CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

cariprazine (Vraylar)

(AbbVie Corporation)

Indication: For the treatment of schizophrenia in adults.

January 8, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions received.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Input

Name of Drug: Cariprazine

Indication: Early Psychosis, Schizophrenia, Bi-Polar 1 & 2, Depression with psychotic features

Name of Patient Groups: Schizophrenia Society of Canada, Institute for Advancements in Mental Health, Schizophrenia Society of Alberta, the Canadian Mental Health Association Alberta Division Association, and Mood Disorders Society of Canada.

Author of Submission: Chris Summerville, CEO, Schizophrenia Society of Canada.

Supporters: Mary Alberti, CEO, Institute for Advancements in Mental Health; and Dave Gallson, National Executive Director, Mood Disorder Society of Canada.

About Your Patient Group

The Schizophrenia Society of Canada **(SSC)** was created by family members in 1979 to advocate for their loved ones who lived with schizophrenia. SSC's mission is to: "Build a Canada where people living with early psychosis and schizophrenia achieve their potential." This is based upon the Recovery Philosophy as we work with families and people living with early psychosis and schizophrenia. We address stigma and discrimination due to misunderstanding, misconceptions, and misinformation. Our website is: www.schizophrenia.ca .

The Institute for Advancement in Mental Health **(IAM)** was formerly known as the Schizophrenia Society of Ontario created in 1979. IAM is a connector, collaborator, thought leader and solution driven organization, supporting, innovating and driving change for better mental health. IAM innovates in mental health with a focus on returning solutions back to communities, through partnership and collaboration. Through our own in-house services, we design programs around the needs of our clients - people with complex mental health needs including early psychosis and schizophrenia and their support circles. In 2017, we created a unique, first-of-its kind community-based mental health innovation platform: a designated space for mental health innovation entrenched within a mental health service organization. At IAM, we envision a society that helps anyone impacted by mental health issues thrive. We call this vision *redesigning society for better mental health*. Creating environments that are more inclusive, positive and accepting for people with mental illness is central to our work and our services. www.iamentalhealth.ca/

The Schizophrenia Society of Alberta **(SSA)** exists to improve the quality of life for those affected by schizophrenia and psychosis through education, support programs, public policy and research. For over 40 years the SSA has sought to ensure that everyone living with schizophrenia and psychosis has the supports they need to lead a meaningful and fulfilling life. With the right medical care and emotional and community supports, recovery is possible. www.schizophrenia.ab.ca/

The Canadian Mental Health Association **(CMHA),** Alberta Division is a recognizable and reliable organization where Albertans find compassionate support, responsible care and accessible resources. For over 100 years we have operated as a registered charity within the not-for-profit sector. We work at the intersection of clinical and local mental health care. Our mission is a nation-wide voluntary organization that promotes the mental health of all and supports people experiencing mental illness, with a vision of mentally healthy people in a healthy society. CMHA's focused is on recovery and support for Albertans impacted by mental illness such as early psychosis and schizophrenia. We stand with people living in the community as they achieve their wellness goals. Today our eight CMHA regional offices and the Centre for Suicide Prevention continue to focus on a better future for all people living with mental health challenges. We also recognize that individuals with a mental health challenge are connected to others who need support. www.alberta.cmha.ca/

Mood Disorders Society of Canada (MDSC) was incorporated in 2001 with the overall objective of providing people with mood disorders with a strong, cohesive voice at the national level to improve access to treatment, inform research, and shape program development and government policies with the goal of improving the quality of life for people affected by mood disorders. The MDSC's overall objective is to provide people with mood disorders with a strong, cohesive voice at the national level by: 1) Raising awareness that mood disorders are treatable medical issues and working towards eliminating barriers to full community participation in reducing discrimination and stigma, involving members of the public, government and treatment/service providers. 2) Building a national clearinghouse of information and resources related to mood disorders. 3) Advocating for the creation of adequate and accessible stigma-free programs for Canadians living with or suffering from mental illness. 4) Ensuring that the voices of consumers and family members are accurately understood and communicated on issues of national importance by building on existing networks and alliances. www.mdsc.ca/

Information Gathering

SSC has led and in collaboration with the submitting organizations has involved a wide range of patients and caregivers in this patient input submission. This was achieved by interviews, focus groups, a national survey, and a smaller survey for those with personal experience with Vraylar. This data was gathered between 2021 and 2023. It included people with lived/living experience with early psychosis and schizophrenia, as well as family members and friends. As to the national survey, SSC undertook two surveys, one for persons with lived experience (PWLE) of early psychosis and schizophrenia, and one for family members (FM) of people with early psychosis and schizophrenia. The intent of the surveys was to gain a current understanding of the impact that positive symptoms, **negative symptoms**, and cognitive symptoms have on the lives of individuals with early psychosis and schizophrenia, from both the lived experience perspective and the family perspective. And finally, the surveys were intended to better understand the journey of personal recovery that people with early psychosis and schizophrenia, and family members, engage in and what helps or hinders that journey. SSC engaged with the provincial Schizophrenia Societies across Canada, and other mental health organizations, associations, and networks that provide services to people with early psychosis, schizophrenia, and their family members to promote uptake of the surveys. The majority of survey respondents (66%) were between the ages of 18 and 34. Family completed survey totaled 121. Patient surveys were 118. An additional survey was conducted for people using Vraylar as well as several interviews.

As part of this continued advocacy in support of having Vraylar recommended for coverage on provincial formularies, SSC guided the development of a short survey of four questions for people who are using or have used Vraylar. The survey questions focused on people's overall experience with the medications and how it has impacted some of their positive, negative, and cognitive symptoms. It is important that the voices of people using Vraylar be considered in its assessment. Provincial schizophrenia organizations and various psychiatrists known to be working with people who are using/have used Vraylar were asked to distribute the survey. The survey was distributed in both English and in French languages and was also available on SSC social media accounts. The survey was open between November 8, 2023, and December 25, 2023.

Disease Experience

Early psychosis and schizophrenia are terrible illnesses, often "enduring," and most difficult to live with due to the challenges of symptom control **AND** dealing with the more troubling aspects of stigma and discrimination. Psychosis as related to schizophrenia is not a "kiss of death diagnosis" as once thought. But most patients, families and the public still think this to be a reality. This is due to misunderstanding, misinterpretation, misconceptions, and misrepresentation (by media, movies, etc.). To understand the impact of schizophrenia on a person's quality of life one must use the word "functionality." For individuals and family members, their main question upon diagnosis is, "Will I (they) be able to function in life, to regain functionality." (To finish my education, have friends, get married, hold down a job, etc.) Due to the positive symptoms and negative symptoms, as well as any cognitive challenges along with depression and anxiety, the person is near incapacitated until "stabilization" is achieved. But "stabilization" is not the only goal or issue. Re-integrating back into life and being able to enjoy full "citizenship" is a challenge. This lack of social inclusion is one of the main causes of the high rates of suicide among this population. This is fueled by the stigma and discrimination as the public is "fearful" and continues to believe in the myth that "schizophrenics are dangerous." "Lock them up and throw away the key." From our patient and family engagement, we learned that it is the **negative symptoms** of schizophrenia (reduced motivation or apathy; reduced emotional expression or feeling; loss of interest; reduced verbal communication; social withdrawal; change in daily functioning; change in productivity) that most people (the public) are fearful of and uncomfortable with. Research articles now address that the stigma and discrimination is mostly due to negative symptoms of schizophrenia. Patients and family members have repeatedly and passionately asked why there is no antipsychotic medication that targets the negative symptoms of schizophrenia. To live in society with any degree of "success" requires that one be able to engage in a warm, social, conversational, and relational way. **The negative symptoms of schizophrenia greatly diminish social engagement and integration.** There is no quality of life. Quality of life is about life satisfaction, being able to enjoy the pleasures of life and to engage in the pursuit of happiness and self-fulfillment. A medication that addresses negative symptoms such as Vraylar is needed. The burden of care and the grief and

sorrow experienced by family members is unacceptable. They worry as they come to the end of their own lives, "What will happen to my son/daughter?" "Who will care enough for them to extend love and compassion, and help," Government can't do that. People do! **But we need a medication that can address the negative symptoms along with psychosocial rehabilitation, family education, recovery-oriented mental health services, psychological support services, substance use issues care, and trauma-informed care. *ALL* part of "the treatment plan."** So very much has been learned since SSC began in 1979! It's not just about medication. But medication can be the catalyst to recovery!

Experiences with Currently Available Treatments

None of the typical or atypical antipsychotics seem to truly target negative symptoms of schizophrenia, as hoped! Dr. Murry Enns, Chief of Psychiatry in Manitoba noted, "If only antipsychotics did everything promise." Obviously this would be based upon the severity of the illness: mild, moderate, severe, enduring. No existing antipsychotic medication targets the negative symptoms of schizophrenia.

The writer recognizes that more than one antipsychotic may be needed to "control" the positive and negative symptoms. Clinical Practice Guidelines are important at this level. Schizophrenia is heterogeneous. So is the treatment! As is true in cancer care treatment, a holistic approach is required as noted by Dr. Doug Turkington, a psychiatrist who has worked with several of the schizophrenia societies in utilizing CT alone with medication. There is no current antipsychotic medication on the market that addresses all of the complex issues of enduring mental illness. Thus, doctors must have access to newer medications that can indeed address the unresolved symptoms of early psychosis and schizophrenia.

Improved Outcomes

The SSC undertook two national online surveys, one for persons with lived experience (PWLE) of early psychosis and schizophrenia, and one for family members (FM) of people with early psychosis and schizophrenia. The intent of the surveys was to:

- Gain a current understanding of the impact that positive symptoms, negative symptoms, and cognitive symptoms have on the lives of individuals with early psychosis and schizophrenia, from both the lived experience perspective and the family perspective.
- Consider the side effects of anti-psychotic medications that most impacted individuals' quality of life, and
- Better understand the journey of personal recovery that people with early psychosis and schizophrenia, and family members, take and what helps or hinders that journey.

