

CADTH Reimbursement Recommendation

Cariprazine (Vraylar)

Indication: For the treatment of schizophrenia in adults

Sponsor: Allergan (an AbbVie company)

Final recommendation: Do not reimburse

Note: This document was initially published on August 26, 2022, and subsequently revised on February 2, 2023, to provide additional details on the expert committee's deliberations and the request for reconsideration filed by the sponsor.

ISSN: 2563-6596

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian Copyright Act and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines.

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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

What Is the CADTH Reimbursement Recommendation for Vraylar?

CADTH recommends that Vraylar not be reimbursed by public drug plans for the treatment of schizophrenia in adults. Vraylar was discussed at the March 2022 meeting of the CADTH Canadian Drug Expert Committee (CDEC) and reconsidered at the July 2022 meeting.

Why Did CADTH Make This Recommendation?

- Based on evidence from 5 clinical trials, treatment with Vraylar improved symptoms of schizophrenia or delayed relapse compared with placebo. Vraylar also improved negative symptoms of schizophrenia compared with risperidone. Although these results were statistically significant, it is not clear whether any of these effects result in a clinically meaningful improvement in patient-identified needs.
- It is not clear whether cariprazine offers any clinical benefits over other treatments that are available for schizophrenia because there were no clinical trials in patients with acute schizophrenia that compared Vraylar with any other treatments. The committee did not have confidence in the results of the indirect comparative evidence because it had too many limitations.
- There was not enough robust evidence to show that Vraylar filled a treatment gap.

Additional Information

What Is Schizophrenia?

Schizophrenia is a severe and long-lasting psychiatric disease that can vary in presentation, course, treatment response, and outcome. Symptoms of schizophrenia may include hallucinations, delusions, and disorganized thoughts (which are labelled as positive symptoms), and social withdrawal and lack of motivation (which are labelled as negative symptoms). Schizophrenia also includes cognitive symptoms affecting, in general, concentration and memory. In 2016, the estimated incidence of schizophrenia in Canada was 49 per 100,000, with 58 per 100,000 in males and 41 per 100,000 in females.

Unmet Needs in Schizophrenia

Patients expressed a need for treatments which minimize the negative and cognitive symptoms of schizophrenia, provide an additional option for those who do not respond to existing treatments, are administered less often, and have fewer side effects.

How Much Does Vraylar Cost?

Treatment with Vraylar is expected to cost approximately \$1,789 per patient per year.

Recommendation

CDEC recommends that cariprazine not be reimbursed for the treatment of schizophrenia in adults.

Rationale for the Recommendation

Although evidence from three 6-week double-blind randomized controlled trials (RCTs; MD-16, MD-04, and MD-05) in adults experiencing an acute exacerbation of schizophrenia showed that cariprazine was associated with statistically significant improvements in schizophrenia symptoms and overall severity compared with placebo, the clinical relevance of these results is uncertain. Further, in a 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 this difference was statistically significant, the clinical relevance of the differences in these outcomes was unclear because the minimal important difference (MID) to show a clinical effect was uncertain (for negative symptoms scores) or was not exceeded (for functional status). In addition, the extensive screening and exclusion criteria in Study 188-05 limit the generalizability of the results.

Despite the number of treatments currently available, no direct comparative evidence of cariprazine versus other antipsychotic drugs was available in patients with acute schizophrenia. Available indirect evidence from 2 published and 2 sponsor-submitted network meta-analyses (NMAs) for the treatment of acute schizophrenia or prevention of relapse were limited by the heterogeneity in the study designs and patient populations across the included studies and by the considerable uncertainty in the indirect estimates of effect. Given these limitations, the results were associated with too much uncertainty to make any inference regarding the comparative efficacy and safety of cariprazine.

Patients expressed a need for treatments that minimize the negative and cognitive symptoms of schizophrenia, provide an additional option for therapy for those who do not respond adequately to existing drugs, provide a greater range of strengths and dosages, have lower frequency of administration, and minimize adverse effects. CDEC concluded that there was insufficient evidence to demonstrate that these needs were fully met by cariprazine. Furthermore, conclusions could not be drawn about the impact of cariprazine on health-related quality of life (HRQoL), functional status, hospitalization, or persistence with therapy because of study limitations or lack of evidence.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse cariprazine (Vraylar) for the treatment of schizophrenia. CDEC discussed each of the issues identified by the sponsor in their Request for Reconsideration. The following points encompass the discussions that occurred during both the initial and reconsideration meetings.

