Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Cariprazine (Vraylar)

Indication: The treatment of schizophrenia in adults.

Sponsor: AbbVie Corporation

Recommendation: Reimburse with Conditions

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that cariprazine be reimbursed for the treatment of schizophrenia in adults only if the conditions listed in **Error! Reference source not found.** are met.

This recommendation supersedes the CADTH CDEC recommendation for this drug and indication dated August 26, 2022.

Rationale for the Recommendation

Schizophrenia is an incurable, chronic, heterogenous, and debilitating illness. Although several drugs are available for the treatment of schizophrenia, most are only effective in treating positive symptoms. CDEC recognized that substantial unmet needs still exist for the treatment of negative symptoms, which have significant impacts on health-related quality of life (HRQoL) and long-term function. While there was evidence of treatment benefit in the Positive and Negative Syndrome Scale (PANSS) total score relative to placebo, and some evidence suggestive of improvement of negative symptoms compared to risperidone, it remains uncertain whether cariprazine offers a treatment benefit compared to other reimbursed treatments for schizophrenia. However, CDEC acknowledged that cariprazine may represent an additional treatment option with an acceptable safety profile.

As outlined in the 2022 CDEC final recommendation for the original review of cariprazine, three 6-week double-blind randomized controlled trials (RCTs; MD-16, MD-04, and MD-05) demonstrated that cariprazine was associated with statistically significant improvements in symptoms of psychosis compared with placebo in adults experiencing an acute exacerbation of schizophrenia. In the 26-week RCT (188-05) in adults with schizophrenia and predominant negative symptoms (PNS), treatment with cariprazine led to a greater improvement in the Positive and Negative Syndrome Scale (PANSS) factor score for negative symptoms and functional status compared with risperidone. Although the between-group differences were statistically significant, the clinical relevance of these outcomes is uncertain because the minimal important difference (MID) to show a clinical benefit in negative symptom scores is unknown, and the between-groups difference for functional status based on the Personal and Social Performance Scale (PSP) did not exceed the identified MID. Comparisons to other available treatments were only available through indirect evidence, though CDEC was unable to determine the efficacy and safety of cariprazine relative to other comparators due to the limitations of the indirect evidence submitted in the original submission and resubmission.

Evidence informing the resubmission was intended to address the gaps identified in the previous review. This included a post-hoc responder analysis of the MD-16, MD-04, and MD-05 trials, an updated analysis of the sponsor-submitted network meta-analysis (NMA), and 2 real-world evidence studies. In the 20% responder analysis of PANSS total score, cariprazine was favoured over placebo. In the updated NMA, there was no difference between cariprazine and other antipsychotics for outcome of change from baseline in PANSS total score, proportion of patients with 30% response, or relapse rate. In the RWE studies, patients treated with cariprazine experienced improvements in schizophrenia symptoms, though the clinical relevance remained unclear. Overall, the evidence submitted for the resubmission was aligned with the evidence considered for the original review of cariprazine; however, it was subject to considerable limitations and a high level of uncertainty owing to the post-hoc nature of the evidence, the heterogeneity in the NMA, and the quality of evidence of the RWE studies. As such, this evidence was only considered supportive of the treatment effects observed in the original submission. Patient and clinician groups emphasized the need for treatments that effectively minimize the negative symptoms of schizophrenia due to their debilitating nature and impact on social engagement and integration, and quality of life. Patients and clinicians also cited the need for additional treatment options due to the heterogenous presentation of schizophrenia and for those who do not respond adequately to existing treatment options. Other unmet needs identified include treatments that improve functionality, that are better tolerated and have fewer side effects. As described above, the totality of evidence reviewed generally suggested a consistent positive effect of cariprazine compared to placebo on symptoms in patients with schizophrenia, however, CDEC could not reliably conclude that cariprazine results in improvements in negative symptoms. CDEC considered the tolerability profile of cariprazine to be acceptable, though the short duration of the acute schizophrenia trials may not be representative of the long-term safety of cariprazine and comparative safety evidence is lacking. Additionally, CDEC noted that there was insufficient evidence to evaluate the effect of cariprazine on HRQoL, hospitalization, or persistence with therapy.

At the sponsor submitted price for cariprazine and publicly listed prices for all other comparators, cariprazine is more costly than other atypical antipsychotics, with the exception of paliperidone. Given the uncertainty associated with the comparative clinical

evidence, the total drug cost of cariprazine should not exceed the total drug cost of treatment with the least costly atypical antipsychotic agent.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation and renewal		
1. Eligibility for reimbursement of cariprazine should be based on the criteria used by each of the public drug plans for initiation, renewal, and prescribing of other AAPs currently reimbursed for the treatment of schizophrenia.	No robust comparative evidence for cariprazine was identified. Therefore, the potential benefit of cariprazine relative to other AAPs currently reimbursed for the treatment of adult patients with schizophrenia is not known.	—
Prescribing		
2. Cariprazine should not be reimbursed for use in patients with treatment-resistant schizophrenia or used as add-on therapy to clozapine.	There is no evidence supporting the use of cariprazine in patients with treatment-resistant schizophrenia, as add-on to clozapine treatment, or those for whom treatment with clozapine has failed.	—
3. Cariprazine should not be used in combination with other AAPs.	There is no evidence to support using cariprazine in combination with other AAPs.	—
Pricing		
4. Cariprazine should be negotiated so that it does not exceed the drug program cost of treatment with the least costly reimbursed AAP for the treatment of schizophrenia	Given the uncertainty associated with the comparative clinical evidence there is insufficient evidence to justify a cost premium for cariprazine over the least expensive AAP reimbursed for schizophrenia.	—

AAP = atypical antipsychotic

Discussion Points

- CDEC recognized that management of negative symptoms of schizophrenia is an important unmet need in the current treatment paradigm, which was identified by both patients and clinicians. In the original review of cariprazine, CDEC highlighted the limited generalizability of the results from the RGH-188-05, as well as the uncertainty in the clinical relevance of the results in patients with predominantly negative symptoms due to the lack of an MID and a comparator that has not been shown to have efficacy for negative symptoms (risperidone). CDEC also considered the results of a 16-week prospective, open-label, single-arm observational study (Rancans et al., 2021) included in the resubmission, which evaluated cariprazine in patients with predominantly negative symptoms using the Short Assessment of Negative Domains (SAND). Though the results suggested an improvement in negative symptoms with cariprazine over 16 weeks, there were significant limitations to the study including the non-comparative design, the use of an unvalidated measure of antipsychotic treatment efficacy (SAND), and uncertainty in generalizability of the results. As such, CDEC could not conclude that cariprazine resulted in improvements in negative symptoms from the Rancans study, and the uncertainty in the clinical relevance of the results of the RGH-188-05 study remains. Overall, the committee could not reliably conclude cariprazine adequately addresses negative symptoms based on the available evidence, particularly relative to other treatment options. However, CDEC also discussed whether it is reasonable to allow for greater uncertainty given the burden and severity of living with schizophrenia, and the challenges of conducting clinical trials in this population. Considering this alongside the input received from the clinician input for the resubmission, which indicated that cariprazine may offer a benefit for negative symptoms, CDEC was supportive of cariprazine as an additional treatment option despite the uncertainty in the available evidence for negative symptoms.

