CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

CARIPRAZINE (Vraylar)

(AbbVie Canada)

Indication: For the treatment of schizophrenia in adults.

May 19, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0708
Brand name (generic)	Vraylar (Cariprazine)
Indication(s)	For the treatment of Schizophrenia in adults
Organization	
Contact information[a]	Risk Kronfli, MB FRCPC Clinical Director, ECF Hospital Head, section of Forensic and Correction psychiatry Dalhousie Chair, Drugs & Therapeutics Committee Nova Scotia Health 88 Gloria McCluskey Avenue, Dartmouth, NS B3B 2B8 [redacted]

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

"The clinical relevance is unknown" for the statistical significance!!

The committee does not seem to understand that effectively treated psychotic patients will save money to the government...

And QOL is not a strong argument?

They should have more input from experienced clinicians...

US experience seems to be very positive. The committee needs to review actual clinical data for medications that are used in other jurisdictions

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?

There is a lack of appreciation of the impact of the statistical significance and an erroneous interpretation of the data in our opinion. There is lack of consideration of clinical matters in the treatment of Schizophrenia.

- The tight dosing of the molecule to achieve impact is of importance to us clinically.
- The results of a head-to-head study, which is rare in schizophrenia that shows an impact on the negative symptoms, unlike any other molecule currently available. This is an aspect of the disease that is challenging to us and our patients. The statement of the committee that "the clinical relevance is unknown" is very surprising to us clinicians. Here we have a head-to-head study that showed a difference, unlike any other molecule available, yet that beneficial outcome is discarded!

- The committee did not consider the individual variability in the treatment of schizophrenia and the fact that equal statistical outcome, does not translate well in clinical practice.
- Even though there is equal, or slightly superior statistical data, (3 acute RCTS and 1 Relapse prevention) compared to other recent molecules assessed by CADTH, this molecule received a negative draft recommendation.
- It is frustrating to read the following in the CADTH rationale: “statistically significant but of uncertain clinical relevance” We wonder how CADTH arrived at that opinion. To our knowledge, this is something that we, psychiatrists, take in consideration clinically and to add to that, CADTH never used that rationale in recent reviews. We will specifically comment and compare it to the Brexpiprazole review that one of us was involved with to a degree.
- We will also add that not allowing a company to negotiate favourable pricing, will result in a major ethical dilemma for us and our patient when we choose comparable treatments. I can elaborate on that as the Chair of D&T for NS Health. My committee have an ethicist that provides input in all our decisions. This would lead to patients that has financial stability, to access this option, and others would not. Also consider that CADTH, as mentioned above, gave a positive recommendation for identical data sets.

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.

However, as you can see from the above, there was erroneous interpretation or a standard that was applied in this review, that was never used or mentioned in recent recommendations. We are not sure why, but we wonder if the fact that no psychiatrist was involved, may have led to that opinion.

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.

The rationale used of lack of data regarding the minimal difference to identify a clinical effect, is a departure from other recent reviews. And we may add, frustrating for clinicians.

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.

Please read all the above.

[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		
2. 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.		
3. 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		
4. 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

New or Updated Declaration for Clinician 1	
Name	*Risk Kronfli*
Position	*Clinical Director and Forensic Psychiatrist, Assistant professor*
Date	*09-05-2022*
☒	**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 2	
Name	*Louis Thériault*
Position	*Medical Director of Psychiatric Program, CHU Dumont, Clinical Associate Professor U Sherbrooke*
Date	*10/05/2022*
☒	**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

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Allergan/Abbvie	☒	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Gilbert Dru*
Position	*Psychiatrist FRCPC Bathurst NB*
Date	*13-05-2022*
☒	**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.

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Add company name	☐	☐	☐	☐

CADTH

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Cariprazine
Indication(s)	Schizophrenia
Organization	National Advisory Panel
Contact information[a]	Name: Dr. Pierre Chue [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.

As a group of Canadian psychiatrists and recognized experts in the treatment of schizophrenia we are deeply concerned about the decision of CADTH to not recommend the reimbursement of cariprazine. It is clear that more options are needed in the current treatment of schizophrenia given the heterogeneity of the disorder and the idiosyncrasy of response to treatment. Please see our response to the following questions (references provided to support argument; no new product data included).

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	☒

Patients with schizophrenia continue to be stigmatized at all levels with multiple barriers that prevent equitable access to antipsychotic medications. Several recent studies have confirmed that antipsychotics reduce all –cause mortality in schizophrenia vs. no treatment (Correll et al, 2022; Taipale et al, 2018). There are several atypical antipsychotics that are available in the USA and Europe but not in Canada, and some antipsychotics that are available in Canada are difficult to access (e.g., some provinces require special authorization forms using outdated criteria for long-acting injectable atypical antipsychotics). Patients with schizophrenia in Canada are no different to patients elsewhere in the world and deserve better treatment options. As clinicians who care for the most disadvantaged and marginalized individuals in society but whose lives can be transformed by the right medication, we ask that CADTH reconsider its current decision.