In total, 239 full completed surveys from PWLE and 121 full completed surveys from FM were included in the final analysis. Sixty-eight percent of the PWLE respondents were male and almost half were 24 to 34 years of age. Seventy-seven percent were living with family at the time of the survey. For the FM survey, 65% of respondents were female with age being fairly equally distributed across age ranges. Forty-three percent had a family member with early psychosis or schizophrenia living with them.

Summary Results of Persons with Lived Experience (PWLE) Survey:

Across all three categories of symptoms (positive, negative, and cognitive), a high percentage of PWLE respondents reported experiencing one or more symptoms over the year prior to the survey with:

- 76% reporting one or more positive symptom,
- 94% reported one or more negative symptom, and
- 97% reported one or more cognitive symptom.

The positive symptom experienced by the highest number of respondents over the past year (39%) and in the past week that most impacted quality of life (18%) was delusions. Social withdrawal (39%) and reduced motivation or apathy (38%) were experienced by slightly more respondents than other negative symptoms. The cognitive symptom experienced over the past year (60%) and over the past week that impacted quality of life (45%) by the highest number by respondents was "difficulty with attention and memory of

information". Positive, negative, and cognitive symptoms were reported to have all moderately to greatly affect the quality of life of the PWLE respondents over the past year.

A large majority of PWLE (94%) were taking medications for early psychosis or schizophrenia at the time of the survey. The side effects most experienced by PWLE respondents included:

- Feeling sleepy or sedated (29%),
- Feeling restless (28%),
- feeling nauseous (27%), and
- Weight gain (26%)

A somewhat high percentage of respondents reported experiencing hypertension (31%), diabetes (26%), or cardiovascular problems (29%) since starting their anti-psychotic medications. The degree to which side effects were reported to affect quality of life in the past year were all rated between moderately and greatly.

Despite the side effects and the symptoms experienced by respondents and the reported impact of these on quality of life, most considered themselves as either progressing in their recovery (62%) or in full recovery (31%), with 7% reporting that they are struggling in their recovery. Of the 17 aspects of recovery that were asked about, all were rated as very important to respondents, with having medications that have few side effects as the top-rated aspect. Having the support of family, good sleeping habits, and spending time with the people that they love were also important aspects to their personal recovery journeys.

Results of Family Members (FM) Survey

FM reported that their family member with early psychosis or schizophrenia experienced various cognitive symptoms over the past year (45-48%) to a higher degree than they experienced either various positive (42-45%) or various negative symptoms (36-57%) over the past year.

The positive symptom FM reported in their family member most over the past year and over the past week that impacted quality of life were hallucinations (45%) and disorganized thinking (45%). Reduced motivation or apathy (57%) and social withdrawal (49%) were reported as the most common negative symptom experienced over the past year. There was no specific cognitive symptom that was reported significantly more than the others, however difficulty with daily thinking/organizing and difficulty with attention and memory of information were rated the highest at 27%. Positive, negative, and cognitive symptoms observed by FMs were reported to have moderately to greatly affect the quality of life of the PWLE respondents over the past year.

A large majority of FM (83%) reported that their family member was taking medications for early psychosis or schizophrenia. Feeling sleepy or sedated was the side effect most reported by FM respondents at 39%, with feeling restless and weight gain as the next most reported. The degree to which side effects were reported to affect quality of life in the past year were rated between just less than moderately and greatly, with sexual problems having the highest rated impact on quality of life. FM respondents reported their family member experienced Hypertension (15%), Diabetes (13%), or Cardiovascular problems (12%) since starting their anti-psychotic medications.

74% of FM considered their family member as either progressing in their recovery (43%) or in full recovery (31%), with 26% reporting that their family member was struggling in their recovery. Of the 17 aspects of recovery that were asked about, all were rated as very important to extremely important to respondents, with having a safe and stable place to live as the top-rated aspect.

FM respondents indicated that having the support of family, doing activities that they enjoy, and reaching out for help when they need it were also important aspects to their family member's personal recovery journeys.

Although there are research studies that have considered the above issues, these national surveys have confirmed previous findings and have done so within a current, Canadian context. Future work could attempt to add more qualitative understandings of the results of these two surveys, bringing a more personal description to complement the survey results. Additionally, recruiting persons for discussion who would not have had access to the surveys online would serve to bring an ability to better generalize (or alternatively specialize) the picture of people's experience with early psychosis or schizophrenia. It may also be interesting to corroborate the findings of these surveys with service providers who work with people with early psychosis or schizophrenia.

There continue to be many unmet needs related to broadly accessing therapies and supports that have been shown through evidence to have positive impacts on negative and cognitive symptoms of early psychosis and schizophrenia. Further research and further investment into evidence-based interventions that support recovery are much needed. So too is investment needed to study and develop antipsychotics that have fewer side effects for the individuals using them.

Quality of life continues to be significantly impacted for people with early psychosis and schizophrenia, especially in managing negative symptoms.

Experience with Drug under Review

SSC interviewed 4 patients receiving Vraylar. The patients had access to the drug under review from their psychiatrists through their private health plans. The following questions were asked.

A. *Prior to taking cariprazine, what was the burden of life like for you?*

Patient 1. Chaotic. With ups and downs. I had manic episodes and psychosis for months interfering with my sleep. Delusions were super powerful. I felt I had reckless power and unable to stop. I was sleeping 20 hours a day at times. I had suicidal ideations and made several attempts to kill myself.

Patient 2. I did not know who I was waking up with. Most days I called in to say I could not come in to work. I lost my relationship with my parents. I could not withstand he ups and downs of my illness. I tried cannabis to control it, but it made my symptoms ever worst.

B. *What has been the impact of taking cariprazine on your life?*

Patient 1. Made my life a lot more manageable. The negative symptoms were not having such a negative effect on my life, finally. My extremes are not as extreme anymore. I am regaining friends and fell more hopeful about life and my recovery. AS to my relationships I would use the word, "beautiful." My motivation is so much better and to socialize is not a burden anymore. My only side-effect is grinding my teeth but that may because of the stress of the pandemic.

Patient 2. Amazing! I thank God for this medication. I am experiencing stability for the first time since my diagnosis. I feel more normal and have goals for my life. My peer support worker has been helping me with recovery goals. But before cariprazine, our communication was crazy. I feel I am in my right mind and I do not have the G.I. problems that I had before. I now have a social life and a girlfriend. I can engage in normal conversation. My parents said, "We have our son back!" I have some akathisia, but not as much as I had before.

C. *Do you have anything to add about your experience on this medication?*

Patient 1. I feel limitless…I don't mean perfect but that I can reach some of my goals in life now. This medication has made more of a difference in my life than any other that I have been on.

Patient 2. I am not the same person I was when controlled by my mental illness. I hope this medication will reach people. But I do believe that having supportive families and friends who know how to help you and talk about recovery is important. I am thankful for my peer support worker.

D. Have you switched or gone off therapies in the past and why?

Patient 1. I was very resistant to taking any medications as I was afraid of them. Sometimes I did not take medication and did not tell my doctor. They did not seem to work and the side-effects were too bad. I had no quality to my life. I felt zombie out all the time.

Patient 2. Yes. I did not understand how they worked and I did not think I was crazy. No one explained how they worked and seemed like they were not willing to talk about side-effects like my akathisia. Also, I was not seen or heard as person, but treated as a *diagnosis.*

E. What symptoms tend to be the most difficult to treat and impacted your quality of life?

Patient 1. Depression and mania.

Patient 2. The negative symptoms and not being able to socialize

F. Do you have anything to add about your experience on antipsychotic medications?

Patient 1. Find a medication with none of those most damning side-effects.

Patient 2. Explain in detail what each medication does and why. Develop a long [acting] injectable for cariprazine.

G. For caregivers, what are the most challenging aspects or symptoms when supporting a loved one, and how have they affected your life?

Patient 1. Finding hope for each day. Knowing how to listen and not argue with me. Take care of themselves first. Family problems, dysfunctianalism are shitty for people with a mental illness. Get your own crap fixed first.

Patient 2. My parents took The Leap Program. It helped a lot with communication. I love my family, but there are members who still do not want to be around me. That hurts a lot.

A summary statement of the key values that are important to patients and caregivers with respect to the drug (Vraylar) under review would be:

- I got my life back.
- I enjoy life better.
- I feel closer to my family.
- I feel that recovery is possible.
- I am hopeful.

A specific survey was developed for those using Vraylar.

The following are the four questions and response choices included in the survey:

1. **What has been your experience with Vraylar (cariprazine) in terms of its overall impact on your quality of life?**

   Respondents could choose between the following responses: no impact, slight impact, moderated impact, great impact, or significant impact.

2. **Listed below are several (positive and negative) symptoms that you may or may not experience as part of your schizophrenia diagnosis. If you have experienced any of these symptoms, please indicate for each symptom**

whether you have noticed an improvement or have not noticed an improvement in these symptoms since taking Vraylar (cariprazine).

Negative symptoms listed - reduced motivation or apathy; reduced emotional expression or feeling; loss of interest; reduced verbal communication; social withdrawal; change in daily functioning; change in productivity.

Positive symptoms listed - hallucinations; delusions; disorganized speech and thoughts; disorganized behaviour.

For each of the listed positive and negative symptoms, respondents could choose “yes, I have noticed an improvement”; “no, I have not noticed an improvement”; or “I did not experience this symptom prior to taking Vraylar”.