- CDEC discussed the potential benefits of a treatment that is tolerable, with a long-acting formulation. Input from clinical experts consulted for this review and clinician groups input received for the resubmission suggested that a treatment with these characteristics may support adherence, which is a factor in achieving remission with schizophrenia. CDEC acknowledged the unmet need for tolerable treatment options and the absence of new safety signals identified for cariprazine; however, the committee noted that the available evidence has not reliably demonstrated that cariprazine meets this need.
- CDEC discussed the generalizability of the evidence for cariprazine, and the challenges associated with conducting RCTs of treatments for schizophrenia. Input from the clinical experts consulted for the resubmission indicated that even robust evidence for trials in schizophrenia may not translate to clinical practice, and that treatments for psychiatric conditions often rely on clinical experience to determine their efficacy. Further, clinical expert input and clinician group input received for the resubmission highlighted that the PANSS is not used in clinical practice. This further supports the conclusion of the committee that the evidence of treatment benefit for cariprazine is uncertain, although it may be sufficient to support cariprazine as an additional treatment option for patients living with schizophrenia.
- Despite the number of treatments currently available, no direct comparative evidence of cariprazine versus other antipsychotic drugs was available in patients with acute schizophrenia. In the 2022 recommendation issued for cariprazine, aside from two of the 6-week double-blind studies including aripiprazole (MD-04) or risperidone (MD-16) as active comparators, no statistical comparisons were made. CDEC discussed the lack of conclusive evidence directly comparing cariprazine and other antipsychotic drugs in patients with acute exacerbation of schizophrenia. No new direct comparative evidence was submitted as part of the resubmission, thus, the inability to draw conclusions regarding the direct comparative efficacy and safety of cariprazine compared with aripiprazole or risperidone in patients with acute schizophrenia remains.
- CDEC discussed ethical and equity considerations related to the use of cariprazine for the treatment of schizophrenia in adults. CDEC acknowledged that patients living with schizophrenia face multiple mental, social and occupational challenges, along with psychiatric and physical comorbidities, which present significant burdens for patients, their families and caregivers, and for health systems. CDEC acknowledged the challenges of evidence generation among a heterogenous patient population living with schizophrenia. The committee acknowledged that, despite uncertainty in the clinical evidence, clinical experts stated that they would prescribe cariprazine given the drug's manageable safety profile, significant unmet need for effective treatment (especially for negative and cognitive symptoms), and the potential value of additional treatment options to support individualized treatment for a disease that presents heterogeneously. The committee considered the potential for risk of harm given the uncertainty in the clinical evidence to support benefit over existing treatment options against the potential for benefit in a population where there is an unmet need for more, effective treatment options. CDEC considered the possibility that as an oral, long-acting medication, cariprazine may increase accessibility of treatment for some patients with schizophrenia. CDEC noted the importance of considering health equity in health systems implementation of treatment for an equity-deserving and historically marginalized patient population.
- The committee noted that based on the sponsor's indirect comparison and economic model, cariprazine may be less effective than several atypical antipsychotics available for the treatment of schizophrenia, although limitations were noted with the indirect comparisons. In the sponsor's economic evaluation, based on the sequential analysis, cariprazine was dominated (i.e., more costly and less effective) by olanzapine, asenapine, quetiapine, paliperidone, lurasidone, and risperidone. Given this clinical uncertainty, further price reductions may be warranted.

Background

Schizophrenia is a chronic mental illness that affects the way a person interacts with and understands the world. The condition is characterized by delusions, hallucinations, disorganized speech, disorganized behaviour, negative symptoms, and impaired cognitive ability. The symptoms associated with schizophrenia are categorized as either positive or negative in nature. Positive symptoms reflect a distortion of reality or abundance of perceptual normal functions (e.g., delusions, conceptual disorganization, hallucinatory behaviour, excitement, and hostility), while negative symptoms reflect a loss or restriction of normal functioning (e.g., blunted affect, emotional withdrawal, poor rapport, passive or apathetic social withdrawal, lack of spontaneity and flow of conversation, and disturbance of volition). Other general and cognitive psychopathological manifestations include motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, poor impulse control, preoccupation, and active social avoidance. The severity, duration, and frequency of these symptoms can cause social and occupational challenges.

Despite its relatively low prevalence, schizophrenia is associated with tremendous health, social, and economic burden. People living with schizophrenia are at increased risk for other medical illnesses, suicide, substance abuse, homelessness, and unemployment.

Moreover, the burden associated with schizophrenia extends beyond the individual living with the disease, to families, caregivers, and the wider community. According to national data (2016–2017), 1 out of 100 Canadians aged 10 years or older is living with a diagnosis of schizophrenia of whom 56% are men and 44% are women. The incidence of schizophrenia in Canada has been estimated to be approximately 49 per 100,000 in 2016, with an incidence of 58 per 100,000 in males and 41 per 100,000 in females. In Canada, the all-cause mortality rate in people diagnosed with schizophrenia is 2.8 times higher than in those without, and 374 people died due to schizophrenia in 2004.

Schizophrenia is diagnosed by specific signs and symptoms that prevent reality-based judgment,[7] as well as a physical examination and conduct of a thorough review of an individual's medical, psychiatric, and family history. The most recent updated diagnostic criteria for schizophrenia are defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). To receive an official diagnosis of schizophrenia, an individual must exhibit at least 2 symptoms consisting of delusions, hallucinations, disorganized speech, disorganized behaviour, and negative symptoms for at least a 1-month period, with some level of disturbance being present for 6 months.

Currently, there is no cure for schizophrenia. Treatment focuses on managing symptoms in the community and at work and includes medication and psychosocial interventions. Existing antipsychotic drug therapies fall into 1 of 2 classes: typical and atypical antipsychotics (AAP). Per the clinical experts, both typical and atypical antipsychotic drugs classes are considered to be equally effective in the treatment of positive symptoms. Currently, there are no approved medications to specifically treat the negative and cognitive symptoms, which are the most impairing for long-term function. Canadian guidelines recommend that, following an acute episode of schizophrenia, patients should be offered maintenance treatment with antipsychotic medications. Canadian guidelines also recommend the prescription of clozapine for patients with treatment-resistant schizophrenia.

Cariprazine has been approved by Health Canada for the treatment of schizophrenia in adults. Cariprazine is an AAP. It is available as 1.5 mg, 3 mg, 4.5 mg and 6 mg oral capsules and the recommended dose is 1.5 mg to 6 mg once daily. The suggested initial dose is 1.5 mg, which may be increased in 1.5 mg increments to a maximum of 6 mg daily. Cariprazine and its active metabolites have a long half-life, thus the full dose-related treatment response and the occurrence of adverse effects may be delayed.

The reimbursement request for cariprazine is in line with the Health Canada indication for the treatment of schizophrenia in adults.

Submission History

Cariprazine was previously reviewed by CADTH and received a recommendation to not reimburse for the treatment of schizophrenia in adults. The submission was initially discussed at the March 2022 CDEC meeting and was issued a "do not reimburse" recommendation by the committee. A request for major reconsideration was submitted by the sponsor, which was discussed at the July 2022 CDEC meeting and the original "do not reimburse" recommendation was upheld.

The evidence provided for the original review of cariprazine (SR0708) included 5 double-blind RCTs including 3 short-term placebo-controlled studies (MD-16, MD-04, MD-05), one placebo withdrawal study (MD-06), and one active controlled study in patients with predominant negative symptoms (RGH-188-05), 2 open-label extension studies (MD-17 and MD-11), and 3 ITCs; 2 published and 1 unpublished versus other atypical antipsychotics available in Canada.

In response to the initial draft recommendation, CADTH received written feedback from 3 clinician groups, 2 individual clinicians, and 3 patient groups. This information was discussed as part of the deliberation on the major reconsideration of the recommendation. The feedback received was consistent across stakeholder groups, which spoke to the significant impact of mental health on the lives of patients and caregivers, particularly for those living with schizophrenia, the heterogeneity of the condition and response to treatment, the challenges with conducting clinical trials in this population and correspondingly, the need for additional treatment options.