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

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

Cariprazine has demonstrated efficacy not only in clinical trials but also in real world data given its availability in the USA since 2015 and its approval by EMA (European Medicines Agency) in 2017. It is our opinion that the baseline change of -19 to -23 points on the PANSS scale and between group (vs. placebo) change of -6.8 to -10.4 seen in the cariprazine trials is clinically relevant and impactful for patients. The magnitude of -6.8 to -10.4 between group difference is in line with the results of what is expected for atypical antipsychotics, including other third generation antipsychotics. For example, the between group difference vs. placebo for the pivotal

trials for aripiprazole ranged from -5.9 to -12.7 (USPI – United States Prescribing Information); while for brexpiprazole ranged from -6.47 to -8.72 (USPI). This similarity in the acute efficacy of atypical antipsychotics is also documented in two high quality published network meta-analyses by Hunh et al. 2019 and Leucht et al. 2017 which suggest cariprazine's treatment effect is at least as good as the other atypical antipsychotics currently used in Canada.

Tolerability is a significant concern for patients and can impact adherence, safety and quality of life. It is clear that more effective pharmacological treatment options are needed that have less impact on weight and metabolic parameters. Cariprazine has limited effects on key metabolic, endocrine and cardiac parameters. This tolerability benefit is also demonstrated in several recent articles (Hunh et al. 2019; Pillinger et al. 2020: Leucht et al, 2017), which showed that cariprazine ranked among one of the most favorable atypical antipsychotics with regards to weight gain, total cholesterol shifts, LDL level shifts, QTc prolongation, and prolactin increase, with statistical significance demonstrated in some parameters vs. other atypical antipsychotics (i.e. olanzapine, quetiapine).

Efficacy in treating negative symptoms represents a significant unmet need and any treatment that demonstrates even a degree of benefit needs to be considered. Cariprazine is one of few antipsychotics to be evaluated in a specifically designed study for patients with persistent negative symptoms. A 20% responder rate for PANSS FSNS is accepted as clinically relevant. A significantly greater proportion of patients responded in the cariprazine arm vs. risperidone arm in the study, which also translated into significant changes in functioning on the PSP. While it is difficult to know which specific scale items and how much change may be relevant, it is clear that even relatively small improvements in negative symptoms are impactful for patients. Further, risperidone has been used as the primary drug (NCT00158028) or active comparator in studies of negative symptoms with other second generation antipsychotics (olanzapine; Shaft & Galnipoor 2014), investigational drugs (talnetant; NCT00103727), antidepressants (citalopram; NCT00893256) and even first generation antipsychotics (haloperidol; Chee et al, 2015).

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.
Implementation issues are summarized from drug plans but are general and do address the specific benefits identified above.

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.
Olanzapine should not be considered a valid comparator in Canada; not only is <u>not</u> a first-line option in certain provinces such as BC, but in view of the successful Canadian class action lawsuit* it is not clinically acceptable to put patients on a treatment that even in the short-term will predispose them to the greatest risk of metabolic disruption of any non-TRS antipsychotic. Many psychiatrists therefore consider olanzapine a second line antipsychotic, and at the dose of 20 mg used in the CATIE study (Lieberman et al, 2005) and comparable average dose in Canada for schizophrenia, the direct and indirect costs are significant. * Canadian courts have

approved a $17.6 million settlement in a class-action lawsuit launched by individuals who became diabetic after taking an antipsychotic drug (Toronto Star; 30 June 2010).

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

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	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

New or Updated Declaration for Clinician 1	
Name	*Dr. Pierre Chue*
Position	*Consulting Psychiatrist*
Date	*05-17-22*
☐	**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.				
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HLS	☐	☐	☒	☐
Allergan/AbbVie	☐	☐	☒	☐
Otsuka	☐	☐	☒	☐
Teva	X			
Lundbeck		X		
Eisai		X		
Janssen			X	

New or Updated Declaration for Clinician 2	
Name	*Dr. Thomas Raedler*
Position	*Associate Professor*
Date	*Please add the date form was completed (05-04-2022)*
☒	**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				
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Allergan/Abbvie	☐	☐	☒	☐
Sunovion	☒	☐	☐	☐
Teva	☐	☒	☐	☐
Otsuka/Lundbeck	X			
Boehringer-Ingelheim	X			

New or Updated Declaration for Clinician 3	
Name	*Dr. Jay Bondar*
Position	*Psychiatrist*
Date	*May 2, 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, Allergan Inc.	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Cariprazine (Vraylar)
Indication(s)	Schizophrenia in adults
Organization	Institute for Advancements in Mental Health (IAM) (formerly the Schizophrenia Society of Ontario)
Contact information[a]	Name: Erin Boudreau, [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.

"…substantial uncertainty remains regarding the clinical relevance and importance of the effects observed."

Access to a wide range of treatments and supports has been a long-standing policy priority for IAM. We believe that all treatment types should be easily accessible to individuals and families, including community services, social supports and psychiatric treatments such as medications. We know that 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 schizophrenia medications is particularly heterogeneous, and tolerability and experience of side effects varies from person to person.