3. **Listed below are several more symptoms (cognitive) that you may or may not have experienced as part of your schizophrenia diagnosis. If you have experienced any of these symptoms prior to starting Vraylar, please indicate for each symptom whether you have noticed an improvement or have not noticed an improvement in these symptoms since taking Vraylar (cariprazine).**

   Listed symptom included: difficulty with attention and memory of information; difficulties with memory in general or understanding things; difficulty with daily thinking and organizing; difficulty remembering medical related things.

   For each of the listed symptoms, respondents could choose “yes, I have noticed an improvement”; “no, I have not noticed an improvement”; or “I did not experience this symptom prior to taking Vraylar”.

4. **Is there anything else you would like to add about your experience with Vraylar (cariprazine)? (For example, any comment on side effects, how it has affected your recovery, etc.)**

   Respondents could leave other comments if they so choose.

SURVEY RESULTS

This section summarizes the responses to each survey question above.

Responses to Question 1:

Ninety percent (90%) of respondents indicated that Vraylar had either **greatly impacted (60%) or significantly (30%) impacted their quality of life.** Ten percent (10%) indicated that Vraylar had a **small impact on their quality of life.**

No respondents indicated that Vraylar had “no impact” or “moderate impact” on their quality of life.

Responses to Question 2:

In terms of the **negative** symptoms listed in question 2, the following indicates the percentages of people who experienced the symptom prior to taking Vraylar and who indicated “**yes, I have noticed an improvement**”:

- Reduced motivation or apathy: 88%
- Reduced emotional expression or feeling: 67%
- Loss of interest: 80%
- Reduced verbal communication: 88%

- Social withdrawal: 100%
- Change in daily functioning: 100%
- Change in productivity: 71%

In terms of the **positive** symptoms listed, the following indicates the percentages of people who experienced the symptom prior to taking Vraylar and who indicated "**yes, I have noticed an improvement**" since taking Vraylar:

- Hallucinations: 75%
- Delusions: 80%
- Disorganized speech and thoughts: 100%
- Disorganized behaviour: 100%

Responses to Question 3:

In terms of the **cognitive** symptoms listed, the following indicates the percentages of people who experienced the symptom prior to taking Vraylar and who indicated "**yes, I have noticed an improvement**" since taking Vraylar:

- Difficulty with attention and memory of information: 100%
- Difficulty with memory in general or understanding things: 100%
- Difficulty with daily thinking and organizing: 100%
- Difficulty remembering medical related things: 100%

Responses to Question 4:

Several respondents left comments regarding their experiences with Vraylar, including:

- "Vraylar has been a game changer. I have noticed a difference with my quality of life. I am more ambitious and alert and have a lot more energy."
- "Was the only antipsychotic medication that did not cause intolerable side effects."
- "I was unable to take other antipsychotics (such as aripiprazole and brexpiprazole) due to side effects. Cariprazine is both tolerable (fewer side effects) and effective for me. I find myself enjoying a higher quality of life on cariprazine."
- "Very good!"
- "Excellent side effect profile. No weight gain."

DISCUSSION AND CONCLUSIONS

This survey, while small, has described the current experiences expressed by persons with lived/living experience of schizophrenia in relation to the use of Vraylar.

Ninety percent of survey respondents reported a great impact or significant impact on their quality of life since using Vraylar, which is striking. Past research has demonstrated that the severity of psychiatric symptoms is one of the elements influencing quality of life (Galuppi et al 2010), so the response to this quality-of-life question is not surprising within the context of the responses to the survey questions about the impact of Vraylar on negative, positive, and cognitive symptoms.

A high percentage of respondents reported noticing improvements in all categories of symptoms. Of significant note is the improvement experienced in the negative symptom and cognitive symptom categories. Research suggests that negative symptoms may "contribute more to poor functional outcomes and quality of life for individuals with schizophrenia than do positive symptoms" (Velligan, 2014). It is further recognized that "it is the cognitive deficits that drive much of the disability seen in this illness" that can limit social and occupational functioning (Green et al, 1996). One research study demonstrated that "patients with better cognition are more likely to be in full- or part-time employment within two years of diagnosis" (Tandberg et al, 2011). Findings such as these

indicate how important cognition and the reduction of negative symptoms are to the recovery journey and in gaining meaningful roles in the community.

While there is a large body of research that has demonstrated that antipsychotic medications are effective in reducing positive symptoms of early psychosis or schizophrenia, it is well known that the evidence is less apparent for their effect on negative symptoms. Further, research findings on the effects of antipsychotic medications on cognitive functioning are mixed. Generally, however, it is felt that cognitive deficits are to a great degree unresponsive to previously developed antipsychotic medications, and it has been suggested that “despite a very significant investment by the pharmaceutical industry for over a decade, no proven pharmacological treatments have been found for this disabling aspect of the illness” to date (Carter et al, 2015). The results of this survey offer some hope for the future in this regard!

Clearly, it is critical to have medication options available for people living with schizophrenia that will address their negative and cognitive symptoms, as well as their positive symptoms. Having such options will support a better quality of life and a hopeful recovery journey for many people. This small survey provides a glimpse into the ways in which Vraylar has been successful in impacting quality of life for people living with schizophrenia and the importance of having medication options such as Vraylar available to people who need it

Companion Diagnostic Test

N/A

Anything Else?

We have attempted to address the questions from my 30 years of experience working in the “schizophrenia recovery movement.” I have tried to avoid medical terminology. Near impossible. Schizophrenia is very heterogenic. If you have met one patient with schizophrenia, you have met just ONE patient." Treatments are heterogeneous also at this time. Doctors are challenged with trying to match a medication(s) to the unique cluster of symptoms that the patient presents with. There is no cure for schizophrenia. But there can be better therapies! Doctors need the ability to prescribe accessible medications that may address the unique features of the patient’s symptomology. And if this HAPPENS, then all the other therapeutic treatment outside of pharmacological care ARE ENHANCED!! Negative symptoms are more demoralizing than positive symptoms in my 30 years of experience. They create more social stigma than the positive symptoms. Social inclusion is part of recovery. Unaddressed negative symptoms lead to social exclusion. Talk therapies and addressing unresolved trauma is also important, as is family education from a recovery philosophy.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No. Both affirmed by SSC, IAM, SSA, CMHA Alberta, MDSC.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   For SSC, Fran Schellenberg and Associates (Winnipeg) helped to conduct the surveys.

   For IAM, SSA, CMHA Alberta, MDSC, “We did not receive any help from outside our patient group.”

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Financial Disclosures

Check appropriate dollar range with an “X”. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
For SSC: AbbVie Canada Funding for “Your Recovery Journey” revision			X	
For IAM: 2022: PROGRAM NAME: Expanding knowledge sharing & community education 2023 PROGRAM NAME: Your Toolkit Project			X	
For CMHA ALBERTA We received funding for Major Depressive Disorder research from Janssen Pharmaceuticals over the last three years				
For MDSC: We received sponsorship from the pharmaceutical industry for support for a wide variety of projects and initiatives over the years including; AbbVie Canada for sponsorship of the Defeat Depression mental health campaign, and for sponsorship of the 2023 Report Card on Access to Mental Health Medications in Canada Eisai To support MDSC in our communication, knowledge dissemination and analysis to affect our government engagement on issues related to public policy, also for sponsorship of MIRA (Mymira.ca) the AI mental health chatbot available to all Canadians and organizations, and sponsorship of the 2023 Report Card on Access to Mental Health Medications in Canada Pfizer Inc. For sponsorship of MIRA (Mymira.ca) the AI mental health chatbot and the Defeat Depression mental health campaign Lundbeck for sponsorship of MIRA (Mymira.ca) the AI mental health chatbot and the Defeat Depression mental health campaign, and for sponsorship of the 2023 Report Card on Access to Mental Health Medications in Canada Janssen Inc: for sponsorship of project: Collaborative Innovative Approaches to Improve Mental Health Outcomes in Canada, for sponsorship of MIRA (Mymira.ca) the AI mental health chatbot, and for sponsorship of the 2023 Report Card on Access to Mental Health Medications in Canada, for engagement as a member of the Patient Centricity in HTA initiative committee. Novartis Inc; for support for our national project: MDSC Canadian Patient-Led Mental Health Organizations 2022				X

Forum –and for Sponsorship of MDSC Enabling and Empowering Canadian Patient-Groups 2023				

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

Name: Dr. Chris Summerville
Position: CEO
Patient Group: Schizophrenia Society of Canada
Date: January 5, 2024

Name: Mary Alberti
Position: CEO
Patient Group: Institute for Advancements in Mental Health
Date: January 5, 2024

Name: Dave Gallson
Position: National Executive Director
Patient Group: Mood Disorders Society of Canada
Date: January 5, 2004

Clinician Input

CADTH Project Number	
Generic Drug Name (Brand Name)	**Caripiprazine (Vraylar)**
Indication	**Schizophrenia**
Name of the Clinician Group	**National Advisory Board**
Author of the Submission	**Pierre Chue**

About Your Clinician Group

The National Advisory Board (NAB) group is comprised of psychiatrists with considerable and current clinical Canadian experience in the management of schizophrenia; many of whom have contributed to clinical guidelines, designed care pathways and medication algorithms, developed specialized programs, and been members of drugs and therapeutic committees.

Information Gathering

Clinical experience (interviews and meetings with patients, families, caregivers), advisory board meetings, literature reviews, conferences, and discussions with colleagues and clinical team members.

The NAB group emphasises that evaluation of a drug in this context should be evidence- AND practice-based; the latter informs as to real-world and therefore relevant and meaningful outcomes for Canadian patients.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Schizophrenia is a chronic, disabling and complex disorder to treat. There is considerable heterogeneity in presentation and unique variability in response. Symptoms may involve multiple symptom domains – positive, negative, cognitive and depressive.