The gaps identified by CADTH within the original submission included: uncertainty of the clinical relevance of the results of the submitted RCTs, uncertainty in the reported magnitude of effect in treating symptoms for patients presenting with predominantly negative symptoms, limited evidence of the long-term effects of continued cariprazine use, uncertainty in the comparative effectiveness of cariprazine compared to relevant comparators, and uncertainty in the generalizability of the RGH-188-05 study due to the extensive screening and exclusion criteria.

The sponsor filed this resubmission based on new evidence that is intended to address the gaps identified by CADTH and considered by CDEC in the recommendation for the original submission. The evidence provided in the resubmission included:

- Two real-world evidence (RWE) studies of cariprazine. The first including patients with schizophrenia and predominantly negative symptoms, and the second including patients who met DSM-5 criteria for schizophrenia and cannabis use disorder.
- A responder analysis for the primary endpoint of the acute schizophrenia trials (MD-16, MD-04, and MD-05), as defined by a 20% change from baseline in PANSS total score,
- A meta-regression reanalysis of the originally submitted NMA.

The objective of this report is to review and critically appraise the totality of evidence submitted by the sponsor on the beneficial and harmful effects of cariprazine (Vraylar), 1.5 mg to 6 mg oral capsules in the treatment of adult patients with schizophrenia. The emphasis of the clinical review of the resubmission is to appraise whether the additional evidence submitted addresses the gaps identified in the previous review, as well as consider the new information alongside the evidence that was reviewed and appraised in the original submission (SR0708).

As such, within the present clinical report, a summary of clinical evidence from the original Clinical Review (SR0708) has been included (See Clinical Evidence from SR0708 [Original Vraylar Review]) followed by a summary of the new clinical evidence that was reviewed and appraised as part of the resubmission (See Clinical Evidence from SR0827 [Resubmission]).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 5 double blind RCTs in adults with schizophrenia; 2 long-term extension studies; 3 indirect treatment comparisons; and 2 real-world, observational studies.
- patients' perspectives gathered by 5 patient groups, the Schizophrenia Society of Canada in collaboration with the Institute for Advancements in Mental Health, the Schizophrenia Society of Alberta, the Canadian Mental Health Association (Alberta Division), and the Mood Disorders Society of Canada (MDSC)
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with schizophrenia
- input from 3 clinician groups, the Canadian Consortium for Early Intervention in Psychosis group, the National Advisory Board, and a group of Quebec psychiatrists.
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received one joint input for this review from the Schizophrenia Society of Canada (SSC) in collaboration with the Institute for Advancements in Mental Health (IAM), the Schizophrenia Society of Alberta (SSA), the Canadian Mental Health Association (CMHA) Alberta Division, and the Mood Disorders Society of Canada (MDSC). A series of interviews, focus groups, and surveys including a 2-part national survey for persons with lived experience of early psychosis and schizophrenia (N = 118 responders), and one for family members of people with early psychosis and schizophrenia (N = 121 responders) conducted between 2021 and 2023, as well as a smaller survey for those with personal experience with cariprazine were conducted between November and December 2023.

Among the patient respondents, 76% reported one or more positive symptoms, primarily delusions. One or more negative symptoms were reported by 94% of patients, mainly consisting of social withdrawal and reduced motivation. Cognitive symptoms were reported by 97% of patients and included difficulty with attention and memory. According to the patient group input, more than one antipsychotic drug may be needed to address both positive and negative symptoms of schizophrenia, along with a holistic treatment plan that includes psychosocial rehabilitation, family education, recovery-oriented mental health services, psychological support

services, substance use issues care, and trauma-informed care. The majority of patient responders (94%) were taking medications for early psychosis or schizophrenia, with drowsiness, restlessness, nausea, and weight gain being the most experienced side effects. As the negative symptoms have a major impact on social engagement and integration, patients cite the need for a medication that can address the negative symptoms of schizophrenia. This is also because none of the typical or atypical antipsychotics are able to target negative symptoms. Patients also expressed a need for treatment options that have fewer side effects. Four patients had experience with cariprazine, accessed through private health plans. Most respondents indicated that cariprazine improved the positive, negative, and cognitive symptoms associated with their disease and positively impacted their quality of life (QoL) with tolerable side effects.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Schizophrenia is a lifelong condition, and many individuals with schizophrenia do not respond to currently available treatment options, and of those that do, many become refractory to treatment. Existing treatments have burdensome adverse effects that impact QoL, compliance, and tolerability. The clinical experts emphasized that current available treatment options have minimal to no impact on negative and cognitive symptoms of schizophrenia and there is no approved treatment for negative (and cognitive) symptom domains, which are among the major predictors of functional outcomes.

Antipsychotic medications are the mainstay of schizophrenia treatment, however, treatment with antipsychotic medications is mostly effective on positive symptoms. The clinical experts indicated that the primary goal of treatment with antipsychotic medications is to treat psychosis (i.e., positive symptoms of schizophrenia) which may improve QoL, burden of illness, and safety (i.e., the reduction of suicide/violence) as well as prevent relapse, and progression of the disease. In most cases, antipsychotic medications have equal efficacy in treating the first episode of psychosis. Therefore, the clinical experts highlighted that in clinical practice, treatment usually begins with newer antipsychotic medications (i.e., partial agonists) which have a more benign and manageable side effect profile (e.g., aripiprazole). Treatment guidelines suggest two separate trials of antipsychotic medications of adequate dose and duration, followed by clozapine if response was poor (i.e., treatment-resistant schizophrenia). There are no guidelines for management of schizophrenia after failure of clozapine. Options generally include the addition of a second antipsychotic medication, a mood stabilizer, or electroconvulsive therapy (ECT). According to the clinical experts, full remission of psychotic symptoms is ideal, however, many patients will not achieve full remission. For inpatients, the main goal of treatment is to achieve a degree of symptom control, that is compatible with living in the community. For outpatients, symptom control as well as working on recovery goals (i.e. vocational, leisure, or self-care goals) become the target of treatment.

The clinical experts described the manifestation of schizophrenia as remarkably heterogenous, and thus, treatment goals for each patient could be very different. The experts noted that efficacy is not necessarily predictable, and most often comes down to trial and error. The clinical experts indicated that cariprazine could be used similarly to other AAP medications as monotherapy, though could be useful as a first-line therapy in the first episode of psychosis. Additionally, the clinical experts highlighted its potential for use as add-on therapy to other drugs when needed and may have unique benefits for patients with prominent negative symptoms. Considering there are no other options available to treat negative symptoms, the experts stated that cariprazine is a good option to try and it is expected that some patients will benefit from it. Overall, the clinical experts stated that cariprazine would be another treatment option within their armamentarium. The experts stated that based on their experience, cariprazine is overall well-tolerated and has a better side effect profile than many other antipsychotics, however, for patients sensitive to akathisia, cariprazine may not be most appropriate. The experts stated that psychiatrists are most often involved in diagnosing schizophrenia and initiating therapy, to monitor potential adverse effects. However, the clinical experts also noted that general practitioners currently prescribe and monitor many antipsychotics, thus, should be able to prescribe cariprazine following proper education. Additionally, the experts noted that no specialized setting would be required to prescribe and monitor treatment.

Clinician Group Input

Three clinician groups provided input for the submission: the Canadian Consortium for Early Intervention in Psychosis group (CCEIP; 3 clinicians contributed to the input), the National Advisory Board (20 clinicians contributed to the input), and a group of Quebec psychiatrists (7 clinicians contributed to the input).

