CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

cariprazine (Vraylar)

(Allergan (an AbbVie Company))

Indication: cariprazine is anticipated to be indicated as monotherapy for:

- Acute Treatment of manic or mixed episodes associated with bipolar 1 disorder in adults
- Acute Treatment of depressive episodes associated with bipolar 1 disorder in adults

.

July 28, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

CADTH Reimbursement Review
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Stakeholder information	
CADTH project number	
Brand name (generic)	Cariprazine
Indication(s)	Bipolar Mania and Bipolar Depression
Organization	Ontario and Maritimes Key Opinion Clinicians
Contact information[a]	Name: Pierre Blier

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

1) Potential uncertainty of the generalizability of the mania trials results was raised.

It is standard procedure in mania regulatory trials to exclude patients with comorbidities, rapid cycling, substance use disorder, history of non-response to multiple drugs, and elevated risk of suicide. The inclusion of such additional variables would prevent the interpretation of the results with respect to efficacy.

It is not feasible to treat patients with moderate/severe mania in an outpatient basis, and in fact, the requirement for hospitalization is part of the DSM-5 diagnostic criteria for most manic episodes. Consequently, if it were for safety reasons only, treatment and research trials must be conducted on an inpatient basis.

The mean of daily doses of cariprazine in two of the bipolar mania trials exceeded the maximal daily dose of 6 mg/day set by Health Canada. However, in the third trial carried out with 3 and 6 mg/day regimens (Calabrese et al, J Clin Psychiatry 2015; RGH-33), the difference with placebo was also highly significant. Taken together, the results of these three trials indicate that there is no incremental benefit of higher daily doses and constituted an extremely strong signal of therapeutic action.

2) There was an inconsistent dose-response relationship in the studies of bipolar depression in the 1.5 mg/day and 3 mg/day arms.

Given that cariprazine is a dopamine partial agonist, it is expected to increase dopamine transmission at low doses but able to compete and displace with endogenous dopamine at higher doses. Indeed, this is because of lower intrinsic activity of the partial exogenous drug than the full intrinsic activity of the endogenous neurotransmitter. This is the fundamental mechanism of action of partial agonists. Consequently, it is expected that such drugs will display a U-shaped dose-response that need to be documented for their optimal clinical therapeutic use. The trials with cariprazine in fact clearly document this: 0.75 mg/day did not separate from placebo, 1.5 mg/day was efficacious, whereas 3 mg/day was less effective and led to more discontinuation.

3) There were no active comparator arms in cariprazine clinical trials.

It is common to have only placebo-controlled studies in either phase in the treatment of bipolar disorder.

4) The efficacy of cariprazine in both phases of bipolar I disorder when used in monotherapy is paramount to its therapeutic benefits.

Aside from cariprazine, the only other medication demonstrated to be efficacious in both poles of bipolar I disorder is quetiapine. First, it is important to state that quetiapine is well known to be a weight offender and contribute to hyperlipemia, thereby increasing the risk of developing a metabolic syndrome. Second, it is also a widely recognized problem that the depressive phase of bipolar I disorder is highly treatment resistant. Therefore, the number of options to treat such a depressive phase are limited. Lurasidone is an option, but it has not been studied in the manic phase of the disorder. The olanzapine-fluoxetine combination is plagued by its impact on weight gain.

The clinician input has clearly stated that there are no major contraindications unique to cariprazine. This simplifies its ease of use, for instance in patients who are overweight/obese, have diabetes, or have kidney or thyroid problems. These co-morbidities are quite common in patients with bipolar I disorder. I fail to comprehend how a relative lack of psychiatrists in Canada would significantly restrict the use of cariprazine. Quite the contrary, given its efficacy in both poles of the disorder, this would simplify its use. There is a plethora of medications that can be used successfully to treat mania, however, the most common subsequent episode is depression, whereas cariprazine is efficacious in bipolar depression thus making it an optimal choice.

The patient input has also emphasized the notion that “not every patient responds to one medication,” thereby the need to have medications with different mechanism(s) of action and potentially as well a different side effect profile. Furthermore, they also deplored the “waiting to be approved for coverage by public drug programs and experiencing relapse”. They felt that indeed “outcomes can be improved by increasing equitable access”.

5) The CADTH reanalysis results of economic evidence does not favour cariprazine over risperidone in the manic/mixed setting and quetiapine in the depressive setting.