The range of newer antipsychotics available in Canada is limited by comparison to other countries and further limited by disparate and delayed reimbursement. Existing, available antipsychotics focus primarily on positive symptoms.

There are no treatment options in Canada for patients with persistent negative symptoms, with the exception of clozapine, which is indicated for treatment refractory schizophrenia only. There are however numerous options available in the US, Europe and other jurisdictions.

Even within Canada, there is inequity of access to approved medications. For the drug being considered in this review, cariprazine is now reimbursed for veterans, NIHB, and federal programs as well as those who are in forensic and correctional facilities, and supported private plans, but NOT for patients supported by provincial social programs (with the exception of Quebec), who in fact, represent the majority of patients with schizophrenia. This is morally, ethically, and clinically unacceptable and a violation of rights*.

*"Poor access to medicines for more than a million Canadians is more than a health risk and an economic burden, it is a rights violation."

Perehudoff K, Persaud N, Forman L. The human right to essential medicines applies to Canadians. Can Fam Physician. 2021;67(6):400-402.

4. Treatment goals.

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Schizophrenia is a severe and chronic mental illness correlated with significant physical and psychiatric comorbidities. Ideal treatments would address the constellation of symptoms, the most important being positive, depressive, negative and cognitive symptoms.

Negative symptoms do not currently have effective treatment options; they are strongly correlated with cognitive dysfunction, poorer quality of life (QoL), increased disease burden and higher costs – all of which lead to overall worse outcomes. Poorly controlled symptoms contribute to increased all-cause mortality including suicide in this already disadvantaged and marginalized population.

An ideal treatment should be associated with improved tolerability, and it is the experience of the NAB group that cariprazine is amongst the best tolerated antipsychotic medications, of all the current classes.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

Not all patients respond to available treatments

Patients become refractory to current treatment options

No treatments are available to reverse the course of disease

No treatments are available to address key outcomes

Treatments are needed that are better tolerated

Treatment are needed to improve compliance

Formulations are needed to improve convenience

Response:

Schizophrenia is a difficult disorder to treat, and many individual patients do not respond adequately to currently available treatments. While a third of patients are deemed refractory to currently available treatment options, a much greater proportion show a partial response in various symptom domains. Currently there are no effective treatments for these other symptom domains other than for positive symptoms. Furthermore, limitations of current treatments with respect to tolerability lead to poor adherence and contribute to further physical comorbidity burden.

It is absolutely necessary to be able to offer patients in Canada treatment options for both positive and negative symptoms (and in the future for cognitive symptoms when these medications are available) that are well tolerated and acceptable.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population? Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Up to 60% of schizophrenia patients have negative symptoms (including from the onset of the illness), however current treatments typically focus on the positive symptoms.

Studies that focus on negative symptoms are extremely difficult to conduct in terms of specificity, recruitment, and retention.

Of available options, cariprazine is unequivocally an important addition to the pharmacotherapeutic armamentarium and offers individual patients, the potential of some improvement and therefore, for the first time, hope.

Given the idiosyncratic response to medication individual benefit may appear small at a population level but for the individual it can be life changing. Thus, the rigid application of thresholds for Minimal Important Difference (MID) or Positive and Negative Symptom Scale (PANSS) change is NOT relevant at an individual real-world patient level (for patients who would likely not have been eligible for a registration study). These thresholds have been applied inconsistently across submissions for antipsychotic agents over the last decade. Furthermore, efficacy and safety data are already extensively reviewed by the Therapeutic Products Directorate (TPD) of Health Canada in the context of Notice of Compliance (NOC), which cariprazine received in April 2022.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Cariprazine is a partial dopamine agonist, characterized as a third-generation antipsychotic (TGA), with a strong and unique affinity for the D3 receptor. This mechanism of action (MOA) is believed to have potentially more effects on negative and depressive symptoms. This novel MOA is driving research in a new direction with agents e.g., brilaroxazine (clinical trials NOT conducted in Canada) * and lumateperone (NOT available in Canada) *.

This MOA represents a novel intervention for patients, but TGAs are often introduced after previous treatment with ineffective or poorly tolerated antipsychotics. As mentioned, up to 60% of patients experience negative symptoms and these are often present from the onset of disease. Therefore, a treatment that could and should be offered at the start of the disease will manifestly alter the trajectory and outcome of patients.

Given the NAB group's clinical experience with cariprazine this treatment is undoubtedly a first-line treatment and earlier use of agents such as cariprazine that have the potential to ameliorate the course of the illness are therefore likely to shift the current treatment paradigm in terms of a focus on earlier use. If we use this drug early, we have the greatest potential for improving outcomes including recovery. There is no other area of medicine where the best treatment is not offered at the stage of the illness when it would have the most impact.

The NAB group recommend that given the MOA, results of studies and clinical experience, cariprazine should be available without restrictions early in treatment rather than as a last option.

* Despite the establishment of the Drug Safety and Effectiveness Network (DSEN) in 2009 to develop relationships between CIHR and Health Canada this has not translated into an improved research or reimbursement environment in Canada for psychotropic medications, with the net result that the most disadvantaged Canadians continue to be deprived of access to the latest treatments:

https://lifesciencesontario.ca/canada-may-be-losing-its-status-as-a-top-global- destination-for-new-medicine-launches/

https://www.ispor.org/heor-resources/presentations-database/presentation/euro2023- 3785/132078

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

From a clinical perspective, it is important to choose the BEST treatment for the individual patient based on patient and disease characteristics and who will likely benefit from the selected medication. In many instances, this is likely to be the agent most effective in targeting the RELEVANT symptoms and LEAST likely to produce side effects. Side effects may cause a patient to reduce or discontinue treatment as well as not accept other medications in the future. Therefore, it makes clinical sense to use the best agent as first line treatment. As clinicians, we are sworn to first do no harm “primum non nocere”. We also do not want to create a situation of therapeutic nihilism that will increase patient resistance and worsen adherence.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

The more medications are switched, the less likely patients are going to respond so therefore it is important to choose the “RIGHT drug” for the “RIGHT patient” first.

Therefore, the NAB group considers caripazine as a first line agent for the appropriate patient and it should be used as early as possible in the treatment.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review? Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Approximately 60% of patients have significant negative and/or depressive symptoms. These are patients that have not historically responded to current available treatments. These symptoms are associated with worse outcome, poor QoL and impaired functionality.

Cariprazine, should be offered, and ideally early, in the course of treatment to increase the possibility of better overall outcome. In addition, patients that have not fully responded over time (but not TRS), should also be considered for treatment with cariprazine as individual benefit cannot be fully explored until a patient has had the opportunity to receive the medication for an adequate time (and without the fear that samples will run out).

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify) Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

In general, depressive and negative symptoms are readily identifiable, but at the same time have been difficult to treat; there are very limited options specifically targeting these symptoms. Again, more than 60% of patients with schizophrenia will experience depressive symptoms with at least a third meeting criteria for a Major Depressive Episode. Approximately 10% of patients with schizophrenia will commit sucicide.

In practice, positive, negative, and depressive symptoms are identified through clinical examination. Rating scales such as the Calgary Depression Rating Scale and the NSA-4 are available but typically used in academic and research settings to assess specific symptoms. DASA and WHODAS II (replaced GAF in DSM- 5) are more common in clinical and medical assessment settings.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Treatment refractory patients and patients with co-morbidities (likely individuals with intellectual impairment, acquired brain injury), would be least likely benefit from this treatment.

There is increasing evidence that antipsychotics with partial dopamine agonist activity may be the more effective agents for patients with substance use (the most common comorbidity for patients with schizophrenia).

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

As with other psychiatric (medical) conditions early intervention is associated with better outcomes and this is especially true for schizophrenia. Early psychosis and generally younger patients are most likely to respond to treatment with cariprazine. Patients with predominant/persistent negative symptoms are also likely to benefit. Patients who experience issues with emotional blunting, motivation, anhedonia and possibly cognition (certainly if related to sedation) will benefit from a drug that has a partial dopamine agonist MOA. Finally, patients that experience side effects with existing agents e.g., hormonal dysfunction (leading to sexual dysfunction, osteoporosis) with risperidone and paliperidone, metabolic syndrome (leading to diabetes, dyslipidemia, obesity) with olanzapine, sedation with quetiapine, etc.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

In clinical practice, favorable outcomes are determined by multidisciplinary clinical observation supplemented by patient and caregiver report rather than the use of specific scales. The NAB group emphasize that this be given equivalent value in evaluating the benefit of a treatment in this context.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*
- *Consider the magnitude of the response to treatment. Is this likely to vary across physicians?*

Response:

In clinical trials, response is often defined as reduction in key evaluative scales e.g. PANSSS, however in clinical practice, reduction in symptoms, improvement in quality of life, and functionality represent the most relevant goals. In addition, control of symptoms, gaining stability of illness, and preventing recurrence or relapse are measures of successful treatment.

The magnitude of the response to treatment varies between patients but may be accrued over time. This is where issues of tolerability and persistence with treatment become important. It should be noted that registration trials are typically short-term but long-term experience is gained in the real world (where cariprazine has been available for several years – since 2015 in US). Data from these populations are deemed observational and enriched and thus often given little to no credence even though this a measure of a drug's real-world effectiveness.

There is growing research initiative to conduct clinical trials with novel design that are e.g., adaptive /evolutive, focus on Patient Reported Outcome Measures (PROMs - QoL, subjective wellbeing, functionality, use multiple endpoints (including AI-measured), and actually recruit the target population rather than the standard registration Randomized Control Trials (RCTs). These data are just as important, if not more so, when considering individual benefit.