The nature of schizophrenia is such that relapse is common, and the majority of individuals living with the illness will need longer-term treatment because relapse is associated with significant personal costs. This reinforces the need for access to medications throughout one's lifespan.

Because people with schizophrenia respond differently to different medications, they require a range of options. The Canadian Psychiatric Association is very clear in its Clinical Practice Guidelines for the Treatment of Schizophrenia that "medications must be individualized because the individual response is highly variable" and that "the choice of medication should be guided by individual patient factors". This is an experience that has been echoed by many of the individuals and families/caregivers that our organization works with. Many people living with the illness have told us that they have had to try several different medications before they found the right one for them.

The need for individualized treatment is due partly to the fact that there is substantial individual variation in clinical response to the drug treatment of schizophrenia. In addition to this, one must consider the side effects associated with particular drugs and the impact those might have on the patient. Given the wide range of adverse effects and individual responses, treatment with antipsychotics needs to be tailored to the patient.

What our organization has found in speaking to people affected by schizophrenia is that when one does find the medication that is best suited to them, it can be devastating if that medication is not fully accessible to them through the Ontario Drug Benefit Formulary. Even fail-first requirements can have a negative impact on the patient, as they are required to take medications that may not be suitable for them before being allowed to access the one that might be best. Listing of medications on the Formulary can also affect physicians' prescribing practices: a recent survey of Ontario psychiatrists showed that 50% of psychiatrists would not prescribe a medication that was not listed on the Formulary, even if, in their mind, it was the best treatment option for their patient.

For these reasons, in order to ensure optimal treatment, people with schizophrenia and their treating physicians must have access to all available treatment options through the Ontario Drug Benefit Formulary.

For more, see attached "Schizophrenia Society of Ontario Position on Access to Medication".

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 recognition that mental health medication treatment is not "one size fits all"; that access to a variety of medications and affordability of medications is key to supporting an individual's recovery.

With respect to affordability, individuals with mental illness who are on ODSP can only access the medications that are listed on the Formulary. The significant disability associated with schizophrenia and subsequent reliance on the Formulary to access medications in a way that is financially sustainable should be a consideration when deciding whether to list a new medication. For these individuals, who live in poverty on ODSP, paying out-of-pocket for their medication is often impossible – even if it is the most appropriate medication for them, therefore, jeopardizing their recovery.

The draft recommendation also speaks to disparities in the drug-review process. Research 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.

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.

DR. TOM JANZEN, M.D.
Parkwood Institute, Mental Health Care Building
550 Wellington Road
London, Ontario N5C 0A7
[redacted]

May 18, 2022

Dear Ms. Wong and Mr. Dicerni,

Re: **Reimbursement of cariprazine in Ontario**

I am a primary care physician who left my family practice in 2003 to pursue a full time position working in mental health at our tertiary care psychiatric hospital here in London, Ontario. I have had the unique privilege of working along side psychiatrists at London Health Sciences, St. Joseph's Health Care and the St. Thomas Elgin General Hospital. I have also travelled the country speaking about the importance of early detection and appropriate management of mental illness.

Over my 34 years of practice I have witnessed the introduction of many new medications intended to help individuals suffering with mental illness. Some have delivered as advertised and many have quickly faded after being introduced to the Canadian market.

Perhaps the most challenging area of my practice has been the management of individuals suffering with schizophrenia. As you know there are many choices in this category however each has it's challenges with respect to efficacy and the tolerability profile. Patients with schizophrenia have both positive symptoms (hallucinations and delusions) as well as negative symptoms (withdrawn from society with flat affect and emotionless). Traditional medications introduced in the 1950's have managed positive symptoms well but have largely not dealt with the negative symptoms. Newer generation antipsychotics have increasingly addressed some of the negative symptoms however there is still plenty of room to improve on their efficacy in this domain and their tolerability.

The latest entry to the Canadian market of antipsychotics is cariprazine which has a novel mechanism of action unique to this medication. From my exposure to psychiatrists south of our border, cariprazine has been very well tolerated and has helped manage patients who have not responded to other options. I have several patients in my practice who I believe would benefit from this option.

It is my understanding that CADTH has recommended that cariprazine not be reimbursed through provincial drug plans. I believe that this should be challenged based on the 7+ years of experience reported in the US as well as the unique pharmacological profile of this molecule. I continue to have patients suffering with schizophrenia who do not respond sufficiently to available options or are intolerant of the side effects. Cariprazine may address some of these concerns based on the unique profile. Hearing of the experiences of patients in the US suggests that this could become an important tool in out toolbox for managing patients with schizophrenia.

I am always happy to discuss my thoughts and answer any specific questions you might have related to this letter. Please feel free to reach out to me at [redacted] at my office at [redacted]

Sincerely,

Tom Janzen, M.D.
Primary Care with Focus in Mental Health

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0708-000
Brand name (generic)	Vraylar
Indication(s)	For the treatment of schizophrenia in adults.
Organization	Canadian Consortium for Early Intervention in Psychosis
Contact information[a]	Dr Phil Tibbo [redacted]

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

CADTH recommendations note "for the acute population- based on the sponsor's submitted MMA, no differences were observed in the efficacy of cariprazine compared to other oral AAPs". This in fact indicates that cariprazine is as good as available treatments when looking at a grouped response. It has as well been available and has been used in the United States for 6 years, where patients have benefited form this treatment. Furthermore, as Schizophrenia is a highly heterogeneous illness and as responses to medication vary significantly, there will be individuals for whom cariprazine is the best treatment.