- CDEC discussed the comparison of cariprazine with placebo and the reported magnitude of effects in the acute trials. During both the initial and reconsideration deliberations, CDEC highlighted the uncertainty with defining a minimally important between-group difference based on the PANSS total score. CDEC discussed the issues raised in the Request for Reconsideration on the interpretation of the clinical relevance of the within-group and between-group change in the PANSS total score and the Clinical Global Impressions-Severity (CGI-S) score. Considering several estimates of the MID for the PANSS score, the within-group change suggests both the cariprazine and placebo groups showed clinically relevant improvement. However, the clinical importance of the between-group differences remains unclear because there was no predefined threshold for a clinically relevant difference versus placebo. CDEC noted that, for the CGI-S score, the within-group but not the between-group differences for cariprazine and placebo exceeded the MID threshold. Further, CDEC noted that the trials did not consistently detect a difference between cariprazine and placebo in the proportion of responders, which defined a clinically meaningful response as at least a 30% improvement in the PANSS total score. Given these findings, CDEC considered cariprazine treatment effects to be of uncertain clinical relevance.
- CDEC discussed the results from Study MD-06, which suggested that continued cariprazine treatment resulted in a longer time to relapse than switching to placebo; however, this randomized withdrawal design study enrolled an enriched population and included only patients who tolerated and showed a good response to cariprazine. Additionally, a large proportion of patients discontinued the trial, which affects the generalizability of the results. Due to the enriched population and attrition issues, the treatment effects observed may be inflated relative to the broader population of patients with an acute schizophrenia exacerbation and the adverse effects experienced by those who remained in the study may differ from real-world safety.
- CDEC noted that there was no direct evidence available to assess the safety and efficacy of cariprazine versus other antipsychotic drugs in patients with acute exacerbation of schizophrenia. Acute schizophrenia is almost always treated with pharmacotherapy, and there is a choice of available drugs. As such, comparison of effectiveness against a placebo has limited meaning in clinical practice. Although aripiprazole or risperidone were included as active comparators in 2 of the 6-week double-blind studies to establish assay sensitivity, there were no statistical comparisons made between cariprazine and an active comparator. Given the limitations of the studies, the committee could not draw any conclusions regarding the comparative efficacy and safety of cariprazine compared with aripiprazole or risperidone in patients with acute schizophrenia.
- CDEC considered all of the safety and efficacy evidence that was available for the drug under review, including the submitted NMAs. This evidence was limited by the lack of direct comparative data and lack of clarity on the minimum clinically relevant treatment effects for both the acute schizophrenia and predominant negative symptom populations. The NMAs had a high potential for bias due to heterogeneity in the patient and study characteristics that could not be fully accounted for in the statistical methods. Based on its interpretation of the evidence, CDEC concluded that the treatment effects of cariprazine were of uncertain clinical relevance, and the indirect evidence was associated with too much uncertainty to draw conclusions about the comparative efficacy and safety of cariprazine.

- During the initial and reconsideration meetings, CDEC discussed the input and feedback received from 3 patient groups, 3 clinician groups, and 2 individual clinicians. The groups described the profound impact that schizophrenia may have on patients' lives, their difficulty in accessing treatments, heterogeneity in treatment response, issues of tolerability, and the need for other treatment options. CDEC acknowledged that management of negative symptoms of schizophrenia is an important unmet need in the current treatment paradigm, and this gap in current treatment was also identified by patients. CDEC heard from the clinical expert that negative symptoms of schizophrenia are challenging to treat and the predominance of negative symptoms typically appear after resolution of the acute phase. CDEC acknowledged that the particular challenges schizophrenia poses to treatment adherence, the impact of nonadherence on the health system, and the particular socioeconomic factors of this patient population increase the importance of treatment options. However, based on the committee's review of the available evidence, and the information provided by the clinical expert, the committee concluded the data did not demonstrate that cariprazine would fully meet the needs expressed by patients.
- Among patients with PNS, there is uncertainty in defining the change needed in symptom scores that is clinically important. The committee reviewed the post hoc analyses of Study 188-05 provided by the sponsor in the Request for Reconsideration and considered that, because of the limitations of these data, the post hoc analyses did not resolve the uncertainty in the MID for the PANSS factor score for negative symptoms. In addition, the committee and the clinical expert discussed the limitations of risperidone as a comparator. Although statistically significant differences were detected between cariprazine and risperidone in terms of negative symptoms or functional status, substantial uncertainty remained regarding the clinical relevance and importance of the effects observed.
- CDEC noted the importance of treatment tolerability to patients with schizophrenia and its potential impact on adherence to therapy. In the clinical trials, extrapyramidal symptoms, headache, and insomnia were the most common adverse events among those who received cariprazine, and some patients reported clinically significantly increased body weight. The safety data were limited by the short duration of the acute schizophrenia RCTs, the enriched population enrolled in the withdrawal design study, and the number of withdrawals and the lack of control group for the longer-term data. The committee could not draw any conclusions regarding the comparative safety of cariprazine versus other antipsychotic drugs from the indirect evidence due to the limitations and uncertainty in the results of the NMAs. Thus, it is unclear if cariprazine meets patients' expectations for tolerability.