These are unfair comparisons as risperidone is not indicated in depressive episodes of bipolar I disorder. Indeed, that the mixed setting includes a combination of manic and depressive symptoms. Since risperidone is not indicated in depressive episodes therefore represents a challenge. Despite the similar indications of quetiapine as cariprazine, it is also not taking into account the side effect profiles of these two comparators, notwithstanding the issue of treatment of non-response, which contributes to increased hopelessness.

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

Expert committee consideration of the stakeholder input

	Yes	☐

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	No	☒
An input from this group of experts submitted on February 18, 2022 has not reached the CADTH Committee and was thus not considered. An attempt was made to inquire about this, but no reply was obtained. This document is also attached.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
The information provided needs to take into account the five issues raised above and requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
The information provided needs to take into account the five issues raised above and requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
The information provided needs to take into account the five issues raised above and requires clarification.		

[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	☐
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 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

Declaration for Clinician 1

Name: Pierre Blier, MD, PhD

Position: Professor, Department of Psychiatry and Cellular & Molecular Medicine, University of Ottawa; Director, Mood Disorders Research Unit, The Royal's Institute of Mental Health Research, Ottawa

Date: 28-07-2022

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Allergan/Abbvie			Consultancy/lectures/expert testimony	Research grant
Otsuka/Lundbeck			Consultancy/lectures	
Janssen			Consultancy/lectures	Research grant

Declaration for Clinician 2

Name: <Martin A. Katzman>

Position: <Clinician Scientist>

Clinic Director: START Clinic for the Mood and Anxiety Disorders;
Professor: Adler Graduate Professional School;

Adjunct Professor: Department of Psychiatry, Northern Ontario School of Medicine;
Adjunct Professor: Department of Psychology, Lakehead University;
Adjunct Professor: Edward S. Rogers Sr., Department of Electric and Computer Engineering, University of Toronto
Board Member: American Professional Society ADHD and Related Disorders APSARD)

Date: <27-07-2022>

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Abbvie		Advisory Board, Speaker's Bureau		Research
Eisai			Advisory Board, Speaker's Bureau	

Martin A. Katzman Continued

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bausch Health		Speaker's Bureau		
Lundbeck		Advisory Board, Speaker's Bureau		Research
Otsuka		Advisory Board, Speaker's Bureau		
Purdue Pharma	Advisory Board,			Investigator-Initiated Research Grant
Tilray	Advisory Board			
Biohaven			Clinical Trial	
Pfizer	Speaker's Bureau			
Takeda	Speaker's Bureau			
Sante Cannabis	Speaker's Bureau Advisory Board			
Cannopy	Speaker's Bureau			

New or Updated Declaration for Clinician 3	
Name	*Michael Van Ameringen*
Position	*Professor, McMaster University*
Date	*Please add the date form was completed (26-07-2022)*
☒	**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**
Allergan	☒	☐	☐	☐
Almatica	☒	☐	☐	☐
Bausch Health	☒	☐	☐	☐

Brainsway	☒	☐	☐	☐
Elvium (Purdue)	☒	☐	☐	☐
Empowerpharm	☒	☐	☐	☐
Jazz	☒	☐	☐	☐
Lundbeck	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
Tilray	☒	☐	☐	☐
Vistagen	☒	☐	☐	☐
Abbvie	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Sunovion	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Biohaven	☒	☐	☐	☐
UptoDate	☒	☐	☐	☐
Canadian Institute for Health Research	☒	☐	☐	☐
Michael G DeGroote Centre for Medicinal Cannabis Research	☒	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Ayal Schaffer*
Position	*Professor, Department of Psychiatry, University of Toronto*
Date	*July 25, 2022*
☒	**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	☒	☐	☐	☐
GSK	☐	☒	☐	☐
Janssen	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Risk Kronfli*
Position	*Clinical Director and Forensic Psychiatrist, Assistant professor*
Date	*22-07-2022*
☒	**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**
Allergan/Abbvie	☒	☐	☐	☐
Eisai	☒	☐	☐	☐
Janssen	☐	☒	☐	☐
Lundbeck	☒	☐	☐	☐
Otsuka	☐	☒	☐	☐
Sunovion	☒	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*Michael Rosenbluth, MD, FRCP©*
Position	*Chief, Department of Psychiatry Michael Garron Hospital (formerly Toronto East General)*
Date	*26-07-2022*
☒	**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
Allergan/Abbvie	☐	☒	☐	☐
Sunovion	☒	☐	☐	☐