CADTH recommendations also note "For the PNS population – based on the pivotal trial and clinical expert feedback, it is unknown whether the difference in PANSS mean score between cariprazine and risperidone is clinically relevant, because the minimally important difference in negative symptom scores is unknown" However, this study also explored functionality using the Personal and Social Performance (PSP) scale. On that scale a 4.63 mean difference in improvement was seen between groups with cariprazine patients demonstrating greater improvement (14,3 vs. 9,66 mean change from baseline). On this scale 4 points is considered the minimally relevant clinical difference and here cariprazine did meet this threshold for improvement.

CADTH recommendations do not discuss cariprazine pharmacology, specifically at the dopamine D3 receptor where cariprazine's affinity is 3 fold higher than all other available oral AAPS. The D3 receptor is thought to play a role in mood, motivation, reward and addiction.

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	☒

CADTH recommendations note "CCEIP noted the unmet need in young adults in the early phase of psychosis, in whom the current treatments may not optimize their long term outcomes." Schizophrenia is a potentially devastating illness with long-term consequences. If cariprazine is the ideal treatment for even a small number of first episode patients, this can have long-term positive implications, including the potential for fewer relapses, hospitalizations and therefore overall reduced health care costs for those individuals. CCEIP's original declaration highlighted the first 5 years of illness as the critical period to avoid deterioration and this was not properly considered by CADTH. As most patients with schizophrenia do not have personal funds or private insurance to purchase cariprazine directly, CADTH recommendations essential deprive these Schizophrenia patients from the potential benefits of this treatment.

CCEIP's original declaration highlighted the potential use of cariprazine as a first line agent and highlighter it's unique mechanism of action at the D3 receptor. This was not considered by CADTH in their recommendations.

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

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

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A. Assistance with Providing the Feedback		
2. 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.		
3. 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		
4. 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

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Hello.

I am a Psychiatrist at William Osler Health System where I have practised in the area of Acute Mental Health services in inpatient and outpatient setting for the past 25 years.

It is my understanding that the draft recommendation released for stakeholder feedback on May 5th, 2022 recommends that cariprazine not be reimbursed for the treatment of schizophrenia.

Even before this medication was in the radar for Canadians, I started to get questions about it from our patients. We have several options in Psychiatry but we also have a good no of patients who don't respond to available treatments. We are always looking for options- my understanding is that cariprazine has particular nuanced benefit for our patients with this serious illness in the area of negative symptoms, while being effective for positive symptoms as well. Negative symptoms are the main drivers of lack of functional improvement even when positive symptoms are controlled.

We are looking for options for patients who have tolerability issues as well. And we do need any new options we can get.
Most of our patients rely on ODB for their treatment and not having ODB coverage creates an unfair social factor in not being able to provide best possible treatment to an already impoverished and marginalized group in the society.

My conscience is always uncomfortable with the notion that our patients don't always get all potentially beneficial treatments due to their financial status and lack of advocacy for their needs.

I strongly advocate that Cariprazine option be reimbursed in Ontario to treat this difficult disease which even with the best of options has serious impact on patients and their families.

I am happy to make myself available for any questions/ copncerns and for any further discussion on this topic.

Thank you for supporting our patients and giving further consideration to this important issue.

Sincerely.

Harmeet Bami MD, FRCPC
Clinical Lead Mood Disorder Program,WOHS
Women's Mental Health Clinic,
Assistant Professor, McMaster University

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0708
Name of the drug and Indication(s)	Cariprazine (Vraylar) for the treatment of schizophrenia 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	SR0708-000
Brand name (generic)	cariprazine
Indication(s)	Schizophrenia
Organization	Schizophrenia Society of Canada and CMHA AB
Contact information[a]	Name: Chris Summerville

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

The draft recommendation Rationale section acknowledges that "cariprazine was associated with modest improvements in schizophrenia symptoms and overall severity at 6 weeks relative to placebo that were statistically significant" based on evidence from three 6-week double blind RCTs (page 3). Yet as the same time as noting the statistical significance, the draft recommendation calls the evidence of "uncertain clinical relevance" (page 3).

Further along in the Rationale section, the draft recommendation acknowledges that "treatment with cariprazine led to greater improvement in PANSS factor score for negative symptoms and functional status compared with risperidone" according to a 26-week RCT, calling the difference "statistically significant" (page 3). Yet again, at the same time as noting the statistical significance, the draft recommendation claims "the clinical relevance of the differences in these outcomes in unclear since the minimally importance difference to show a clinical effect is unknown or was not exceeded" (page 3).