Clinicians highlighted that early intervention with pharmacologic and non-pharmacologic approaches can help address important treatment goals such as improving the course of psychosis to lead to a period of stability, returning to pre-illness social and occupational levels of functioning, and decreasing the risk of suicide. The clinician groups agreed with the clinical experts consulted by CADTH on the place in therapy of cariprazine; as a first line antipsychotic and is particularly relevant for patients with adherence concerns and reluctance to the use of long-acting injectable antipsychotics, and those who have encountered tolerability issues given the longer half-life, and the more favourable metabolic tolerability profile of cariprazine. However, the clinician groups highlighted that patients with treatment-refractory schizophrenia or with comorbidities would be least likely to benefit from treatment with cariprazine. They also highlighted that it is necessary to offer patients treatment options for both positive and negative symptoms, and in multiple formulations to reduce symptom burden and maximize health-related quality of life (HRQoL).

In alignment with the clinical experts consulted by CADTH, the clinician groups noted that response is assessed through multi-disciplinary clinical observation to establish a reduction in positive and negative symptoms, improvement in QoL, and ability to function more independently, however, key evaluative scales for response in trials (e.g., Positive and Negative Syndrome Scale [PANSS]) are not routinely conducted in clinical practice. The clinician groups stated that discontinuation of therapy should be considered based on lack of or suboptimal response, tolerability issues (generally including excessive drowsiness, cognitive disturbance, sexual dysfunction, metabolic effects, and hormonal and weight-related changes), as well as nonadherence, of which they state that tolerability and adherence issues are less of a concern with cariprazine.

As noted by the clinical experts consulted by CADTH, the clinician groups highlighted that treatment of patients with schizophrenia is provided in both inpatient and outpatient settings, as well as the Emergency Department, often under the care of a multi-disciplinary team, with medication decisions and choices usually determined by the psychiatrist.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The 3 pivotal studies included in the original review of cariprazine were placebo-controlled trials and did not compare cariprazine to other oral antipsychotics. The resubmission includes additional evidence, including 2 RWE studies, an updated NMA designed to address CDEC's specific concerns, and a responder analysis for the primary endpoint of the acute schizophrenia trials.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Would cariprazine be used as a first-line treatment or should patients have failed less expensive options prior to consideration of cariprazine? *If not used as a first-line treatment, how many well-established AAPs do you recommend before initiating cariprazine?*	In first episode psychosis, cariprazine would be used as monotherapy in line with current guidelines for the management of schizophrenia (i.e., as one of the 2 adequate trials of antipsychotic medications of adequate dose and duration). The clinical experts noted that in more complex cases, or in treatment-resistant schizophrenia, cariprazine could be used as add-on therapy to clozapine and other antipsychotics. However, CDEC highlighted that there is no evidence in this submission to support the use of cariprazine as an add-on therapy to clozapine and/or other antipsychotics.
Per the CDEC recommendations for other AAPs (i.e., aripiprazole, brexpiprazole, and ziprasidone) treatment should be reimbursed for patients who have failed a trial of less expensive antipsychotic agents due to contraindication, intolerance, or lack of response.	CDEC noted that similar to other AAPs (aripiprazole, and brexpiprazole), cariprazine is a partial agonist, which are different than typical D2 blockers. As a general rule, partial agonists are more efficacious in the earliest stages of schizophrenia (i.e., first-episode psychosis) stabilizing the dopamine system before

Implementation issues	Response
Should initiation criteria of cariprazine be aligned with that of other AAPs in the same therapeutic space?	dopamine-related changes have occurred in the brain, which renders partial agonists less effective. As such, it is expected that cariprazine would used similarly to other partial agonists, as one of the trials of antipsychotic prior to clozapine initiation. For patients who have already been treated with multiple trials of antipsychotics, the clinical experts felt that it may be beneficial to try cariprazine as there are so few options with strong efficacy and tolerability, particularly for negative symptoms.
Considerations for continuation or renewal of therapy	
Considering the long half-life of cariprazine, changes in dosage may not be fully reflected for several weeks, requiring increased monitoring for adverse effects for several weeks. How would this be managed in rural areas where consistent monitoring and psychiatric services may be unavailable?	Clinicians would follow similar guidelines for the management of other partial agonists, which are readily prescribed in by general practitioners. The clinical experts noted that side effects associated with cariprazine are manageable, and the most frequently reported adverse event, akathisia, could be managed by a family doctor. Dosing increases and/or changes for cariprazine occur in 3-week, 1.5 mg increments to achieve the adequate dose and adequate duration. Once the adequate dose is achieved, response is assessed over a 6 to 8-week period. If patients experience some response or improvement, clinicians will try to continue treatment, but would monitor tolerability and patient preferences about the treatment experience. If there is absolutely no response, then clinicians would switch to an alternative option. The clinical experts noted that it is important to ensure that a patient has truly failed to respond to a treatment, otherwise, patients could exhaust all options within a year.
Consider alignment with renewal criteria for other drugs in the same therapeutic space (i.e., aripiprazole, brexpiprazole, and ziprasidone).	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
Psychiatric services are not always readily available in certain areas; thus, there may be issues related to accessing clinical specialists and/or special settings.	CDEC and the clinical experts noted that in line with other partial agonists and antipsychotic treatments for schizophrenia, cariprazine could be prescribed by general practitioner.
Some oral and injectable antipsychotic drugs are regular benefits on drug plans. *Would cariprazine be prescribed as monotherapy, and would all other oral or injectable antipsychotic drugs be discontinued?*	According to the clinical experts, cariprazine would be used in the same manner as other partial agonists as described above. The clinical experts indicated that cariprazine could be used as monotherapy in the right person (i.e., those with minimal relapses and minimal treatment exposure), however, in many cases a combination of therapies is required to control symptoms. CDEC noted that there is no evidence supporting the use of cariprazine as combination therapy. Lastly, the experts noted that there is a risk of relapse with every treatment switch, so patients and clinicians are hesitant to switch treatments, particularly if positive symptoms are in remission.
Consider alignment with prescribing criteria for other drugs in the same therapeutic space (i.e., aripiprazole, brexpiprazole, and ziprasidone).	This is a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
System and economic issues	
At the submitted price, cariprazine is significantly more costly than other currently listed AAPs, most of which are generic and offer cost savings. Compared to the currently listed brand alternatives it is still a more expensive option.	This is a comment from the drug programs to inform CDEC deliberations.
There may be confidential product listing agreements with currently listed alternatives.	This is a comment from the drug programs to inform CDEC deliberations.

AAP = atypical antipsychotic; CDEC = Canadian Drug Expert Committee; NMA = network meta-analysis; RWE = real-world evidence.

Clinical Evidence

Clinical Evidence (SR0708)

Pivotal Studies and Protocol Selected Studies

Description of Studies

Five double blind randomized controlled trials (RCTs) met the inclusion criteria for the systematic review, including 3 short term studies (MD-16, MD-04, MD-05), one randomized withdrawal study (MD-06), and one study in patients with predominant negative symptoms (188-05).

The 6-week double-blind studies MD-16, MD-04 and MD-05 evaluated the efficacy, safety, and tolerability of cariprazine compared with placebo in adults with an acute exacerbation of schizophrenia. Patients were randomized to receive placebo or either fixed or flexible dosing of cariprazine (1.5 mg to 9 mg daily). Two studies also included an active control group for assay sensitivity (risperidone 4 mg daily or aripiprazole 10 mg daily). The sample size ranged from 446 to 732 patients and the primary outcome in all trials was the change from baseline to week 6 in PANSS total score. The mean age of patients enrolled in the acute schizophrenia trials ranged from 35.5 years (standard deviation [SD], 9.3) to 39.3 years (SD, 10.8), and the proportion of males ranged from 62% to 78% per treatment group. The mean baseline PANSS total score was approximately 96 points across studies, and most patients were categorized as markedly ill based on the Clinical Global Impressions-Severity (CGI-S) score.