Declaration for Clinician 7

Name: Serge Lessard MD

Position: Assistant Professor, Department of Psychiatry, University of Ottawa; Medical Director Introspect Clinical Research Centre

Date: 28-07-2022

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

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/Allergan			Consultant/Speaker	Research
Otsuka/Lundbeck			Consultant/Speaker	
Add or remove rows as required				

[redacted]

Declaration for Clinician 8

Name: Arun Ravindran, MD, PhD, FRCPC

Position: Professor, Department of Psychiatry, University of Toronto

Date: <28-07-2022>

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Otsuka			Research Grant	
Add company name				
Add or remove rows as required				

CADTH Reimbursement Review: Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**SR0718-000**
Brand name (generic)	Cariprazine
Indication(s)	Bipolar I mania/depression
Organization	**Western Canadian Clinical Advisory Network (WC-CAN) plus** Dr. J. Allen, Dr. J. Banasch, Dr. S Brennan, Dr. M. Cummins, Dr. M. Eleff, Dr. N. Hanon, Dr. K. Kjernisted, Dr. A Kirshner, Dr. L Klassen, Dr. T Oluboka, Dr. W. Song, Ms. Lindsey Ziegler, (clinical pharmacist) (**These are additional clinicians who that were in our and contacted our network – disclosures are in Appendix 2). Dr. Dorothy Reddy from our network was not available to consent and has been subtracted.**
Contact information[a]	Dr. Atul Khullar [redacted]

1. Does the stakeholder agree with the committee's recommendation. – 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

Page 3 paragraph 1: Efficacy for Depression: The report states that **"Reduction of Depressive symptoms inconsistent"–** This is incorrect as 3 trials have shown efficacy at 1.5 mg. The two other agents indicated in Canada for bipolar depression (lurasidone and quetiapine) also demonstrated no dose response curve and potentially less effects at higher doses (1,2). More than 2 publicly available indicated and efficacious options are needed given the clearly reported and acknowledged desperate patient and clinician needs. Many agents do not even attempt a RCT in bipolar depression because of the difficulty and notoriously high placebo rates. Positive results should be taken in the context of the disorder and have not been in this report.

Generalizability of study results – It was repeatedly stated in the document that the study populations were **"highly selected patients that many not represent the intended population"**. This is given far too much weight, and cariprazine is being held to an unfair standard. Inclusion and exclusion criteria in terms of population, study design and trial length for these trials are consistent with other agents assessed for the phases of bipolar I disorder. Translation of results from a clinical trial population is challenge in any clinical trial for a mental health indication.. There is a balance between internal and external validity in clinical trial medicine, especially in mental health research and this is not reflected in the decision.

The committee also expressed concern -**"for bipolar mania studies – conducting the trials in inpatient setting"** . This criticism belies the fact that mania and mixed states are mostly treated initially in an inpatient setting, and, by definition, mania indicates the patient is either psychotic, imminent risk to themselves or others or requires hospitalization. The bipolar depression studies were in outpatients as per treatment in clinical practice.

Secondary outcome data - Although measurements of quality of life, hospitalizations and cognitive impairment would have been helpful, there are very few registration trials for new agents in bipolar disorder that have this data and cariprazine again is being held to an unfair standard. These variables can also take months to detect clinically significant differences. Also, there is increased concern that requiring too many interventions (ie too many clinical assessments) can heighten placebo response, which is already unacceptably high in psychiatric trials.

"adherence/persistence not evaluated" – This was outlined in a systematic review of NNH for various agents for bipolar disorder in 2020. (3) Cariprazine scored favourably with high NNH in discontinuation due to adverse events in bipolar depression. This was pointed out in our initial input and does not appear to have been considered by the committee.

Page 3. Paragraph 2 "multiple drugs are available". This is a misleading statement. In Canada, there are only two indicated drugs for bipolar I depression and only one other indicated drug for both illness phases. There is also one indicated drug in the newer partial dopamine agonist class for mania and none for depression. Given well

established unmet patient needs in this area, any agent that demonstrates positive evidence in the above severely limited areas should be strongly considered for reimbursement. To us, limiting access to only one or two publicly funded indicated agents in these areas is unacceptable to patients and families who suffer from the high disability of bipolar disorder. It must be noted again that bipolar disorder is a syndromic illness with great variability among patients. Approved agents are effective in clinical trials but as noted below with ziprasidone and asenapine, not interchangeable nor always useful in real world patients. There is variability in response and tolerability among individual patients. Accessible indicated newer options with significant evidence are needed.