6.10. How often should treatment response be assessed?

Response:

Patients with schizophrenia are vulnerable and complex patients with both inherent and acquired health issues that do need to be assessed regularly. The frequency and side effect profile of capriprazine is well established and very favorable (compared to other antipsychotics). Therefore, there should no need for additional monitoring as it relates to this treatment (ie: blood tests or other interventions) other than the standard health evaluation of patients with schizophrenia (these standard health evaluations are often missed or ignored which for other medications may have life-threatening complications).

Earlier use of agents that have little to no metabolic, hormonal or neurologic liability is important. Delaying the use of the best tolerated agents unfortunately contributes to chronic health issues and negative attitudes to treatment and consequent poor adherence and even stigma.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Discontinuing or switching treatment is likely to be determined by nonadherence or tolerability that cannot be managed adequately. Such decisions should be considered very carefully and in conjunction with caregivers and patients, with specific objectives in mind, in terms of goals of switching.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Settings would include both inpatient (acute care & rehab) and outpatient (specialist, early psychosis) programs as well as the Emergency Department (ED). The versatility and tolerability of cariprazine is such that it is also appropriate for treatment in primary care settings. In addition, the NAB goup's experience speaks to earlier discharge in inpatient settings and greater overall satisfaction with medication as well as needing less combinations and augmentation with medications for different symptoms. These are not metrics that are typically captured in clinical trials but again reflect real world experience.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

Typically, patients with schizophrenia will be managed in specialist programs by a multi- disciplinary team involving a psychiatrist. Medication decisions and choices are usually determined by the psychiatrist but after discussion with patients, team members and care givers. Family physicians in a shared-care model can play an important role in the treatment, monitoring, and support of patients with schizophrenia.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

Consistent with the collective clinical experience of the NAB group, several recent reviews and studies demonstrate the benefits of cariprazine in schizophrenia and other psychiatric conditions (as with all the other SGAs & TGAs) including acute mania (over other TGAs), negative symptoms, bipolar depression and dual diagnosis patients.

Romeo B, Blecha L, Locatelli K, Benyamina A, Martelli C. Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: Efficacy and safety J Psychopharmacology 2018;32(4): 385–396.

Brasso C, Colli G, Sgro R, Bellino S, Bozzatello P, Montemagni C, Villari V, Rocca P. Efficacy of Serotonin and Dopamine Activity Modulators in the Treatment of Negative Symptoms in Schizophrenia: A Rapid Review. Biomedicines. 2023;11(3):921.

Jain R, McIntyre RS*, Cutler AJ, Earley WR, Nguyen HB, Adams JL, Yatham LN*. Efficacy of cariprazine in patients with bipolar depression and higher or lower levels of baseline anxiety: a pooled post hoc analysis. Int Clin Psychopharmacol. 2023 Sep 20.

Grunze H. The role of the D3 dopamine receptor and its partial agonist cariprazine in patients with schizophrenia and substance use disorder. Expert Opin Pharmacother. 2023 Oct 10:1-8.

*Canadian clinicians and researchers

Many of the NAB group members shared their clinical experiences with cariprazine and several are highlighted below:

“I have previously provided this feedback to the company. I am typically “realistic, if not bordering on the side of skeptical” when it comes to the claims made by pharma when a new medication is brought to market. However, for the first time in years I have seen responses to the medication in the domains of Negative Symptoms and cognition that I have not seen to the same extent with any of the newest of the 2nd and 3rd generation antipsychotics. The improvement in the domains of speech, subjective and objectively observed emotional expression, the collateral reports from caregivers and family in areas related to socialization and engagement, and finally motivation have exceeded my expectations. The single case (in schizophrenia) where I have not seen these same results has been in an individual with co-morbid substance use and confirmed (by pharmacy) non-compliance. In addition, in every one of these patients we had a discussion about Clozapine but the patients for one reason or another chose not to trial it, but the results with Cariprazine were as, or better, than we all would have expected. Although probably not related to this submission, I have seem improvements in attentional symptoms in my Bipolar patients with and without ADHD, and have questioned whether similar mechanisms might be at play with the attentional/negative symptom improvement in Schizophrenia and Bipolar Disorder. While I never expect miracles in treating Schizophrenia, probably the most devastating of all mental illnesses, the response to Cariprazine has thus far exceeded my expectations, with my only disappointment being the limited availability due to lack of coverage.” Dr. Kevin D. Kok MD, FRCPC

“Schizophrenia remains a devastating disease, with the negative symptoms even more disabling than the more “dramatic” positive ones. I have a patient in midlife who has neither showered nor brushed his teeth for 6 of 7 months in the context of profound abulia. His positive symptoms are well-controlled. Our current pharmacological treatments, as you point out, are far from ideal. The side effect burden is quite heavy, perhaps even more so with the “gold standard” for treatment-resistant schizophrenia, clozapine. Current medications are also limited in their efficacy across symptom domains, including positive symptoms as well as negative and mood symptoms.” Dr. Michael Eleff MD, FRCPC

Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. **Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.**

   The company that markets cariprazine in Canada, AbbVie, has provided data specific to cariprazine and organized advisory panels with psychiatrists nationwide, but beyond the data provided, AbbVie has not, in any way, influenced the opinions provided in this submission which remain entirely that of the contributory NAB group members.

2. **Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.**

   The NAB group did not receive any help from outside of the group. As scientists, researchers, and clinicians the NAB group feels that we are uniquely poised to be able to synthesize the data and clinical experience in order to comprehensively evaluate cariprazine without bias or prejudice. The NAB group feels that our contribution and our expertise in the Canadian system should be considered at least equally with all other information sources.

   As the CADTH reimbursement reviews are in the public domain this document has been prepared such that it is understandable to the lay person and with the hope that patient associations, mental health advocacy groups, federal and provincial health ministries, and all stakeholders will have sight of the document.

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. Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Pierre Chue

Position: Professor, Department of Psychiatry, University of Alberta *&* Consultant Psychiatrist, Addictions and Mental Health, Alberta Health Services

Date: 1 December 2023

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

Table 1: Conflict of Interest Declaration for Clinician 1

	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		X		
Boehringer Ingelheim	X			
Otsuka		X		
Lundbeck		X		
HLS		X		
Eisai	X			
Teva	X			
Janssen			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Ruth Baruch

Position: Director of Aftercare and Rehabilitation Services, Michael Garron Hospital

Date: 07-12-2023

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

Table 2: Conflict of Interest Declaration for Clinician 2

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		X		
Eisai	X			
Boehringer Ingelheim	X			
Lundbeck	X			
Otsuka		X		
Takeda	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Taylor Kallis

Position: Adult Community Psychiatrist, Section Chief Community Mental Health Red Deer AHS

Date: 09-11-2023

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

Table 3: Conflict of Interest Declaration for Clinician 3

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	X			
Otsuka	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Reid Graham

Position: Psychiatrist

Date: 16-11-2023

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

Table 4: Conflict of Interest Declaration for Clinician 4

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	X			
Otsuka	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Toba Oluboka

Position: Director, Psychiatry Emergency and Outreach Teams, SHC, AHS and Associate Clinical Professor, U of C

Date: 20-11-2023

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

Table 5: Conflict of Interest Declaration for Clinician 5

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 and Lundbeck			X	
Janssen Pharm	X			
Abbvie/Allergan		X		
Pfizer	X			
Sunovion	X			
Purdue	X			
EISAI	X			
VIATRIS	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Atul KHULLAR MD MSc FRCPC DABPN DABSM DABOM

Position: Clinical Associate Professor, University of Alberta Dept of Psychiatry

Date: Nov 15 2023

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

Table 6: Conflict of Interest Declaration for Clinician 5

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		X		
Sunovion	X			
Otsuka			X	
Lundbeck		X	X	
Jazz Pharma		X		
Paladin Pharma	X		X	
Pfizer	X			
Takeda		X	X	
Bausch Health			X	
Elvium			X	
Eisai			X	
Idorsia		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Michael Eleff

Position: Associate Professor of Psychiatry, University of Manitoba

Date: 30-10-2023

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

Table 7: Conflict of Interest Declaration for Clinician 7 – No conflicts to declare.

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Pratap Chokka

Position: Clinical Professor of Psychiatry, University of Alberta

Date: November 30/2023

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

Table 8: Conflict of Interest Declaration for Clinician 8

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		x		
Takeda		x		
Abbvie		x		
Elvium		x		
Janssen		x		
Eisai		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. Risk Kronfli, MB FRCPC

Position: Clinical Director, ECFH

Date: 26/11/2023

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

Table 9: Conflict of Interest Declaration for Clinician 9

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		X		
Eisai	X			
Elvium		X		
ICPDHM			X	
Janssen			X	
Lundbeck			X	
Otsuka			X	
Virtual Hallway	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Dr. Martin Alda

Position: Professor of Psychiatry, Dalhousie University; Director, Mood Disorders Program, Nova Scotia Health Authority

Date: 24 November 2023

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

Table 10: Conflict of Interest Declaration for Clinician 10

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	x			
Janssen Pharmaceuticals	x			
Merck	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Dr. Robert Jay

Position: Psychiatrist

Date: 05-12-2023

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

Table 11: Conflict of Interest Declaration for Clinician 11

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	x			
Otsuka		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Dr. Jeffrey Neil Young

Position: General Adult Psychiatrist, NL Health Services

Date: 27/11/2023

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

Table 12: Conflict of Interest Declaration for Clinician 12

	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	X			
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Martin A. Katzman MD, FRCPC

Position: Clinic Director: START Clinic for the Mood and Anxiety Disorders

Date: December 7, 2023

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

Table 13: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
EISAI				X
ABBVIE		X		X
ELVIUM	X			
JANSSEN	X			
OTSUKA			X	
PFIZER				X
CANNOPY		X		
TILRAY		X		
TAKEDA	X			
LUNDBECK			X	
IDORSIA	X			
BAUSCH		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Dr. Harmeet Bami