Then in the Discussion Points section, it notes that although "statistically significant differences were detected between cariprazine and risperidone in terms of negative symptoms or functional status, those differences were considered small, and substantial uncertainty remains regarding the clinical relevance and importance of the effects observed" (page 4).

In our opinion, the only things that are "uncertain" and "unclear" in CDEC's stated reasoning is what they meant by the words "uncertain" and "unclear". And in terms of the word "small", even small differences provided by treatments can have a significant impact on the lives of people with schizophrenia.

So in the absence of clarity around how these words were used and what they mean, we can only conclude that while the patient input provided by our organizations was acknowledged, it was not reflected in the conclusion of the draft recommendation.

The content of our input is accurately summarized in the Patient Input section (pages 5-6) so much so, that we believe the wording chosen reinforces the need for publicly funded access to cariprazine:

> "Negative symptoms, including social withdrawal and reduced motivation or apathy, diminish their quality of life and social engagement, resulting in challenges with reintegration."
>
> "Two respondents with experience with cariprazine reported that the treatment was able to manage their negative symptoms and improve their relationships with peers."
>
> "Treatment and recovery are a nonlinear, individual process. Finding the right medication that enables the highest level of functioning, while managing adverse effects, is often achieved through a trial-and-error process. To meet their unique needs, patients expect quick, simple, and affordable access to a wide range of therapeutic options to improve their treatment experience."

Given that current medications do not treat "negative or cognitive symptoms, and do not reliably improve psychosocial function" as noted in the Clinician Input section (page 6), it seems even more obvious and unequivocal to us that patients need publicly funded access to cariprazine.

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 negative draft recommendation for public funding demonstrates only that our input was acknowledged, not considered. Had our input been considered, in our opinion the draft recommendation would have been positive.

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.

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	Chris Summerville
Position	CEO, Schizophrenia Society of Canada
Date	*Please add the date form was completed (*19-05-2022*)*
☒	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. EVERSANA assisted with the preparation of our feedback.		
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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Schizophrenia Society of Ontario Position on Access to Medication

The Schizophrenia Society of Ontario (SSO) is a non-profit charitable organization with a mandate to improve the lives of those affected by schizophrenia and psychosis through education, support programs, public policy & research. Reaching over 30,000 people each year, SSO is the largest organization representing people affected by schizophrenia in Ontario. Our organization has been an active advocate for access to treatment since our inception in 1979, which includes access to medications.

Schizophrenia is a serious but treatable brain disease affecting 1 in 100 people – approximately 120,000 Ontarians. Characterized by positive symptoms such as hallucinations and delusions, negative symptoms such as depression, and cognitive symptoms such as thought disorder, schizophrenia is a severe and chronic illness which at this time has no cure. Left untreated, the prognosis of schizophrenia is poor and can lead to deterioration of a person's condition, decreased ability to function, and possible homelessness, suicide, violence and criminalization. The total cost of schizophrenia in Canada was estimated at $6.85 billion in 2004[1].

However, with treatment, the prognosis is much better and people with schizophrenia can lead meaningful, productive lives. It is therefore imperative that people with schizophrenia have access to the psychiatric treatment, community-based mental health services and social supports to aid them in their recovery.

As an organization representing the interests of people affected by schizophrenia, the SSO sees it as our role to help ensure that people living with this illness have access to the best and most appropriate treatment for them. In the area of drug therapy, we advocate that all medications deemed safe and effective by Health Canada for the treatment of schizophrenia be included in the Ontario Drug Benefit (ODB) Formulary. SSO does not endorse individual treatments of any kind nor do we make claims regarding the safety, efficacy or effectiveness of individual medications.

While we understand that there are financial constraints upon the Ontario Public Drug Program that limit its ability to reimburse medications, we believe that schizophrenia is a unique illness and that certain considerations should be made when making a decision about whether to list a particular medication:

1. **Medication is the cornerstone of recovery from schizophrenia**

   As mentioned, there is presently no cure for schizophrenia. Recovery is a term used widely in the mental health field to describe an individual's ability to have a good quality of life with a mental illness. Recovery is supported by many non-medical factors, such as support, knowledge, and meaningful activity, however most individuals with psychiatric disorders indicate that medications are critical to their success[2]. This position is echoed by the Canadian Psychiatric Association (CPA), which states in its Clinical Practice Guidelines for the Treatment of Schizophrenia that "pharmacotherapy with antipsychotic medications is an essential component of a treatment plan for most patients with schizophrenia"[3].

   Unlike several decades ago, individuals with serious mental illness no longer spend their lives in institutions. The process of deinstitutionalization has required that a network of services and

supports be provided in the community. While community-based mental health services and social supports such as income and housing are essential, for many individuals with serious mental illness the success of these interventions is linked to their psychiatric stability. Indeed, the CPA's Clinical Practice Guidelines indicate that "psychosocial interventions work synergistically with medication to optimize treatment adherence and successful community living"[4].

For those who are hospitalized for a period of time, readmission at a later date is shown to be related to these same recovery factors, including access and adherence to prescribed medications[5]. In fact, individuals with schizophrenia may be at significantly increased risk of hospitalization as early as ten days after going off their medications[6]. This suggests that hospital admission rates, and related costs, could potentially be lowered with proper access to medication in the community, amongst other things.