The objective of study MD-06 was to evaluate the efficacy and safety of cariprazine relative to placebo in the prevention of relapse of symptoms. Adults with acute schizophrenia were enrolled and received open label cariprazine (3 mg to 9 mg daily) for up to 20 weeks. Those able to tolerate cariprazine and who met the treatment response criteria were randomized to receive double-blind cariprazine or placebo for 26 to 72 weeks (N = 200). The study was stopped once the last patient randomized had completed 26 weeks in the double-blind period. Time to relapse was the primary outcome of this study. In study MD-06, the mean age of patients who entered the run-in stage was 38.4 years (SD, 10.4) and 71% were male. The mean PANSS total score was 91.3 points (SD, 10.1) and 54% of patients were markedly ill. Treatment responders who had completed the open label cariprazine run-in and were randomized had a mean age of 37.7 years (SD, 10.1) and 39.2 years (SD, 10.9), and 71% and 61% of patients were male in the placebo and cariprazine groups, respectively. At randomization, the PANSS total score was 50.9 points (SD, 6.7), and most patients were mildly ill based on the CGI-S score.

The objective of study 188-05 was to evaluate the safety, efficacy, and tolerability of cariprazine versus risperidone in patients with predominant negative symptoms of schizophrenia for at least 6 months (i.e., PANSS factor score for negative symptoms ≥ 24 and rating of ≥ 4 moderate for 2 of 3 PANSS items for flat affect, avolition and poverty of speech). A total of 461 adults were randomized to receive 26 weeks of double blind cariprazine (3 mg to 6 mg daily) or risperidone (3 mg to 6 mg daily). The primary outcome was change from baseline to week 26 in the PANSS factor score for negative symptoms (FSNS). The mean age of patients enrolled in Study 188-05 was 40.4 years (SD, 10.8), and 57% were male. The mean baseline PANSS score was approximately 76 points, with [redacted] of patients classified as moderately ill and [redacted] classified as markedly ill according to the CGI-S score.

Efficacy Results

Acute Schizophrenia Trials

The primary efficacy objective was met in all 3 acute schizophrenia studies, with all cariprazine dosage groups (1.5 mg to 9 mg daily) showing statistically significant mean differences versus placebo in the change from baseline to week 6 in the PANSS total score. The least squares (LS) mean differences versus placebo ranged from -6.8 (95% confidence interval [CI], -11.3 to -2.4; P = 0.003) for the cariprazine 3 to 6 mg group in MD-05, to -10.4 (95% CI, -14.6 to -6.2; P <0.0001) for the cariprazine 4.5 mg group in MD-16. No statistical testing was performed comparing cariprazine to risperidone or aripiprazole.

The change from baseline to week 6 in the CGI-S score was the secondary outcome in the acute schizophrenia trials. The CGI-S assesses the overall severity of mental disorders on a 7-point scale ranging from 1 (normal) to 7 (extremely ill). The LS mean differences favored all dosage groups of cariprazine versus placebo, with treatment effects that ranged from -0.3 (95% CI, -0.6 to -0.1; P = 0.0115) to -0.6 (95% CI, -0.9 to -0.4; P <0.0001).

The proportion of patients who achieved treatment response (≥ 30% improvement in the PANSS total score) favored cariprazine 1.5 mg, 3 mg and 4.5 mg groups (31.4%, 35.7% and 35.9%, respectively) and the risperidone group (43.5%) compared with the placebo group (18.9%) in study MD-16 (all P <0.05). In study MD-04, the proportion of responders was higher for cariprazine 6 mg (31.8%; P = 0.013) than placebo (19.5%), but with no difference detected for the cariprazine 3 mg group (24.5%; P = 0.28) versus placebo (19.5%). No difference in the proportion of responders was detected between the cariprazine 3 mg to 6 mg (28.6%) or the 6 mg to 9 mg (34.7%) groups compared with the placebo group (24.8%) in study MD-05 (both P > 0.05). There was no control of the type I error rate for the responder analyses, thus any results showing a P < 0.05 should be interpreted as supportive evidence only.

Two studies reported data on health-related quality of life measured using the Schizophrenia Quality of Life Scale Revision 4 instrument. The between group differences favored cariprazine 3 mg to 6 mg groups versus placebo in study MD-04 and MD-05, but no differences were detected between the cariprazine 6 to 9 mg dosage group and placebo in study MD-05. The type I error rate was not controlled for this outcome, and the clinical relevance of the differences is unclear as the minimal important difference (MID) is not known.

Withdrawal Design Trial

Time to relapse was the primary outcome in study MD-06. Relapse was defined as a composite endpoint that included clinical outcomes (hospitalization, self-harm or violent behavior, suicidal or homicidal ideation) as well as criteria based on standardized symptom and disease severity rating scales (e.g., ≥30% increase in PANSS total score; ≥2-point increase in CGI-S, or score >4 on 1 of 7 specific PANSS items).

Among patients who had demonstrated treatment response to cariprazine during the 20-week open-label phase, 47.5% of patients experienced a relapse after being switched to placebo, compared with 24.8% of patients who remained on cariprazine therapy. Between group differences favored cariprazine versus placebo with a hazard ratio (HR) of 0.45 (95% CI, 0.28 to 0.73; P = 0.001).

Predominant Negative Symptom Study

In study 188-05, the primary outcome was the change from baseline to week 26 in the PANSS FSNS (scored from 7 to 49 with a lower score indicating fewer symptoms). Both the treatment groups showed an improvement over time with LS mean change score of -8.9 (standard error [SE], 0.3) for cariprazine and -7.4 (SE, 0.4) for risperidone. The LS mean difference was -1.5 (95% CI, -2.4 to -0.5) favoring cariprazine versus risperidone (P = 0.002). The MID for the mean difference is unclear. The proportion of patients with at least a 20% reduction in the PANSS factor score for negative symptoms at week 26 was 69.2% and 58.1% in the cariprazine and risperidone groups, respectively, with an odds ratio (OR) of 2.1 (95% CI, 1.3 to 3.3; P = 0.002). There was no control of the type I error rate for the responder analysis, thus these data should be interpreted as supportive evidence only.

The change from baseline to week 26 in the Personal and Social Performance Scale (PSP) was the secondary outcome in study 188-05. The clinician-rated PSP is scored from 0 to 100 with higher scores indicating better psychosocial function. In study 188-05, the cariprazine and risperidone groups both reported an improvement in the mean PSP scores at week 26 with increases of 14.3 points (SE, 0.6) and 9.7 points (SE, 0.8), respectively. The LS mean difference was 4.6 points (95% CI, 2.7 to 6.6), favoring

cariprazine versus risperidone (P <0.001). The between group differences did not exceed the MID of 7 to 10 points reported in the literature.

Harms Results

Most patients in the short-term studies (61% to [redacted]) and the longer-term studies (54% to 80%) reported one or more adverse events (AEs), with a frequency that was generally similar between groups within trials. Insomnia, akathisia, and headache were the most commonly reported AEs in the cariprazine groups.

The frequency of serious adverse events (SAEs) ranged from 1% to 9% of patients in the placebo groups, 3% to 6% of those in the cariprazine groups and 3% to [redacted] of patients in the active control groups of the acute schizophrenia trials. In the longer-term studies, SAEs were reported in 7% and 14% of patients in the open label and double-blind phases of MD-06 and in 3% per group in study 188-05. Across all studies, the proportion of patients who withdrew due to adverse events ranged from [redacted] to 15% in the placebo groups, [redacted] to 14% in the cariprazine groups and 9% to 12% in the active control groups. Schizophrenia and psychotic disorders were the most frequently reported SAEs or AEs leading to withdrawal.