Page 3 Paragraph 3 – "there was insufficient potential evidence that these needs could be met by cariprazine" An agent with efficacy in both poles would offer clear distinct benefits. Treatment adherence is improved when patients are required to take fewer medications. Likewise, certain critical side effects, such as weight gain and excess daytime sedation which clearly have a powerful impact of compliance and functionality may improve. The benefit of cariprazine in these areas was noted in the systematic review of NNH for bipolar agents (3) which again was not noted in the committee's response. Non-compliance with treatment remains high (50-60%) and access to another indicated first line agent with a unique mechanism of action, a favorable side effect profile and efficacy in both poles of illness, will help the large number of patients who have not responded or couldn't tolerate to other bipolar treatments.

Page 4. Paragraph 1: The issues with the committee's repeated concerns about the inpatient nature of the mania trials and generalizability of studies are addressed above. The average cariprazine dose was higher than the Health Canada indication in the mania trials but there was an aspect of "dose finding" and, as noted the trial that utilized lower doses in mania were shown to be comparable in its results.
Paragraph 2: Neither asenapine or ziprasidone are typically employed for mixed features in clinical practice. One reason is the challenging bioavailability of asenapine and ziprasidone. Asenapine can only be taken sublingually and patients must follow careful rules to avoid malabsorption. Ziprasidone must be taken twice a day with a certain caloric intake to ensure proper blood levels. Unsurprisingly, neither has been proven to be effective in real clinical patients in Canada, and they are not commonly prescribed for these reasons.
Paragraph 3: Though it was open label, this 16 week study is consistent with Health Canada and FDA approved trials for similar agents and is an adequate period to establish trends towards weight gain.
Paragraph 4; Combination therapy with lithium and divalproex has a low effect size and is reserved for patients with more severe symptoms. Strong clinical data and practice has established that monotherapy with atypical antipsychotics in the early stages of bipolar disorder is both common, usually better tolerated and equally as efficacious. It is our opinion that the lack of combination studies is no longer a limitation.

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH? – NO
If not, what aspects are missing from the draft recommendation?

Our summary was given very limited space in the report (one paragraph vs more than a page for the clinical experts consulted by CADTH) and there were key points of disagreement that were not reflected. We did note that there would be a shift in the treatment paradigm, there were clear reasons to try cariprazine before other treatments, there were certain patients that would be suited for this drug and that the mechanism (specifically the partial dopamine agonism at the dopamine D3 receptor) was quite distinct. Evidence was cited for these claims. This information directly contradicts the assertions of the CADTH experts on page 7. No research to support their opinions was cited in the report. This direct contrast and the issues outlined in question 1 are a key reason why many additional members of our network as well as individual clinicians asked to comment and sign this feedback.

Ultimately, two clinical experts that CADTH consulted have provided an opinion that is in direct opposition to our diverse group of 17 psychiatrists and 1 pharmacist from every province in western Canada. Additionally, our feedback is aligned with the clinical input of CANMAT, a group of over 20 clinicians who constitute the preeminent mood disorders clinical network in Canada and one of the strongest in the world. This significant disparity of clinical input between our group and CANMAT in contrast the two clinical experts consulted by CADTH does not appear to have been considered in the report.

3. Are the reasons for the recommendation clearly stated? - NO

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

Page 5: There should be clarification of the evidence to support the clinical experts' opinions and reasoning, as well as greater detail regarding the basis of their expertise, as our group provided in our submission. Areas of disparate opinion (as noted in question 1) should be addressed with references and data.

Although the critical analysis is mostly valid , as noted above, clarity is needed is to why cariprazine is being held to a much higher standard than other newer approved treatments in bipolar disorder. The report has an unrealistic expectation of what the data can provide and this was especially notable in critically appraising the NMA. Providing clarity on what CDEC believes are appropriate trial goals, which must be achievable and realistic for the study population, would be much more helpful and fulfill the clearly articulated need for more accessible treatments.

The protocol and process for selected studies is also not clear in the report. Clarity on studies that were discounted would be helpful. It is unclear why both a systematic review of NNH of all agents or a 3rd NMA in bipolar depression (4) were not considered.