Position: Consultant Psychiatrist

Date: 24/11/2023

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

Table 14: Conflict of Interest Declaration for Clinician 14

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	X			
OTSUKA, LUNDBECK	X			
ASTRAZENECA, BOEHRINGER, JANSSEN	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 15

Name: Dr. Irene Zouros

Position: Interim Chief Psychiatry, Brockville General Hospital ACTT Physician, Brockville General Hospital

Date: December 4, 2023

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

Table 15: Conflict of Interest Declaration for Clinician 15 – NONE TO DECLARE

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
N/A				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 16

Name: Dr. Danilo Rocha De Jesus

Position: MD, MSC, Psychiatrist, Providence Care Hospital, Kingston ON,

Date: Dec/07/2023

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

Table 16: Conflict of Interest Declaration for Clinician 16

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	X			
Otsuka	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 17

Name: Kathryn Fung

Position: Psychiatrist, Vancouver Coastal Health + UBC Clinical Associate

Date: 22/11/2023

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

Table 17: Conflict of Interest Declaration for Clinician 17

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		x		
Lundbeck		x		
AbbVie		x		
Teva	x			
Pfizer		x		
Janssen			x	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 18

Name: Dr. Kevin D. Kok, MD, FRCPC

Position: Consultant Psychiatrist, Mental Health and Addiction Services, Saskatchewan Health Authority / Clinical Associate Professor, Department of Psychiatry, University of Saskatchewan

Date: 29/11/2023

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

Table 18: Conflict of Interest Declaration for Clinician 18

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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 19

Name: Dr Kevin Dwight Kjernisted

Position: Psychiatrist in clinical practice

Date: 22/11/2023

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

Table 19: Conflict of Interest Declaration for Clinician 19

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	x			
AZT	x			
Biogen		x		
Boehringer Ingelheim	x			
Eisai	x			
Elvium	x			
Green Valley	x			
Janssen	x			
Lundbeck		x		
Novo Nordisk	x			
Roche	x			
Shire	x			
Sunovion	x			
Takeda	x			
Servier	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 20

Name: Diane McIntosh

Position: Clinical Assistant Professor, UBC

Date: 22/11/2023

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

Table 20: Conflict of Interest Declaration for Clinician 20

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: SR0827-000

Generic Drug Name (Brand Name): cariprazine

Indication: Schizophrenia

Name of Clinician Group: The Canadian Consortium for Early Intervention in Psychosis Author of Submission: Dr Philip Tibbo

About Your Clinician Group

The Canadian Consortium for Early Intervention in Psychosis (https://www.epicanada.org) is a national and bilingual not-for-profit organization of clinicians and researchers who are associated with early psychosis programs. With 55 members nation-wide, the CCEIP represents 22 early phase psychosis (EPP) programs and is a national leader in EPP service delivery, research, and education.

VISION: Towards a healthy future for Canadians in the early phase of psychosis.

MISSION: To enhance optimum care for Canadians in the early phase of psychosis through improved service models, the generation and translation of knowledge, and engagement and partnership with multiple stakeholders.

Our overall objectives include:

- Effective advocacy for development, implementation, and improvement of early intervention services
- Clinical research across the spectrum of biological, psychological and social determinants of illness and interventions, including studies of service delivery models to effect evidence-based care and policy
- Training across programs for clinicians, researchers, and trainees from all disciplines
- Development of standards for service delivery
- Engagement, partnership, and support of stakeholders in the early psychosis intervention community
- Promotion of equity, diversity and inclusion in our leadership, membership, and activities

Information Gathering

In consultation with CCEIP members and through the CCEIP Executive Board discussions, our organization identified the key information to be included in this submission. In addition, the authors reviewed the literature specific to schizophrenia in the first five years of illness (early phase of psychosis) as related to this medication.

Key clinical trials that have been reviewed:

- Durgam et al. 2014
- Durgam et al. 2015
- Kane et al. 2015
- Durgam et al. 2016
- Németh et al. 2017
- Dombi et al. 2020
- Fagiolini et al. 2020
- Rancans et al. 2021

Current Treatments and Treatment Goals

Schizophrenia is a complex, heterogeneous, and disabling psychiatric disorder that impairs cognitive, perceptual, emotional, and behavioral functioning.

There are a range of antipsychotic treatments available in Canada (though much less options than antibiotics) both in oral and injectable formulations (short and long acting). It is recommended that preference be given to second and third generation antipsychotics in the treatment of early psychosis patients due to not only their efficacy, but importantly their side effect profiles (effectiveness). Antipsychotic medications that are currently available in Canada focus primarily on positive symptoms (e.g., delusions and hallucinations) which is important for early symptom control. However, there is currently no medication available in Canada that targets predominant or persistent negative symptoms (e.g., anhedonia, alogia, amotivation), an important consideration as negative symptoms are a major driver of short- and long-term functional outcomes (not positive symptoms). There are options available that appear to be better (i.e., amisulpride) in Europe and other jurisdictions for the treatment of negative symptoms, but these currently do not exist in Canada. Cariprazine is one medication that may help this important treatment gap in Canada.

Additionally, while long-acting formulations may address high rates of partial/non-adherence in early psychosis and therefore should be offered during all phases of psychotic disorders, including the early phase, for patients who have a preference for oral medication, cariprazine has the longest half life of the available oral options due to its DDCAR metabolite.

To improve functional outcome aligned to patient goals it is ideal to have a sustained remission of illness. Early intervention during the critical period (first 5 years, in young adulthood) can help achieve the following desired outcomes:

- Improve the course of psychosis and lead to a period of stability

- Return to pre-illness social and occupational levels of functioning
- Result in a better outcome compared with intervention after the critical period
- Decrease risk of suicide

These goals are best achieved with evidence-based pharmacologic and non-pharmacologic approaches that include not only positive symptoms amelioration, but negative symptoms as well.

Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There are many obstacles to improving outcomes, which may include but are not limited to:

- Low rates of remission and remission not sustained
- Nonadherence to treatment
- Delay in adequate treatment
- Substance use
- Limited response to medication for negative symptoms, a major driver of functional outcome

At least one third of patients are refractory to currently available treatment options. Limitations of current treatments, including limited available long-acting formulations, may lead to poor adherence and contribute to further physical and psychological comorbidities. It is necessary to offer patients treatment options for both positive and negative symptoms that are well tolerated and acceptable, and when possible, in a long-acting formulation (injectable). When an oral formulation is preferred, consideration for duration of action (half-life) would be preferred.

There is a rapid period of progression of psychosis prior to and in the 3–5 years following the first presentation. The risk of relapse is high within 2 years and nearly three quarters of patients can expect to relapse within 5 years. Suicide risk is high during the early phase following a relapse.

Up to 60% of schizophrenia patients have negative symptoms as an important feature of their illness. However, current treatments typically focus on the positive symptoms. Cariprazine would be an important addition to the pharmacotherapeutic armamentarium and would offer patients another treatment option as there are promising literature/studies that illustrates it can have a specific beneficial effect on negative symptoms. There have been analyses of clinical trial data that shows promising signals for cariprazine use in early phase psychosis, including a post-hoc analysis (Dombi et al., 2020) of short-term (6 week) clinical trials that suggests efficacy of cariprazine in patients early in their disease trajectory. Dombi et al. looked at patients from 3 separate cariprazine acute phase schizophrenia trials, of which 29% had duration of illness less than 5 years. Comparing the primary trial publication n-values (Durgam et al. 2015, Kane et al. 2015, and Durgam et al. 2014) with the Dombi et al. poster, 304 of a potential 1044 (29%) CAR-treated ITT patients met criteria for duration of illness less than 5 years. In another recent publication, European psychiatrists recommended the use of cariprazine in the context of first episode psychosis based on their real-world clinical experience (following EMA approval of cariprazine in 2017) (Fagiolini et al, 2020).

Thus, our patient population that we are advocating for are those young adults in the early phase of psychosis (within the first 5 years of illness), with a focus on optimizing their long-term outcomes. The additional tool of cariprazine would indeed help these young adults with negative symptoms achieve better long-term outcomes.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Cariprazine is a partial dopamine agonist, characterized as a third-generation antipsychotic (dopamine partial-agonist), with a strong affinity for the D3 receptor. In fact, it is the only available antipsychotic that specifically targets the D3 receptor with an affinity that is

higher than dopamine itself. This unique mechanism of action is believed to have potentially more effects on negative and depressive symptoms and therefore represents a novel intervention for patients. As mentioned above, up to 60% of patients experience negative symptoms; these are often present from the onset of disease. Therefore, a treatment that could be offered at the start of the disease could alter the trajectory and outcome of patients.

Given this mechanism of action and results of studies, it would be recommended to try the treatment early, and as a monotherapy, rather than as a last option or in polypharmacy, for the majority of patients.

From a clinical perspective, it is important to choose the best drug for the individual patient based on patient and disease characteristics, and who will likely benefit from the medication. In many instances, this is likely to be the agent most effective in targeting the symptoms and least likely to produce side effects; side effects that may cause the patient not to accept other medications in the future. Therefore, it makes clinical sense to use the best agent as first line treatment. Cariprazine would be considered as a first choice among the available first line treatment options (which include other molecules such as aripiprazole and risperidone to name a few) for anyone in early phase psychosis, and with priority in those with significant negative symptoms, a current treatment gap. Also, the longer half-life of cariprazine will be beneficial for those patients choosing an oral formulation who are partially compliant; another factor in remission control.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Approximately 60% of patients have significant negative and/or depressive symptoms. These are patients whose symptoms have not historically responded to current available treatments. These symptoms are associated with worse outcomes, poor quality of life, and impaired functionality. Cariprazine should be offered, and ideally early, in the course of treatment to ameliorate negative outcomes. In addition, patients that have not fully responded over time (but not TRS), would also be considered for treatment with cariprazine**.**

In general, depressive, and negative symptoms are readily identifiable, but at the same time have been difficult to treat; there are very limited options specifically targeting negative symptoms.