Two patients died in the 6 mg cariprazine dosage group of study MD-04 (suicide; ischemic stroke and myocardial infarction), and 1 patient died in the risperidone group of study 188-05 (carcinoma). No deaths were reported in the other treatment groups.

In the 6-week studies, treatment emergent EPS were reported by [redacted] of patients in the placebo groups, [redacted] of patients in the cariprazine groups, and [redacted] of patients in the aripiprazole and risperidone groups, respectively (**Error! Reference source not found.**). The frequency of EPS was similar in the cariprazine and risperidone groups of study 188-05 (14% versus 13%). In study MD-06, EPS were reported in 40% of patients receiving open label cariprazine, in 21% of patients who remained on cariprazine and 7% who switched to placebo during the double-blind phase. The frequency of discontinuation due to EPS AEs was low, ranging from [redacted] per treatment group across the short-term and longer-term studies.

Suicidal ideation or behaviour was infrequently reported in the acute and longer-term studies. Based on the Columbia-Suicide Severity Rating Scale (C-SSRS), [redacted] of patients reported suicidal ideation and [redacted] reported suicidal behaviour across treatment groups. One completed suicide and [redacted] suicide attempt was reported among patients receiving cariprazine, as well as [redacted] suicide attempt in a patient on risperidone.

In the 6-week studies, [redacted] of patients who received cariprazine reported a clinically important increase in body weight (defined as ≥7%), versus [redacted] in the placebo group, [redacted] in the aripiprazole group and [redacted] in the risperidone group. In study MD-06, [redacted] of patients reported a ≥7% increase in body weight during the open label cariprazine phase, and in [redacted] of those in the cariprazine and placebo groups of the double-blind phase. In study 188-05, 6% and 7% in the cariprazine and risperidone groups, respectively, reported at least a 7% increase in weight.

Critical Appraisal

The design of the trials were consistent with European Medicines Agency (EMA) guidance for the investigation of drugs for schizophrenia. All studies were double blind and the methods used to randomize patients and conceal allocation appear to be appropriate. The baseline patient characteristics were similar between groups within studies, but all the trials reported a high proportion of early withdrawals (23% to 57% per treatment group) and with some withdrawal imbalances between treatment groups within trials. It is possible that the high proportion of discontinuations may have compromised randomization, and both the measured and unmeasured characteristics of the treatment groups may not have remained similar over time. Furthermore, many of the endpoint measurements reported in these trials had to be estimated by imputation, which may introduce bias. However, a number of sensitivity analyses were conducted that explored different missing data assumptions, and these analyses supported the primary findings of the studies. Interpretation of the change in PANSS scores and HRQoL data were limited by the lack of MID. In addition, the type I error rate was not controlled for several outcomes of interest, such as the 30% responder analyses and change in HRQoL scores.

In the study that enrolled patients with predominant negative symptoms, the use of risperidone as a comparator is a potential limitation, given its lack of demonstrated efficacy on negative symptoms. The clinical importance and relevance of the observed

differences in outcomes in this trial are uncertain due to the lack of evidence for what is considered a significant difference in negative symptoms trials.

With respect to external validity, all trials excluded patients with psychiatric and medical comorbidities, including those with substance use disorders or who were at risk of harming themselves or others. According to the clinical expert consulted, the numerous exclusion criteria have the potential to affect the external validity, as most patients seeking psychiatric care in Canada have complex medical and psychiatric conditions. Older adults (>60 years) and those with schizoaffective disorders or treatment resistant schizophrenia were also excluded thus the efficacy and safety in these populations is unknown. By design, the withdrawal study randomized an enriched population with a demonstrated response to treatment, thus the treatment effects observed may be inflated, and the frequency of adverse effects under-reported relative to the broader population of patients with an acute schizophrenia exacerbation.

The available evidence consisted of 4 placebo-controlled studies and 1 active-controlled trial in a select patient population (predominant negative symptoms). While 2 of the 6-week studies included an active control group, there was no a priori hypothesis evaluating risperidone or aripiprazole versus cariprazine, thus head-to-head data on the comparative efficacy and safety in acute schizophrenia are lacking. None of the studies were designed to test for differences in hospitalization or treatment persistence. The impact of treatment on HRQoL was assessed in two studies, but the type I error rate was not controlled for these analyses. Only the predominant negative symptom study assessed functional outcomes. Thus, the treatment effects of cariprazine on these outcomes of importance to patients is unclear. The sample size and duration of the RCTs may have been insufficient to detect infrequent AEs.

Indirect Comparisons

Description of studies

One unpublished indirect treatment comparison (ITC) that was used to inform the pharmacoeconomic analysis, and 2 published ITCs submitted by the sponsor, were included in this report.

The unpublished ITC evaluated the efficacy and safety of cariprazine versus other oral atypical antipsychotic drugs used in Canada for the treatment of acute schizophrenia and the prevention of relapse. Data from 70 RCTs for acute schizophrenia and 12 RCTs on relapse prevention were used to inform the fixed or random effects Bayesian network meta-analysis (NMA). The primary outcome for the acute model was the proportion of patients who achieved at least a 30% improvement in PANSS total scores (or other response criteria) at week 4 to 8. For the maintenance therapy model, the primary outcome was the proportion who relapsed at week 26 to 72.

The published ITCs focused on short-term efficacy and safety (Huhn et al. 2019), or metabolic effects (Pillinger et al. 2020) of antipsychotics in patients with acute schizophrenia.

Results

For the acute treatment of schizophrenia, the results of the unpublished NMA [redacted] for the proportion of responders, but [redacted]. The indirect evidence suggests that [redacted].

The results of the two published ITCs [redacted] showed no difference in short-term symptom severity, and possible differences in some adverse effects for cariprazine versus other antipsychotic drugs. The authors of both ITCs rated confidence in the evidence for cariprazine as low or very low.

Critical Appraisal

Several sources of heterogeneity were noted across trials in the unpublished ITC including differences in the baseline PANSS score, disease duration, publication year of study, timing of the outcome assessment, outcome definitions and placebo response rate. The statistical methods could not fully account for the heterogeneity, thus the potential for bias is high and should be considered when interpreting the findings of the acute schizophrenia NMA.

The relapse prevention network had several limitations which affected the ability to draw conclusions from these analyses. Due to differences in study design across trials there were important differences in the patients included, as well as heterogeneity in the timing of the outcomes, and the definition of relapse. Moreover, the network was sparse, with many comparisons showing wide credible intervals (CrIs), and high uncertainty. Considering these limitations, the results of this ITC may not be representative of the true effect of cariprazine relative to placebo or comparators.

Comparative evidence for HRQoL or functional status, which were identified as important endpoints by patients, is lacking as the ITC did not analyze these outcomes.

Other Relevant Evidence

Description of studies

Two open-label extension studies (MD-17 and MD-11) provided longer-term safety and tolerability data for patients with schizophrenia who completed one of the 6-week pivotal studies and had responded to treatment (CGI-S ≤3). New patients who met the inclusion criteria were also eligible for study MD-11.

In study MD-17, 93 patients received cariprazine (1.5 mg to 4.5 mg daily), and 50% of the patients completed 48 weeks of therapy. Of the 586 patients who received cariprazine (3 mg to 9 mg daily) in study MD-11, 39% completed 48 weeks.

Efficacy Results

The mean PANSS total score decreased from baseline by –5.0 points (SD 14.0) in study MD-11, and –6.8 points (SE, 1.3) in study MD-17 (last observation carried forward [LOCF] for missing data). Minimal changes in the CGI-S scores were reported in both studies.

Harms Results

No new safety signals were reported based on the 48-week safety data in MD-17 and MD-11. AEs were reported by 81% to 83% of patients, including akathisia (14% to 16%), extrapyramidal disorder (7%), and headache or insomnia (9% to 14%). A ≥7% increase in body weight was reported by 26% and 33% of patients in study MD-11 and MD-17, respectively. In both studies, 11% to 13% of patients discontinued due to AEs or experienced a SAE. One completed suicide was reported in the extension studies.