4. Ha*ve the implementation issues been clearly articulated and adequately addressed in the recommendation? – NO*

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

Page 8: Drug program input: It was unclear what advice experts gave and specifics about therapy considerations
Page 15: Economic evidence: using one medication for both phases may intuitively do this reduce the overall medication cost, it is unclear if this has been factored into the model. Aripiprazole would be a more fair comparator in mania, as it is in the same secondary class of partial dopamine agonist as cariprazine. Also, the economic burden of untreated bipolar disorder and even bipolar disorder as it is treated today may be much larger than the "premium" that was described. (5)
Page 17: It is unclear how flat pricing would increase the cost

Question 5. NOT APPLICABLE

WC- CAN Feedback Conclusion
Although there are limitations in the data set, the actual comments in the CDEC report show a fundamental misunderstanding of the nature and clinical realities of treatment of bipolar disorder in Canada, as well as the limitations of standard research studies that constitute the body of evidence for pharmacologic intervention. Unfortunately, this was also compounded by not reflecting a clear divergence of opinion between two clinical specialists consulted by CADTH versus input and guidelines from CANMAT and a group of seasoned clinicians with national and international experience who provided thoughtful evidence-based feedback. This has led to additional clinicians in the network (including senior department heads of large mental health programs across Western Canada) who subsequently contributed to this feedback after significant disagreements with this draft report.

All the clinicians in our group strongly feel cariprazine is a critical first line tool for the treatment of bipolar disorder, especially bipolar I depression, which is under-recognized, inappropriately treated and associated with tremendous morbidity and mortality. The two indicated agents with public coverage are simply inadequate, as many people in clinical practice fail both agents quickly. More indicated options that are accessible are needed to help change the lives of countless patients who fail to respond adequately to these scarce options

The Government of Canada has repeatedly acknowledged the existence of a mental health crisis, which has worsened due to the COVID pandemic, and have made a commitment to improve treatment and funding. Potentially limiting access to an indicated and guideline based first line treatment with advantages in tolerability such as cariprazine is discordant with the government's objectives. The current response also demonstrates exceptionally unreasonable expectations on standard bipolar clinical trials which if continued, will lead to the continued use of more unproven, off-label treatments in bipolar disorder, especially during the disabling and predominant depressed phase, further marginalizing and stigmatizing patients already struggling with a difficult to treat illness.

CADTH

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	☒
If yes, please detail the help and who provided it. Due the nature of the draft decision and the disagreement with the rationale, other network members and individual clinicians contacted us to add their feedback. Their disclosures are enclosed below		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
None except from the above additional clinicians		
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	☒
Unchanged: Dr. J. Swainson, Dr. A. Khullar, Dr. P Chokka, Dr. R Thomas, Dr. D McIntosh, Dr. M Oakander. New additions: Dr. J. Allen, Dr. J. Banasch, Dr. S Brennan, Dr. M. Cummins, Dr. M. Eleff, Dr. N. Hanon, Dr. K. Kjernisted, Dr. A Kirshner, Dr. L Klassen, Dr. T Oluboka, Dr. W. Song, Ms. Lindsey Ziegler, (Disclosures below)		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Judith ALLEN
Position	*Psychiatrist*
Date	*21-07-2022*
☒	**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**
No Conflicts	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Dr. Jan BANASCH
Position	*Consultant Psychiatrist GNCH/Addiction and MHS 108 ST Clinic*
Date	*Please add the date form was completed (15-07-2022)*
☒	**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**
Janssen	☐	☐	☒	☐
Otsuka	☒	☐	☐	☐
Lundbeck	☒	☐	☐	☐
Abbvie	X			

New or Updated Declaration for Clinician 3	
Name	Dr. Stefan BRENNAN
Position	***Assistant Professor, Department of Psychiatry, University of Saskatchewan***
Date	*18-07-2022*
☒	**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**
Janssen-Ortho	☐	☐	☒	☐
Takeda	☐	☐	☒	☐
Otsuka	☐	☐	☒	☐
Lundbeck	☐	☐	☒	☐
Abbvie	☐	☒	☐	☐

New or Updated Declaration for Clinician 4	
Name	Dr. Mary CUMMINS
Position	*Psychiatrist*
Date	*21/07/2022*
☒	**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**
I have no disclosures	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	Dr. Michael ELEFF
Position	*Community psychiatrist and Associate Professor of Psychiatry, University of Manitoba*
Date	*19-07-2022*
☒	**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**
None to declare	☐	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	Dr. Neil HANON
Position	*Psychiatrist*
Date	*27-07-2022*
☒	**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**
Lundbeck	☐	☐	☒	☐
Janssen	☐	☒	☐	☐
Allergan	☒	☐	☐	☐
Liv	☒	☐	☐	☐