The nature of schizophrenia is such that relapse is common, and the majority of individuals living with the illness will need longer-term treatment because relapse is associated with significant personal costs[7]. This reinforces the need for access to medications throughout one's lifespan.

2. **Because people with schizophrenia respond differently to different medications, they require a range of options**

The CPA is very clear in its Clinical Practice Guidelines for the Treatment of Schizophrenia that "medications must be individualized because the individual response is highly variable" and that "the choice of medication should be guided by individual patient factors" [8]. This is an experience that has been echoed by many of the individuals and families that our organization works with. Many people living with the illness have told us that they have had to try several different medications before they found the one that was right one for them.

The need for individualized treatment is due partly to the fact that there is substantial individual variation in clinical response to the drug treatment of schizophrenia[9]. In addition to this, one must consider the side effects associated with particular drugs and the impact those might have on the patient. Given the wide range of adverse effects and individual responses, treatment with antipsychotics needs to be tailored to the patient[10].

What our organization has found in speaking to people affected by schizophrenia is that when one does find the medication that is best suited to them, it can be devastating if that medication is not fully accessible to them through the Ontario Drug Benefit Formulary. Even fail-first requirements can have a negative impact on the patient, as they are required to take medications that may not be suitable for them before being allowed to access the one that might be best. Listing of medications on the Formulary can also affect physicians' prescribing practices: a recent survey of Ontario psychiatrists showed that 50% of psychiatrists would not prescribe a medication that was not listed on the Formulary, even if, in their mind, it was the best treatment option for their patient[11].

3. **Individual responses to medications impact treatment adherence**

Although antipsychotic medication has been shown to improve psychopathology, reduce relapse, and improve functioning, non-adherence to treatment is common. At a system level, non-adherence is associated with an increased use of Emergency Room visits and psychiatric hospitalizations, with one study finding that hospital expenditures of those who were non-adherent were more than three times higher than the hospital expenditures of those who were adherent[12].

Medication side effects can significantly impact adherence to treatment along with the relationship with the clinician, patient and family knowledge about the illness, and understanding of the risks of non-adherence to medication[13]. Indeed, we have heard from many individuals with schizophrenia that the side effects of their medications can be truly debilitating. This, again, reinforces the needs for options on the Formulary, so that physicians can freely prescribe medications which they believe will have the least side effects for that individual patient.

4. **People with schizophrenia are reliant on the Ontario Drug Benefit Formulary to access their medications.**

Many Ontarians are fortunate enough that when they fall sick, they are able to get ready access to medications without significant financial strain. These individuals are often covered by employer-provided or personal health care coverage plans, or have illnesses which are temporary and require only short-term treatment.

This is not the case for the majority of individuals living with schizophrenia. Schizophrenia is a chronic disease that often requires an individual to take medication for the course of their lives. Moreover, an estimated 80% of people with schizophrenia are unable to work for various reasons and rely on the Ontario Disability Support Program (ODSP) for income. Overall, approximately one-third of people receiving ODSP have a psychiatric disability, and 35,000 of those have psychosis-related diagnoses such as schizophrenia.

Individuals with mental illness who are on ODSP can only access the medications that are listed on the Formulary. The significant disability associated with schizophrenia and subsequent reliance on the Formulary to access medications in a way that is financially sustainable should be a consideration when deciding whether to list a new medication. For these individuals, who live in poverty on ODSP, paying out-of-pocket for their medication is often impossible – even if it is the most appropriate medication for them.

For these reasons, in order to ensure optimal treatment, people with schizophrenia and their treating physicians must have access to all available treatment options through the Ontario Drug Benefit Formulary.

Sources:

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[1] Goeroo R, Farahati F, Burke N, Blackhouse G, O'Reilly D, Pyne J et al. (2005). The economic burden of schizophrenia in Canada in 2004. *Curr Med Res Opin 21(12);* 2017-2028.

[2] Sullivan, W.P. (1997). A long and winding road: The process of recovery from severe mental illness. In L. Spaniol. C. Gagne and M. Koehler (Ed.), *Psychological and social aspects of psychiatric disability* (pp.14-24). Boston: Centre for Psychiatric Rehabilitation.

[3] Canadian Psychiatric Association. (2005). Clinical Practice Guidelines: Treatment of Schizophrenia. *Canadian Journal of Psychiatry 50(Suppl 1);* 1S-56S.

[4] Ibid.

[5] Canadian Institute of Health Information. (2008). *Hospital Length of Stay and Readmission for Individuals Diagnosed with Schizophrenia: Are They Related?* (Ottawa: CIHI, 2008).

[6] Law MR, Soumerai SB, Ross-Degnan D, Adams AS. (2008). A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. *Journal of Clinical Psychiatry 69(1);* 47-53.

[7] Kane JM and Garcia-Ribera C. (2009). Clinical guideline recommendations for anti-psychotic long-acting injections. *The British Journal of Psychiatry, 195;* s63-s67.

[8] Canadian Psychiatric Association, 2005.

