicians, recognizing that gastroenterologists and specialists are not accessible, especially in some rural and remote areas and even in some busy IBD centres.

Again, thank you for helping individuals living with ulcerative colitis have access to Omvoh™, a welcome new treatment option!

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	☐

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

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	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	*08-28-2023*
☒	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	SR0773-000
Brand name (generic)	Omvoh
Indication(s)	mirikizumab
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 disagree with the recommendation insofar as it would require patients to have first failed on conventional therapy. This 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." The patient we interviewed also expressed dissatisfaction and concern around steroid use as well as other aspects of conventional therapy such as having to administer nightly enemas. We further note the input from the GI Society that "only 24% of patients with IBD found available medications to be adequate, 56% found them to be only somewhat adequate and 20% found then (sic) not at all adequate." We further note the input from the clinician group, identified in CADTH's recommendation report as "gastroenterologists recognized as experts in the management of IBD" who emphasized that mirikizimumab would have "a broad range of uses in clinical practice" including "first line advanced 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	☒

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

The recommendation report captured our feedback for the most part and fairly summarized our input on disease experience, however, as noted above, we feel that patient concerns around systemic steroid use and unhappiness with conventional therapy continue to be ignored as novel therapies continue to be relegated to second line treatment options with a requirement that patients first fail conventional therapy.

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	*30-08-2023*
☒	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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