New or Updated Declaration for Clinician 7	
Name	Dr. Alla KIRSHNER
Position	*Attending psychiatrist, Medical Director Edgeland Clinic*
Date	*Please add the date form was completed (19-07-2022)*
☒	**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**
Lundbeck	☒	☐	☐	☐
Takeada	☒	☐	☐	☐
Elvium	☒	☐	☐	☐
Abbvie	X			

New or Updated Declaration for Clinician 8	
Name	Dr. Kevin Dwight KJERNISTED
Position	*Psychiatrist in clinical practice*
Date	*18-07-2022*

☒	**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**
Allergan	☒	☐	☐	☐
AZT	☒	☐	☐	☐
Biogen	☐	☒	☐	☐
Boehringer Ingelheim	☒	☐	☐	☐
Eisai	☒	☐	☐	☐
Elvium	☒	☐	☐	☐
Green Valley	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Lundbeck	☐	☒	☐	☐
Novo Nordisk	☒	☐	☐	☐
Roche	☒	☐	☐	☐
Shire	☒	☐	☐	☐
Sunovion	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Servier	☒	☐	☐	☐

New or Updated Declaration for Clinician 9

Name	Dr. Larry KLASSEN
Position	*Research Chair, Eden Mental Health Centre*
Date	*25-07-2022*
☒	**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**
Otsuka	☒	☐	☐	☐

Lundbeck	☒	☐	☐	☐
BMS	☒	☐	☐	☐
Abbvie	☒	☐	☐	☐

New or Updated Declaration for Clinician 10	
Name	Dr. Toba OLUBOKA
Position	*Director, Psychiatry Emergency and Outreach Team, SHC, AHS. and Associate Clinical Prof, U of C. Calgary*
Date	*Please add the date form was completed (15-07-2022)*
☒	**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	☐	☒	☐	☐
Pfizer	☐	☒	☐	☐
Janssen	☒	☐	☐	☐
Otsuka and Lundbeck Alliance			X	
Sunovion	X			
Purdue	X			

New or Updated Declaration for Clinician 11	
Name	Dr. Wei SONG
Position	Head, Department Psychiatry Medical Director, MHSU, Island Health, Clinical Professor, Faculty of Medicine, UBC
Date	*18-07-2022*
☒	**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**

Eisai	☐	☒	☐	☐
Janssen	☐	☒	☐	☐
Otsuka/Lundbeck	☐	☒	☐	☐
Abbvie	☐	☒	☐	☐

New or Updated Declaration for Clinician 12	
Name	Ms. Lindsey ZIEGLER, PharmD
Position	Pharmacist, Clinical Pharmacist – Psychiatry Support Team, Mental Health Clinic, Saskatchewan Health Authority
Date	*27-07-2022*
☒	**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	☒	☐	☐	☐

References for feedback document

1. Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, Sachs G. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014 Feb;171(2):160-8. doi: 10.1176/appi.ajp.2013.13070984.
2. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: a systematic review and meta-analysis. Drug Des Devel Ther. 2014 Jun 25;8:827-38. doi: 10.2147/DDDT.S63779.
3. Bai Y, Yang H, Chen G, Gao K. Acceptability of acute and maintenance pharmacotherapy of bipolar disorder: a systematic review of randomized, double-blind, placebo-controlled clinical trials. J Clin Psychopharmacol. 2020 Mar/Apr;40(2):167-79.
4. Bahji A, Ermacora D, Stephenson C, Hawken ER, Vazquez G. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: A systematic review and network meta-analysis. J Affect Disord. 2020 May 15;269:154-184. doi: 10.1016/j.jad.2020.03.030.
5. Bessonova L, Ogden K, Doane MJ, O'Sullivan AK, Tohen M. The Economic Burden of Bipolar Disorder in the United States: A Systematic Literature Review. Clinicoecon Outcomes Res. 2020 Sep 7;12:481-497. doi: 10.2147/CEOR.S259338.