[9] Reynolds GP, Templeman LA, Godlewska BR. (2006). Pharmacogenetics of schizophrenia. *Expert Opin. Pharmacother. 7(11);* 1429-1440.

[10] McKenzie E. (2009). *Understanding the Classes*. Applied Management: 2009.

[11] Innovative Research Group Inc. *Psychiatrist Survey*. Toronto: The Schizophrenia Society of Ontario; November 2009.

[12] Gilmer TP et al. (2004). Adherence to Treatment with Antipsychotic Medication and Health Care Costs Among Medicaid Beneficiaries With Schizophrenia. *American Journal of Psychiatry 161;* 692-699.

[13] Canadian Psychiatric Association, 2005.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0708-000
Brand name (generic)	Vraylar (cariprazine)
Indication(s)	For the treatment of schizophrenia in adults
Organization	Allergan (an AbbVie Company)
Contact information[a]	[redacted]

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

AbbVie disagrees with the CDEC's recommendation that Vraylar should not be reimbursed, and respectfully requests that CDEC reconsider. The basis of this reconsideration request is three-fold:
(1) The recommendation and cited reasons of "uncertain clinical relevance" are inconsistent with the submitted evidence, as well as CADTH's review of the evidence [as detailed in the Clinical Review Report (CRR)].

- CDEC Stated: *"Cariprazine was associated with modest improvements in schizophrenia symptoms and overall severity at 6 weeks relative to placebo that were statistically significant but of uncertain clinical relevance."* (draft reco [DR], pg. 3) However, the effect sizes in the acute schizophrenia studies of Vraylar are clinically relevant based on several MID benchmarks suggested by literature, past HTA reviews, and when appraising the evidence in the context of the comparative treatment effect for commonly used atypical antipsychotics (AAPs).
  - It has been well documented in the literature that a 15-point change in PANSS total score from baseline is considered clinically meaningful for patients. This MID (minimal important difference) has also been referenced in the CRR. Hermes *et al.* 2012 reported that the MID for change from baseline ranged from -11.6 to -18.7, with 15 points being the average across all baseline severities. Even the higher value of 18.7 was exceeded in the Vraylar acute schizophrenia studies (changes from baseline in PANSS ranged from -23.0 to -20.2).
  - A between-group MID has been referenced and used by CADTH and the Pharmaceutical Benefits Advisory Committee (PBAC) in the past. Notably, CADTH's review of Rexulti and PBAC's review of Invega, Latuda, and Rexulti references a between-group MCID of 7 for total PANSS score. When applying this between-group threshold (7 points) to Vraylar's clinical data, Vraylar meets or exceeds this threshold in 6 out of the 7 treatment arms evaluated across the three acute studies.
  - Vraylar's results vs. placebo in change from baseline total PANSS score (-6.0 to -10.4) are in line with that of other commonly used AAPs, assessed in similarly designed studies, such as Abilify (-5.9 to -2.7), Rexulti (-3.1 to -8.7), and Latuda (-2.1 to -16.2). Hence, if the effect of Vraylar on total PANSS score is of uncertain clinical relevance, the same conclusion may apply to other AAPs that are widely reimbursed and used across Canada.
  - CDEC misinterpreted the published within-group MID for CGI-S and applied it to the between-group difference to assess clinical significance. The 1-point change in CGI-S is applied to within-group difference to determine if patients are improving in disease severity from baseline. It is very common for between-group differences vs. placebo for CGI-S to not exceed 1 point in AAP trials. Vraylar had a between-group difference vs. placebo for CGI-S (LSMD: -0.3 to -0.6) which is within range of what is expected in acute clinical trials of other antipsychotics including Abilify (-0.33 to -0.48), Rexulti (-0.19 to -0.38), Latuda (-0.4 to -0.8), and Perseris (-0.35 to -0.4).

- In Rexulti's clinical reviewers report (pg 71), the clinical expert noted that Rexulti's PANSS and CGI-S LSMDs are clinically relevant for patients. Given Vraylar has numerically higher LSMDs in similarly designed studies, Vraylar's treatment effect is also clinically relevant.
- The results of AbbVie's unpublished NMA, and two well-cited, high-quality published NMAs (Huhn et al. 2019 and Leucht et al. 2017) conclude that the treatment effect of Vraylar is superior to placebo and similar across commonly used AAPs. These findings demonstrated by Vraylar on total PANSS score are in line with current AAPs that are deemed to be clinically relevant by CADTH and clinicians. The NMA results discussed in the CRR were entirely omitted from CDEC's reasons for the recommendation, even though these analyses provide crucial evidence regarding comparative efficacy and safety between different antipsychotics.