Critical Appraisal

Limitations of the extension studies include selection bias, lack of a control group and lack of blinding. Reporting of harms and subjective measures (such as symptoms) may be biased by knowledge of treatment received. As only descriptive statistics were published, and without comparator groups, the interpretation of the results is limited. Moreover, there is potential for selection bias, as patients who discontinued the parent RCTs due to adverse events, lack of efficacy or other reasons were excluded. In addition, some patients in study MD-11 received a higher daily dose of cariprazine than is recommended by Health Canada.

Clinical Evidence (SR0827 – Resubmission)

Systematic Review

Description of Studies

As part of the resubmission to CADTH, a post-hoc responder analysis for the primary endpoint of the acute schizophrenia trials (MD-16, MD-04, and MD-05) was submitted, which used a 20% within-group threshold for change from baseline in PANSS total score. Pivotal studies in the acute population have previously been described.

Efficacy Results

In study MD-16, the proportion of patients with a 20% or greater improvement in the PANSS total score at week 6 among the cariprazine 1.5 mg, 3 mg and 4.5 mg groups was [redacted]. For the comparison of cariprazine to placebo, the OR was [redacted] for the 1.5 mg group[redacted] for the 3mg group; and [redacted] for the 4.5 mg group. The comparison of risperidone 4 mg to placebo corresponded to an OR of [redacted].

In study MD-04, the proportion of 20% responders at week 6 for cariprazine 3 mg, and 6 mg was [redacted] For the comparison of cariprazine to placebo, the OR for the 3 mg group was [redacted], and the OR for the 6 mg group was [redacted]. The comparison of aripiprazole to placebo corresponded to an OR of [redacted].

In study MD-05, the proportion of patients with a 20% or greater improvement in the PANSS total score at week 6 for the cariprazine 3 mg to 6 mg group, the cariprazine 6 mg to 9 mg group, and the placebo group were [redacted] respectively. For the comparison of the cariprazine groups to placebo, the OR for the 3 mg to 6 mg group was [redacted], and the OR for the 6 mg to 9 mg group was [redacted].

Harms Results

No additional harms analyses were included as part of the resubmission.

Critical Appraisal

The pivotal trials submitted are the same as the previous submission and the appraisal points raised by CADTH related to the MD-16, MD-05, and MD-04 trials still apply. Results of the three post-hoc analyses were in favour of cariprazine, demonstrating that [redacted] of patients treated with cariprazine experienced a 20% or greater improvement in PANSS total score compared to placebo (range of scores: [redacted]) across trials. As the included data were derived from a post-hoc analysis, and the outcome was not part of any multiple testing procedure that controlled for type I error, any results showing a $P < 0.05$ was considered supportive. Because the threshold of clinical relevance was not defined, there is an uncertainty in our conclusions about the true magnitude of effect of cariprazine compared to placebo in reducing PANSS scores by 20%.

Long-Term Extension Studies

Beyond MD-17 and MD-11 which were included in the original review of cariprazine, no additional long-term extension studies were included as part of this resubmission. Of note, MD-17 and MD-11 are summarized under *Clinical Evidence (SR0708), Other Relevant Evidence*.

Indirect Comparisons

Description of Studies

In response to the identified gaps and concerns raised by CADTH in the original submission, the sponsor submitted an updated NMA that includes novel analyses of change from baseline in PANSS, 30% response rate, and relapse rate. The NMA was submitted to address the high levels of heterogeneity in the patient and study characteristics that could not be fully accounted for by the statistical methods, and uncertainty about the comparative efficacy and safety of cariprazine within both the acute schizophrenia population and the population presenting with predominantly negative symptoms.

Analyses for other outcomes including discontinuation due to adverse events (DAEs), discontinuation due to other reasons (DORs), weight gain, EPS, and sedation and somnolence were rerun utilizing the same data inputs as the original NMA. As such, the authors noted that there was no difference between analyses. Inputs from these new NMAs were used in the pharmacoeconomic model for cariprazine, also included in the resubmission to CADTH.

Efficacy Results

<u>Change from Baseline in PANSS and 30% Response Rate</u>

Comparisons of cariprazine to the other active treatments included in the NMA [redacted] based on the change from baseline in PANSS in the random effects NMA adjusted for placebo effect, year of publication, and treatment duration. [redacted].

Comparisons of cariprazine to other active treatments [redacted] in the response to treatment based on the 30% response rate in the random effects NMA adjusted for placebo effect. [redacted].

Results of sensitivity and subgroup analyses that aimed to address the sources of heterogeneity and methodological concerns were generally consistent with the primary analyses, [redacted].

Relapse Rate

[redacted]

Results of the sensitivity and subgroup analyses in the relapse network were in line with the primary analysis, though results were associated with extremely wide 95% CrIs.

Harms Results

The models for other outcomes presented in the original submission, namely discontinuation due to AE, weight gain, EPS, and sedation and somnolence were not rerun, as the data inputs remained unchanged. Following a request for clarification by CADTH, the authors highlighted several corrections that were applied to 3 studies that were included in the acute network dataset. Results for these outcomes were consistent with the original NMA.

For the relapse network, results for the outcomes of discontinuation due AEs, discontinuation due to other reasons, weight gain, and EPS remained unchanged from the original NMA.

Critical Appraisal

Given the similarities in conduct and statistical analysis between the original NMA and the updated NMA included in this resubmission, the key criticisms from the original NMA still apply (see Indirect Evidence in the Clinical Evidence from SR0708). These included the potential for bias due to heterogeneity in the study characteristics that could not be fully accounted for, and the resulting uncertainty of the magnitude of the comparative efficacy and safety of cariprazine. To address the heterogeneity concerns outlined in the previous review, meta-regression was conducted to adjust for the heterogeneity of the study-reported treatment effect caused by potential effect modifiers, as well as supplementary analyses to remove or modify the heterogeneity introduced by the effect modifiers.

The studies included in the updated NMA were identical to those included in the original NMA summarized in SR0708 and therefore subject to most of the same limitations that were previously described. However, the authors applied various outcome-specific exclusions to further reduce the number of studies in each analysis. Despite this, given the heterogeneity across the included studies' patient populations, it was unclear if the transitivity assumption was met. There was notable variation across trials with regards to the baseline PANSS, duration of time since diagnosis, study publication year, and some patient demographics. Other potential sources of heterogeneity included the definition of relapse, which was based on the study specific criteria. Data were missing on the patient subtype (not first episode, or mixed population) for up to 40% of studies, and it was unclear if patient subtypes were comparable across studies. Due to the heterogeneity in the timepoints of assessment for the outcomes included in the studies of the NMA, a 24-week time of assessment was selected as it was common across studies of the relapse network, as opposed to the longest evaluable timepoint for each study which ranged from 26 to 72 weeks.

Novel analyses were conducted for the change from baseline in PANSS, and 30% response in PANSS in the acute network, and for the outcome of relapse rate in the relapse population network. Per the authors, metabolically neutral AAPs — aripiprazole, brexpiprazole, lurasidone, and ziprasidone — were considered the most relevant comparators as these were identified as the treatments that cariprazine would most likely replace based on the original CADTH review of cariprazine, other published NMAs, and the INESSS recommendation for cariprazine.[14] This assumption was not considered invalid by the clinical experts, though, they also noted that comparisons to other antipsychotics (i.e., asenapine, clozapine, olanzapine, paliperidone, quetiapine, and risperidone) are also relevant. Throughout the base case and all supplementary analyses, [redacted] for outcomes of change from baseline in PANSS, 30% response in PANSS, and relapse rate. Other antipsychotics (asenapine, olanzapine, paliperidone, and quetiapine) [redacted]. However, results for all comparisons were uncertain due to the wide 95% CrIs, with many estimates crossing the 0 or 1 threshold suggesting notable imprecision and precluding conclusions on which treatment is favoured for these outcomes, thus, may not be representative of the true comparative effect of cariprazine.