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0718
Name of the drug and Indication(s)	Cariprazine (Vraylar) as monotherapy for: • Bipolar Mania: acute management of manic or mixed episodes associated with bipolar I disorder in adults, and • Bipolar Depression: acute management of depressive episodes associated with bipolar I disorder in adults.
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	X

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.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0718
Brand name (generic)	Vraylar
Indication(s)	Bipolar I disorder
Organization	Institute for Advancements in Mental Health
Contact information[a]	Name: Erin Boudreau, director of operations, Institute for Advancements in Mental Health; [redacted]

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.

The Institute for Advancements in Mental Health (IAM) disagrees with CADTH's recent draft recommendation not to publicly reimburse Vraylar (Cariprazine) for Bipolar I disorder. IAM provides services for people with our without a mental health diagnosis, and their caregivers. IAM serves people with schizophrenia or psychosis or bipolar disorder.

Treatment types should be easily accessible to individuals with bipolar, including community services, social supports and psychiatric treatments such as medications. Mental health medication treatment is not "one size fits all". In fact, response to psychiatric medications is highly individualized, variable and related to several components such as genetics, age, gender and socio-environmental factors. Research finds that response to antipsychotic medications is particularly heterogeneous, and tolerability and experience of side effects varies from person to person. For these reasons, we are urging CADTH to reconsider its draft decision and encourage it to recommend Vraylar for public reimbursement.

Of additional importance is research that finds mental health medications in general are not prioritized compared to other types of medications by health technology and decision-making bodies. A recent report by the Canadian Health Policy Institute found that a higher percentage of non-mental health medications compared to psychiatric medications are given a positive recommendation (with or without conditions) for public drug plan coverage by CADTH's Reimbursement Reviews. Overall, treatment decisions come down to the individual and their prescriber, often with support of caregivers, and that everyone should have easy access to care that is effective for the individual.

Further, a lack of psychiatric representation on CDEC arguably poses an additional systemic barrier to approving and ultimately publicly reimbursing medications for mental illness. The following statement speaks to the need for CDEC to appoint an individual who is an expert in mental health:

CDEC noted that it is common for clinical trials for bipolar mania/mixed episodes to be conducted in an inpatient setting, as was the case RGH-MD-31, RGH-MD-32, and RGH-MD-33. However, there is

uncertainty regarding whether similar results would be observed in an outpatient treatment setting where the majority of patients with bipolar disorder are managed.

Though speculative, it is likely that a mental health professional would question the pragmatism of this approach and whether it sets unrealistic standards for future innovative medicines in mental health.

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?

Mental health medication treatment is not “one size fits all”. In fact, response to psychiatric medications is highly individualized, variable and related to several components such as genetics, age, gender and socio-environmental factors. Research finds that response to antipsychotic medications is particularly heterogeneous, and tolerability and experience of side effects varies from person to person.

The greater the variety and affordability of medications on the market, the more treatment adherence we are likely to see among individuals with bipolar and other psychotic disorders, and by extension, greater levels of recovery.

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.

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	*Institute for Advancements in Mental Health*
Position	*Director, Operations*
Date	*28-07-2022*
☒	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**
HLS Therapeutics Inc.	☒	☐	☐	☐
Janssen Inc.	☐	☐	☒	☐
Otsuka	☐	☐	☒	☐
AbbVie	☐	☐	☒	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0718
Brand name (generic)	Vraylar (Cariprazine)
Indication(s)	Bipolar Disorder
Organization	Mood Disorders Society of Canada
Contact information	Name: Dave Gallson

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.

On page 3 of the Draft Recommendations, it states: Patients expressed a need for treatments that control the symptoms of bipolar I disorder, provide an additional therapy for those who do not respond adequately to existing drugs, lower the frequency of administration, and minimize adverse effects. CDEC concluded that there was insufficient evidence to demonstrate that these needs were met by cariprazine.

MDSC believes that within these recommendations, there could have been more weight put on the patient choice and access considerations and that indeed the approval of cariprazine would have a direct positive impact on addressing these priority issues for patients as we had submitted.

What has been very apparent is that medications affect one person differently than how it may affect the next. That is why often, it takes a period of time, and trying different treatments for the patient to find the treatment that works for them. They need to be able to see what they can manage and which side effects they are best able to accept. The goal is to take the treatments that help them live manageable lives with Bipolar Disorder, and not get exposed to additional side effects that may cause other issues for them to then need to cope with.

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?