In practice, positive and negative symptoms are identified through clinical examination as well as rating scales such as the Positive and Negative Symptom Scale (PANSS), Calgary Depression Rating Scale, and the NSA-4 to name a few, which aid in assessing severity of both positive and negative symptoms (and differentiating them from depressive symptoms).

Early psychosis patients are most likely to respond to treatment. With routine outcome measurement it would be possible to measure cariprazine's effects on those patients with significant negative symptoms at onset and follow up.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

In clinical practice, positive outcomes are determined by multi-disciplinary clinical observation supplemented by patient and caregiver reports, as well as the use of specific scales. For the most part, the scales used in clinical trials map onto what is used in clinical practice.

In clinical trials, response is often defined as reduction in symptoms scales (e.g. PANSS), however in clinical practice, reduction in positive and negative symptoms, improvement in quality of life, and ability to function more independently are the most relevant treatment goals. Reduction and ideally elimination of positive and negative symptoms, gaining stability of illness, and preventing recurrence or relapse are measures of successful treatment. The magnitude of the response to treatment varies between patients but is monitored on a regular basis as part of EPP service delivery.

Treatment response in an early phase psychosis population is a priority (symptom and functional response). Clinicians in Canada will follow the Canadian Schizophrenia Guidelines (2017) for specifics and additionally through standards that exist for EPP service delivery (Nolin et al. 2016).

What factors should be considered when deciding to discontinue treatment with the drug under review?

The most common factors for discontinuing or switching treatment is treatment non (or suboptimal) response, or intolerability to side effects. In early phase psychosis, if adherence is an issue, there would be the possibility of switching to a long-acting injectable antipsychotic.

What settings are appropriate for treatment with cariprazine? Is a specialist required to diagnose, treat, and monitor patients who might receive cariprazine?

Both inpatient (hospital) and outpatient (hospital outpatients and community clinics) settings. Most early intervention for psychosis programs are specialty teams located in community outpatient settings.

Additional Information

As mentioned earlier, our organization of physicians (CCEIP) work in early phase psychosis and thus with a young adult population. Publications to date allow us to feel comfortable in the use of, and welcome, this medication in our EPP clinical settings. Cariprazine's current use in the Quebec system underscores its ability in filling a treatment gap in this population. We furthermore are of the opinion that cariprazine will in fact be the optimal treatment choice for a significant percentage of patients and given the complexity of this illness, having this additional treatment option will be crucial for those individuals. Ultimately, clinicians need to find the right treatment for the right patient at the right time, and cariprazine is one of those treatments.

Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. **Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.**

   No

2. **Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.**

   Yes. AbbVie has provided data specific to cariprazine. AbbVie has not influenced the opinions provided in this submission which remain that of the contributory authors/board members.

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. Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Phil Tibbo, MD, FRCPC

Position: President CCEIP; Professor, Dr Paul Janssen Chair in Psychotic Disorders

Date: 04-01-2024

☒ 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
Janssen			X	
Abbvie	X			
Otsuka Lundbeck	X			
Boehringer-Ingelheim	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Andrea Bardell, MD, MSc, FRCPC

Position: Medical Director, On Track First Episode Psychosis Program, Ottawa

Date: 04-01-2024

☒ 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

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	X			
Janssen	X			
Abbvie	X			
HLS Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Howard C. Margolese, MD, CM, MSc, FRCPC

Position: Director, PEPP-MUHC; Director, Schizophrenia Program, MUHC; Director, Clinical Psychopharmacology Unit, MUHC; Program Director, Clinical Pharmacology and Toxicology residency program, McGill University Associate professor, Department of psychiatry, McGill University

Date: 04-01-2024

☒ **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 3: Conflict of Interest Declaration for Clinician 3

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		X		
Janssen	X			
Lundbeck		X		
Otsuka	X			
Teva	X			
BI (Boehringer Ingelheim)	X			
Newron	X			
HLS Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: SR0827-000

Generic Drug Name (Brand Name): Cariprazine (Vraylar)

Indication: Schizophrenia

Name of Clinician Group: Quebec psychiatrists working in public sector

Author of Submission: Dr. Jean-Francois De La Sablonnière

About Your Clinician Group

A group of Quebec psychiatrists who work in the public sector and who practice in both urban and rural settings. This group of clinicians want the best for their patients. They are fortunate enough to benefit from the reimbursement of carizaprine for schizophrenia, which was authorized in Quebec by INESSS in April 2023. They have been using cariprazine since June 2022 for their patients.

Information Gathering

The clinicians convened to share their perspectives on the benefits of having cariprazine reimbursed for schizophrenia in Canada. As chair, Dr. De La Sablonnière wrote the initial draft, which was subsequently reviewed and commented by his colleagues.

Current Treatments and Treatment Goals

Cariprazine is a 3rd generation antipsychotic which is indicated in the treatment of patients with schizophrenia as well as in the maintenance of schizophrenia. In Canada, it is also indicated for the acute management of manic episodes associated with bipolar affective disorders type 1 and for the acute management of depressive episodes associated with bipolar disorder. Cariprazine may also be considered in patients whose unipolar depressive symptoms have not responded to a first antidepressant treatment, given that the Canadian Network for Mood and Anxiety Treatments (CANMAT) recommends the use of alternatives for these patients. In December 2022, the FDA approved the use of cariprazine as an adjunctive therapy with an SSRI or SNRI antidepressant in the treatment of unipolar depressive episodes. In Quebec, INESSS recognized the added value of having reimbursement for cariprazine for the treatment of schizophrenia.

Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Efficacy

Short-term placebo-controlled studies have demonstrated the efficacy of carizaprine in the treatment of schizophrenia in acute psychotic episodes. Maintenance studies in schizophrenia have also shown positive efficacy results. One study by Nemeth et al. (2017) published in the Lancet showed the added value of carizaprine versus risperidone monotherapy for negative symptoms in schizophrenia. On the basis of efficacy alone, this molecule is an effective antipsychotic preventing recurrence of psychotic illness and also has the added value of improving the negative symptoms of schizophrenia compared to risperidone. To date, few molecules have been able to show a benefit for reducing the negative symptoms associated with schizophrenia. In that regard, carizaprine responds to an unmet meet, and this is supported by Nemeth's study (2017).

Safety

Based on the clinicians' experience using carizaprine, they recognize that this molecule has an exceptional tolerability profile, placing it in the therapeutic arsenal with one of the most favorable tolerability profiles. Carizaprine has minimal metabolic impact, low risk of weight gain, and absence of metabolic-related complications in terms of hyperglycemia, risk of diabetes, and alterations in lipid levels. The reported adverse effects associated with cariprazine include transient extra-pyramidal symptoms and akathisia, which are manageable and do not pose significant obstacles to long-term treatment. Adverse events that are more likely to cause treatment

discontinuation include excessive drowsiness, cognitive disturbance, sexual dysfunction, metabolic effects, as well as hormonal and weight-related changes. These events are less of a concern with dealing with cariprazine.

Carizaprine has demonstrated excellent tolerability in the majority of patients. In our experience, even patients who initially show ambivalence toward treatment or who have fears of impaired cognitive function associated with antipsychotic interventions find themselves willing to try cariprazine due to its positive tolerability. After trying it, many patients are much less reluctant to continue with the medication because they experience a lack of adverse effects or a change of their subjective sense of self. The absence of perceived cognitive disturbance represents a significant added value, improving treatment adherence, compliance, and overall acceptability, which is imperative for the success of therapeutic interventions in schizophrenia and for recovery.

Adherence

While adherence has not been specifically addressed in studies involving cariprazine *compared to other antipsychotics*, there is a suggestion of potential added value for patients with this medication. A key factor contributing to relapse in schizophrenia is treatment discontinuation, which is primarily driven by the presence of side effects and the convenience with which patients can stop their oral medications. Injectable drugs have emerged as a compelling alternative to overcome adherence problems. However, as we will demonstrate it later in this text, the real-life practice highlights a general underutilization of these treatment options.

Relying solely on evidence-based data to form clinical opinions can sometimes be precarious. It's important to remember that the scientific process aims only to reject the null hypothesis, demonstrating that an association is not due to chance. Clinicians' empirical perceptions may thus underestimate the relevance of one therapeutic alternative compared to another. For example, initial attempts to show the added value of injectables were faced with challenges, exemplified by Leucht et al. (2011), which initially found little difference in efficacy between oral and injectable drugs for schizophrenia. However, further studies shed light on the discrepancy between laboratory settings and real-life scenarios using mirror-image studies (Kishimoto et al., 2013). Notably, real-life studies unveiled that in the 30 days after being hospitalized, 50% of patients abandoned their treatment (Tiihonen et al., 2018).

In the real world, studies looking at treatment in chronic conditions show that, at best, 25% of patients take their medication as prescribed, 25% do not take it and 50% make efforts to take their medication as prescribed despite challenges, which results in skipping doses from time to time. The link between missed doses and the risk of schizophrenia relapse is well established in the literature, which suggests a need for a molecule that can address problems with adherence.

In real-world practice, clinicians tend to consider that a medication with demonstrated efficacy, fewer side effects, more benefits compared to risks (favorable benefit-to-risk ratio), and a long half-life should be considered the best treatment option. These are all characteristics shared by cariprazine

Long half-life of cariprazine

The long half-life of cariprazine, while not yet clinically demonstrated, is regarded by clinicians as a potentially impactful characteristic. Specifically, the second metabolite (didesmethyl cariprazine) has a half-life of up to three weeks. This allows clinicians to view the molecule like a long-acting oral drug. Cariprazine's half-life, nearly on par with certain injectables, offers a forgiving aspect for patients who occasionally miss doses, owing to the extended duration of the medication's effectiveness.