Studies Addressing Gaps in the Evidence from the Systematic Review

During the original review of cariprazine, CADTH noted the following gaps in the submitted evidence: generalizability of the results to the population of schizophrenia patients in Canada, uncertainty in the comparative efficacy of cariprazine in treating negative symptoms, and limited evidence of long-term effects after continued cariprazine use.

To strengthen the totality of evidence for cariprazine and to address the concerns with the included evidence identified during the original review of cariprazine, the sponsor submitted 2 real-world, observational studies: Rancans et al., 2021 and Szerman et al., (manuscript in progress).

Rancans et al., 2021

Description of Study

The study by Rancans et al., 2021 was a prospective, observational, open label, single arm 16-week study of cariprazine conducted in 9 psychiatric clinics in Latvia (N = 116). Patients with insufficient symptom control with their previous antipsychotic treatment were included. The primary outcome of the study was the change from baseline in the short assessment of negative domains (SAND). Additional outcomes included the CGI-I and the CGI-S scales, and safety.

At baseline, the mean age was 37.4 years (SD, 11.3), and most patients were diagnosed with paranoid schizophrenia (82 [70.7%]). Inadequate control of negative symptoms occurred in 103 (88.8%) patients, and the most frequent antipsychotic therapies were quetiapine (38 [32.8%]), olanzapine (24 [20.7%]), haloperidol (23 [19.8%]), and aripiprazole (22 [19.0%]).

Results

The mean change from baseline in SAND total score at week 16 was −7.3 points (95% CI, −8.3 to −6.2), with greater changes occurring in negative symptom domains (−6.3 points [95% CI, −7.3 to −5.4]) than in positive domains (−0.9 points [95% CI, −1.2 to −0.6]). Results for the CGI-I and CGI-S suggested mean improvements of 2.6 points (95% CI, 2.4 to 2.8) and −0.9 points (95% CI, −1.0 to −0.7), respectively.

A total of 46 (39.7%) patients experienced TEAEs including but not limited to akathisia (15 [12.9%]), and anxiety (12 [10.3%]).

Critical Appraisal

General principles of appraisal of prospective observational studies were applied to the study by Rancans et al., 2021, however, the study was non-comparative. In the absence of a frame of reference for comparison, it is not possible to determine whether the observed treatment effects of cariprazine on the outcomes were solely due to the drug, a placebo effect, or natural history of the disease. Additionally, the outcome assessment was at a greater risk of measurement or reporting bias due to lack of blinding and awareness of treatment assignment.

The primary outcome of this study was the change from baseline in SAND. It was not possible to assess the clinical importance of the change in SAND as it is not yet validated as a measure of antipsychotic treatment efficacy. A total of 17% of patients did not complete the study, and the amount of missing data was not reported, which may introduce selection bias into the reported estimates.

Overall, the transportability of the reported results to patients with schizophrenia in Canada is uncertain. The difference between Latvian and Canadian populations in their access to care, social support, patient characteristics, and the prognosis of patients with schizophrenia remain unknown.

Szerman et al., (Manuscript in Progress)

Description of Study

Szerman et al., (manuscript in progress) was a retrospective, cross-sectional, observational, review of adult patients who met the DSM-5 criteria for schizophrenia and cannabis use disorder and were treated with cariprazine maintenance therapy for at least 6 months. A total of [redacted] patients were enrolled at [redacted] centers in Spain. The primary objective was to describe the change in PANSS and

Clinical Global Impression – Schizophrenia (CGI-SCH) from the start of treatment to 6 months later among patients who completed at least 6 months of treatment with cariprazine.

In the [redacted] patients included, the mean age at baseline was [redacted]. Most patients ([redacted]) had multiple previous episodes of schizophrenia, while [redacted] patients had a first episode of schizophrenia. Patients included in the study were receiving treatment with cariprazine for 6 months; the most frequently administered doses being 4.5 mg ([redacted]) and 3 mg ([redacted]). Most patients were also receiving other treatment [redacted]

Results

At baseline, the mean score of the PANSS positive and negative subscales were [redacted], respectively. At the 6-month follow up, the mean PANSS positive and negative subscale scores were [redacted], respectively.

From baseline to the 6-month mark, the CGI-SCH positive symptom scores decreased from [redacted], and the negative symptom scores decreased from [redacted]. For the CGI-I, scores decreased from [redacted] at baseline to [redacted] 6-months later, and for CGI-S, scores decreased from [redacted] at baseline to [redacted] at 6-months.

No harms were evaluated in the study.

Critical Appraisal

General principles of appraisal of observational studies were applied to the study by Szerman et al., (manuscript in progress). The study was non-comparative, which limits the ability to interpret the observed changes from baseline as it is not possible to distinguish between the effect of cariprazine, a placebo effect, or natural history of the disease in the absence of a frame of reference for comparison. The population was selected retrospectively based on 6 months of continuous treatment with cariprazine, which introduces selection bias in the study. Any patients with poor adherence, negative response or early important AEs were not represented by the study and the reported results are not generalizable to the entire population of adults with schizophrenia and cannabis use disorder.

Overall, the transportability of the reported results to patients with schizophrenia in Canada is uncertain. The difference between Spanish and Canadian populations in their access to care, social support, patient characteristics, and the prognosis of patients with schizophrenia remain unknown.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with schizophrenia
Treatment	Cariprazine
Dose regimen	Recommended starting dose is 1.5 mg once daily and can be increased gradually in 1.5 mg increments until a maximum recommended dose of 6 mg once daily
Submitted price	Cariprazine: $4.90 per 1.5 mg, 3 mg, 4.5 mg, or 6 mg capsule
Submitted treatment cost	$1,790 per patient annually
Comparators	• Aripiprazole • Asenapine • Brexpiprazole • Lurasidone • Olanzapine • Paliperidone • Quetiapine

Component	Description
	• Risperidone • Ziprasidone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	2 years
Key data source	Sponsor submitted network meta-analysis (NMA)
Key limitations	• The efficacy and safety of cariprazine relative to other atypical antipsychotics for the treatment of schizophrenia is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMAs. Indirect evidence submitted by the sponsor [redacted]. Key limitations include a high potential for bias due to heterogeneity that could not be fully accounted for in the statistical analysis and wide credible intervals. Furthermore, new evidence in the form of 2 real-world evidence studies were included as part of the resubmission to support the efficacy of cariprazine and address the gaps identified by CDEC in the original review. These studies were not used to inform the economic model.
CADTH reanalysis results	• There is insufficient clinical evidence to justify a price premium for cariprazine relative to currently available treatments for schizophrenia.

LY = life-year; NMA = network meta-analysis; QALY= quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: market share estimates for cariprazine may be underestimated; cariprazine market uptake from only metabolically neutral comparators is uncertain; and, uncertainty with the use of a claims-based approach to estimate market size. Based on the CADTH reanalysis, the three-year budget impact to public drug plans of introducing cariprazine for the treatment of adult patients with schizophrenia is expected to be $26,072,195 ($4,795,446 in year 1, $8,406,469 in year 2, and $12,870,280 in year 3). Uncertainty remains in this estimate due to the use of a claims-based approach, in addition to the limitations with the sponsor's estimation of comparator capture rates.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: June 27, 2024

Regrets:

3 expert committee members did not attend.

Conflicts of interest:

None