In our patient group submission, we had been specific about how a medication is a foundational necessity in treating bipolar disorder. It is a recurrent illness, often requiring long-term treatment. Many people will need a number of medications to manage their symptoms and maintain wellness. Finding the right combination of these treatments will rely on monitoring and discussion with their doctor or psychiatrist. While frustrating, the reality is that it can take long periods of experimentation to get the most effective treatment(s)That is why we stated, that it is crucial to increase patient access to, and choice of, medications. That medications affect one person differently than how it may affect the next and for many patients, the most significant challenge is accessing treatment. We also

believe that access to new treatments, that could work best for them, is of a significant benefit to patients. his barrier to equal access is detrimental to the well-being of Canadians.

In our MDSC national mental health survey conducted in September of 2021, 45% of respondents identified improving access to medications and treatment as their number 1 election issue for the Government of Canada, with 94% of them identifying it as important. It was the number one priority specified by respondents, and our 2018 MDSC national survey showed 69% of respondents have been dealing with their depression for more than 11 years. With an incredible 49% of the respondents indicated they were not doing well with their symptoms.

MDSC holds the position that with 69% of our 2018 survey participants indicating having been dealing with depression for over 11 years, there is a distinct need to increase treatment options and increase access. Obviously, there are many people who have not found the medication that works for them. If they had, we wouldn't be getting the number of calls for help that we are.

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.

As we stated in our patient group submission, it takes years for the patient (as well as their families and carers) to go through many experiences to fully understand this complex mental illness, and the challenges in researching and trying various treatments and therapies on their way through, places such an incredible burden and on the health and wellbeing of full family unit, that it often leads to significant negative impacts within their lives. Bipolar disorder very rarely only affects the patient. It hits the full family. The right medication for maintenance is so very important for people with bipolar disorder.

It is therefore our belief that patient needs are not being met in regards to the choice and coverage of treatments for bipolar disorder. The value and the benefit for patients in having a new treatment available for Canadians through Cariprazine cannot be under-emphasized.

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.
Currently, this is not recommending reimbursements conditions, we hope you reconsider this.

[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	*Dave Gallson*
Position	*National Executive Director*
Date	*27-07-2022*
☒	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**
Abbvie Inc	☐	☐	☒	☐
Janssen Inc	☐	☐	☒	☐
Pfizer Canada	☐	☐	☐	☒
Lundbeck Canada	☐	☐	☐	☒
Eisai	☐	☐	☒	☐
	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0718
Brand name (generic)	Cariprazine
Indication(s)	
Organization	Canadian Mental Health Association, Alberta Division
Contact information[a]	Name: Kolbi Kukurba, [redacted]

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

CMHA believes that access to treatment options for all Canadians is extremely important to the wellbeing and mental health of all. CADTH's negative draft recommendation on a proven and effective medication such as Cariprazine limits access to treatment for those living with bi-polar disorder. As we know, treatment for bi-polar disorder is individualized, and without access to a wide variety of treatment options, many Canadian go without adequate treatment for their mental health. Canadians need tolerable, effective and accessible options without barriers to said treatment options.

Further, we believe that mental health medication is not provided adequate consideration by CADTH. Mental health treatment and physical illness treatment must be measured differently, and therefore CADTH may consider developing more adequate processes for mental health treatments and molecules. With other jurisdictions like the USA and Europe recognizing Cariprazine as a top tier treatment option for bipolar, CMHA would encourage CADTH to review their recommendation with the understanding of its positive benefits compared to other leading pharmaceuticals on the market today.

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	☐

CMHA, Alberta Division did not submit stakeholder input prior to the draft recommendation.

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

Although the reasoning is clearly stated, it is unclear as to how the reasons align with patient needs. The draft recommendation report clearly identified Canadians identified need for a wider array of treatment options that have tolerable and limited side effects. Cariprazine fills this need and could be used to improve the lives of many people living with bipolar disorder, as well as their family, workplaces and communities.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

CMHA is unclear how the expectation of conducting an outpatient study, or including those with addictions, with those living with bipolar is an adequate measurement. Mental illness medication must be considered under an ethical lens, especially considering agents that treat those living with mania

or depressive episodes. We encourage you to reconsider how these implementation requirements could be better addressed for medications treating mental illness.		
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.

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 thefor further details.

A. Patient Group Information	
Name	*Kolbi Kukurba*
Position	*Director, Advancement & Social Enterprise*
Date	*26-07-2022*
☒	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**
Jansen Pharmaceuticals	☐	☐	☐	☒
Lundbeck Canada	☐	☐	☒	☐
	☐	☐	☐	☐