Pharmacodynamics

Cariprazine distinguishes itself from other antipsychotic alternatives given its unique pharmacodynamic profile. Notably, it has the strongest affinity for D3 receptors compared to other antipsychotics. These receptors are a key focus in current studies on substance use disorders and impulse control disorders, believed to influence motivation, the desire to engage in activities, and alertness. A pivotal study by Nemeth et al. (2017) supported the hypothesis of D3 receptor significance by comparing the effects of cariprazine versus risperidone in treating the negative symptoms of schizophrenia. The findings underscore that targeting the D3 receptor can indeed improve negative symptoms, alertness, and deficit schizophrenia. In essence, this study provides empirical evidence for the influence of D3 on negative symptoms (Nemeth et al., 2017).

Acceptability

The impression among clinicians is that cariprazine has remarkable tolerability and minimal side effects, which renders it more acceptable than alternative antipsychotic medications. Since patients may view this option as more acceptable, their adherence to the treatment tends to improve. Even patients with partial adherence can reap the benefits. We can draw a parallel with clozapine,

which, despite being an oral medication with many side effects, maintains surprisingly high treatment adherence. This is likely attributed to clozapine's efficacy in cases where other antipsychotics falter, contributing to improved adherence. While cariprazine may not surpass clozapine in terms of efficacy in treating resistant disorders, its acceptability among patients underscores its distinctive value.

In several patients experiencing negative or treatment-resistant symptoms, including those already on clozapine, there is indeed an added benefit of using cariprazine in terms of increased alertness, vigilance, and a reduction in negative symptoms. When dealing with treatment-resistant patients on clozapine, the clinicians also noticed a decrease in clozapine-induced drowsiness. The added benefits of cariprazine in conjunction with clozapine treatment may allow a decrease in the dose of clozapine without adversely affecting the treatment of positive symptoms. The heightened alertness and reduction of clozapine-induced drowsiness may also facilitate an augmentation of the clozapine dosage, therefore increasing the likelihood of treatment response and remission. Moreover, for some patients, the impact on negative symptoms is substantial enough to mitigate the drowsiness and lack of energy associated with clozapine, improving overall adherence and acceptability.

Real-world evidence from clinical practice

These psychiatrists have been using cariprazine in their clinical practice for the past year. Their experience is that cariprazine works as well as the evidence suggests. It is an effective anti-psychotic, an effective antimanic and an effective bipolar and unipolar (in adjunct treatment) antidepressant. The large majority of patients have virtually no side effects. Dr. De La Sablonnière's personal experience involves over 100 patients to whom has prescribed cariprazine for various indications (the vast majority for schizophrenia, but also bipolar disorders, schizo-affective disorders, unipolar depression disorder, with and without substance use disorders).

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Comparison with long-acting injectable antipsychotics

Some may argue that long-acting injectable antipsychotics should be favoured to oral antipsychotics. However, the literature consistently shows that even in the most rigorous clinical settings with an algorithmic approach that favors access to injectable medication, there are still 65% of patients on oral medications (Agid et al., 2022). In Canada, the reality is that only about 6% of patients undergoing treatment for schizophrenia opt for injectable medications. Most patients forego injectable treatment for various reasons, including refusal, tolerability issues, or a lack of response to injectable medications. Therefore, it is evident that injectables are not a universal solution. In general, cariprazine stands out as the most coherent oral alternative to address the challenge of non-adherence. By doing so, cariprazine can ensure robust maintenance of schizophrenia treatment in the real-world.

Antidepressant effects of cariprazine

The antidepressant benefits of cariprazine are apparent, even in cases where it is not employed for the treatment of bipolar depression. When administered to schizophrenic patients, there were improvements in daily functioning and adaptive capacities compared to alternative treatments. Notably, even in individuals who are not in a depressive phase, like those with schizoaffective disorder, cariprazine is reported to bring a sense of happiness. While our focus is not on treating depression, many patients on cariprazine express improved alertness and vitality, a result that has been confirmed by other psychiatrists. In Dr. De La Sablonnière's experience, cariprazine has proven to be transformative for patients struggling with severe substance use disorders. It significantly diminishes the desire for substance use, facilitating greater adherence to psychosocial rehabilitation efforts. The observed impact of cariprazine on reducing substance use cravings has been a pivotal factor in promoting engagement in rehabilitation for these patients struggling with both a psychotic illness and substance use.

We should therefore consider the potential impact on substance use. Remarkably, 50% of individuals with schizophrenia also have a substance use disorder, predominantly involving alcohol or drugs such as cannabis. Moreover, approximately 10-15% have an opioid use disorder, which contributes to the ongoing opioid crisis in Canada. Cariprazine may have a positive impact on concomitant substance use disorders by attenuating the reinforcing circuits and the appetite for substance use. To date, clozapine is the only molecule with such a benefit. Therefore, cariprazine would introduce a promising option for intervention in patients with concomitant substance use disorders given its benefit-to-harm profile compared to clozapine. More research efforts should aim at demonstrating the potential benefits of cariprazine on substance use.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

First and foremost, cariprazine can be promising for schizophrenia patients who have not yet demonstrated resistance to treatment. It can also be useful in patients with persistent negative symptomatology despite the use of standard-of-care therapies, and patients who have experienced partial benefits from clozapine but still have treatment-resistant symptoms. Finally, cariprazine could be a favorable intervention for patients with schizophrenic disorders featuring an affective component (ex. bipolar disorder spectrum).

Cariprazine is particularly relevant for patients with treatment adherence concerns and reluctance to the use of long-acting injectable antipsychotics. This might include individuals facing challenges with treatment adherence, those who have not responded well to previous treatments, and those who have encountered tolerability issues with the limited available injectable alternatives, which only include variations of paliperidone and aripiprazole. In these scenarios, cariprazine presents itself as a compelling and potentially beneficial option for patients.

What factors should be considered when deciding to discontinue treatment with the drug under review?

The exceptionally long half-life of cariprazine is a significant protective factor against withdrawal symptoms, as there is essentially no withdrawal effect. With a half-life of up to 3 weeks, it may take approximately 15 weeks to completely eliminate the drug from the system. This extended duration helps mitigate the risk of withdrawal, rebound psychosis, and other adverse effects such as cholinergic rebound. However, the potential concern associated with a lengthy half-life is the prolonged presence of side effects. Given cariprazine's tolerability profile, this is rarely a concern.

Additional Information

Clinicians with experience using cariprazine conclude that cariprazine works effectively and demonstrates remarkable tolerability. It delivers the added value anticipated for our clientele with schizophrenia. Canadian patients with schizophrenia deserve access to this beneficial treatment option.

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Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. **Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.**

Yes, assistance was received to complete this submission. A medical writer from a medical education agency transcribed my (Dr. De La Sablonnière's) responses to each question and translated them to English. Furthermore, the medical writer compiled all the comments and incorporated them into the document. The final version was approved by the clinician group.

2. **Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.**

   No help was received to analyze the information used in this submission. However, as mentioned above, the medical writer collected the responses from me, Dr De La Sablonnière, and transcribed them into the document. The medical writer also compiled any comments received from the clinician group and added them to the document.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr Jean-François De La Sablonnière

Position: Médecin psychiatre, CISSS du Bas St-Laurent

Date: December 21, 2023

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

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie		X		
AMPQ / CPA / AMO(Q/BSL/RSL/Y)			X	
HLS	X			
Janssen	X			
Jazz Pharmaceuticals	X			
Lundbeck/Otsuka	X			
Animateur chronique santé mentale SRC – l'Heure de l'est	0$			
External expert: INESSS				
Expert Clinique de référence				

• HLS • Lundbeck				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr Marc-André Roy

Position: Full professor, Department of Psychiatry and Neurosciences, Faculté de Médecine de l'Université Laval; Director, RAPPSoDIS Lab and CAP-Rétablissement Research Teams, Centre de Recherche CERVO; Psychiatrist and medical director, Clinique Notre-Dame des Victoires (Institut universitaire de Santé mentale de Québec du Centre intégré universitaire de Santé et Services sociaux de la Capitale nationale)

Date: December 28, 2023

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

Table 1: 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	X			
Viatris	X			
Otsuka-Lundbeck	X			
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr Luc Cossette

Position: Psychiatre, chef de service en psychiaatrie, Hôpital de Alma

Date: December 21, 2023

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

Table 3: Conflict of Interest Declaration for Clinician 3

	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	X			

Eisai			X	
Lundbeck		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr Louis-Martin Dussault

Position: Psychiatre, CISSS Montérégie-Centre

Date: December 23, 2023

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

Table 4: Conflict of Interest Declaration for Clinician 4

	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			X	
HLS Therapeutics		X		
Janssen Pharmaceuticals	X			
Lundbeck		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dre Myriam Lemire

Position: Psychiatre, Hôpital Charles LeMoyne

Date: January 2, 2024

☒ **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 5: Conflict of Interest Declaration for Clinician 5

	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		X		
Otsuka Lundbeck		X		
Jansssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr François-Xavier Roucaut

Position: Psychiatre Professeur adjoint de clinique chez Université de Montréal

Date: January 4, 2024

☒ **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 6: Conflict of Interest Declaration for Clinician 6

	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	x			
Lundbeck	x			
AMOM	x			
Takeda	x			
Janssen	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr Joël Des Rosiers

Position: Psychiatre, Charlemagne

Date: December 27, 2023

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

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Lundbeck	x			
AbbVie	X			
Otsuka	X			

* Place an X in the appropriate dollar range cells for each company.