- CDEC stated: *"this difference was statistically significant [PNS study], the clinical relevance of the differences in these outcomes [PANSS-FSNS] was unclear."* (DR, pg. 3) However, the effect sizes in the PNS study of Vraylar are clinically relevant, especially in the context of there being no other treatment option available for Canadian patients.
  - Meaningful change for the PANSS-FSNS was evaluated by Czobor *et al*. 2022 using data from the PNS study. This was done using a CGI-I as the anchor. It was determined that a **between-group** difference of -1.5 on the PANSS-FSNS represents a meaningful mean change. Vraylar meets this MID of -1.5 points in the FSNS and therefore demonstrates clinically meaningful change vs. risperidone in improving negative symptoms.
  - As noted in the CRR (pg. 118, table 55) and Edgar et al. 2014, a 20% improvement in PANSS-FSNS is considered clinically meaningful for patients. Although the responder rate analysis in the PNS study has inherent statistical limitations as it was not tested for type 1 error (as CADTH noted), such analysis should not be completely discarded due to this limitation. Vraylar had significantly more responders vs. risperidone (69.2% vs. 58.1% OR=2.1, P=0.002) resulting in a NNT of 9. A NNT <10, when comparing to another intervention, is considered clinically significant in psychiatric studies.
  - Moreover, several analyses were submitted to substantiate the clinical meaningfulness of the PNS study results by varying the definition of responders. With more stringent responder definitions applied, the treatment effect further favours Vraylar with lower NNT values.
  - The observed improvements in PANSS-FSNS also had a corresponding significant improvement in psychosocial functioning for Vraylar versus risperidone-treated patients, as measured by the PSP scale [LSMD of 4.6 points (2.71 to 6.56; p <0.0001)]. An analysis based on responders, defined as 10-point improvement in PSP score, was completed for the EMA submission. This analysis favored Vraylar vs. risperidone (CAR: 58% vs. RIS: 43%; OR: 2.17; p<0.001; NNT=8) and is also suggestive of clinically meaningful outcomes of improved psychosocial functioning for PNS patients.
- CDEC stated: *"Although one randomized withdrawal design study showed that patients who continued with cariprazine had a longer time to relapse than those who were switched to placebo, this study enrolled an enriched population and included only patients who tolerated and showed a good response to cariprazine."* (DR, pg. 3) Although the study included an enriched population of patients who responded to therapy, this was required for the overall study objective which was to determine if there is an added benefit to continue treatment in patients who respond to therapy in the acute phase. Such study design is mandated by EMA and FDA. CDEC should not completely discount this evidence as it provides insights into the long-term durability of Vraylar in patients who initially respond to therapy.
- CDEC stated: *"Patient groups noted additional therapy is needed which minimize adverse events however there was insufficient evidence to demonstrate that these needs were met by cariprazine."* (DR, pg. 3) There is sufficient evidence to conclude there is added benefit for Vraylar over select AAPs. These benefits were not considered by CDEC. In light of the similar efficacy of Vraylar in the treatment of acute schizophrenia, the tolerability profile of Vraylar could provide advantages over other treatments for some patients with respect to weight gain, LDL, total cholesterol, prolactin

levels, and sedation, as suggested by the submitted NMAs. These benefits were also supported by 3 acute schizophrenia studies which demonstrated there were placebo like effects on metabolic parameters including LDL, HDL, total cholesterol, and triglycerides over first 6-8 weeks.

(2) The recommendation is inconsistent with the positive reimbursement recommendations previously issued by CDEC for antipsychotic treatments for schizophrenia, despite the fact that previous products were submitted with similar (or arguably, inferior) evidence.

- In the past 5 years, CDEC has deliberated on two antipsychotic therapies for the treatment of schizophrenia – Rexulti (2017) and Perseris (2021).
- Since these reviews, CDEC appears to have changed its benchmark or standard for effect sizes that are considered clinically relevant for schizophrenia treatments, without citing any evidence or rationale to support this change. Vraylar's between group LSMD on the PANSS and CGI-S change was numerically higher than what was seen in the Rexulti and Perseris acute studies, which were similarly designed with similar population characteristics at enrollment. Despite this, CDEC noted that the clinical relevance of the LSMDs seen for Vraylar was considered uncertain and provided a negative recommendation, while providing the other products a positive recommendation.
- CDEC did not consider the unpublished or published NMAs submitted as part of the Vraylar evidence package in developing its recommendation for Vraylar, due to their perceived limitations. In contrast, NMAs employing very similar methods and having similar limitations were considered by CDEC in developing its recommendations for Rexulti and Latuda. The reason for the inconsistency in how NMA results were used is unclear.

(3) The recommendation fails to recognize that the submitted clinical evidence package for Vraylar addresses specific treatment gaps that were raised by patient and clinician groups via the stakeholder input process.

- As noted by patient group feedback, more alternatives are needed to individualize treatment and find a therapy that will strike the right balance between efficacy and tolerability that will ensure patients are stabilized with minimal/acceptable tolerability impacts over the long-term. Vraylar has a clinically relevant treatment effect which is in line with other commonly used AAPs.
- Overall, Vraylar is a treatment alternative that can address some of the tolerability concerns that patients and clinicians have discussed with respect to current AAPs.
- Negative symptoms remain a significant unmet need, and there is sufficient evidence to conclude that some patients with negative symptoms may benefit from Vraylar.

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 refer to commentary above.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
Please refer to commentary above.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
Not applicable		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
Not applicable		

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