Background

Schizophrenia is a chronic mental illness that affects the way a person interacts with and understands the world. When active, the condition is characterized by delusions, hallucinations, disorganized speech, disorganized behaviour, and impaired cognitive ability. The symptoms associated with schizophrenia are categorized as either positive or negative in nature. Positive symptoms reflect a distortion or abundance of normal functions, while negative symptoms reflect a loss or restrictions of normal functioning. The severity, duration, and frequency of these symptoms can cause social and occupational challenges. According to national data (2016 to 2017), 1 in 100 people living in Canada aged 10 years or older

is living with a diagnosis of schizophrenia. Antipsychotic medications, which target the characteristic symptoms of schizophrenia, form the cornerstone of treatment. Cariprazine, an atypical antipsychotic drug, has been approved by Health Canada for the treatment of schizophrenia in adults. It is available as 1.5 mg, 3 mg, 4.5 mg, and 6 mg oral capsules; the recommended dosage is 1.5 mg to 6 mg once daily.

Sources of Information Used by the Committee

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

- a systematic review of 5 double-blind RCTs in adults with schizophrenia
- patients' perspectives gathered by patient groups: the Institute for Advancements in Mental Health (IAM) and a joint submission from the Schizophrenia Society of Canada (SSC) and the Canadian Mental Health Association (CMHA) Alberta Division
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with schizophrenia
- input from 2 clinician groups, including the Canadian Consortium for Early Intervention in Psychosis group (CCEIP) and a national advisory board composed of psychiatrists in Canada with experience in the management of schizophrenia
- indirect evidence from 3 indirect treatment comparisons (ITCs)
- additional data from 2 open-label extension studies
- a review of the pharmaco-economic model and report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described below).

Stakeholder Perspectives

Patient Input

Two responses to CADTH's call for patient input for this review were received: a submission from the IAM and a joint submission from the SSC and CMHA Alberta Division. IAM, SSC, and CMHA are organizations that serve individuals living with mental illnesses, including schizophrenia, their families and community members.

Patient input was based on 2 online surveys of members of IAM's client network that were conducted in 2021 and 2018. Among the 19 respondents of the 2021 survey, 26% identified as living with symptoms of schizophrenia or psychosis, 37% were relatives of someone with lived experience, 5% were friends of someone with lived experience, and 32% were caregivers of someone with lived experience. Among the respondents of the 2018 survey, 12% self-described as personally diagnosed, 50% were caregivers, 63% were family members or friends of someone diagnosed, and 18% worked in social services. SSC drew information from their national online surveys, focus groups, and interviews that were conducted mostly in Canada in 2021. Among the 239 survey respondents, 118 were patients with lived experience of early psychosis and schizophrenia and 121 were family members.

Patients indicated that symptoms of psychosis, including cognitive impairment, delusions, and hallucinations, have a significant impact on their day-to-day functioning. Negative symptoms, including social withdrawal and reduced motivation or apathy, diminish their quality of life and social engagement, resulting in challenges with reintegration. Patients also experience a lack of insight into their illness, which affects their ability to access treatment and support. This can cause significant strains in their relationships with their support network, ultimately leading to social isolation.

The respondents indicated that the advantage of taking antipsychotic medications is experiencing fewer episodes of mental illness, while the disadvantage is having to take the medication daily. The most common adverse effects of antipsychotic medications per the respondents were drowsiness, restlessness, and weight gain. Two respondents with experience with cariprazine reported that the treatment was able to manage their negative symptoms and improve their relationships with peers.

The respondents stated that antipsychotic medications can be improved by having fewer adverse effects and reducing its cost, which has been identified as a significant barrier to access. Additionally, the respondents believe psychosocial therapy is most effective when provided together with pharmacological therapy. Treatment and recovery are nonlinear, individual processes. Finding the right medication that enables the highest level of functioning, while managing adverse effects, is often achieved through a trial-and-error process. Patients living with schizophrenia have unique needs, and expect quick, simple, and affordable access to a wide range of therapeutic options to improve their treatment experience.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert indicated that current medications treat only the positive symptom domain in schizophrenia, but not negative or cognitive symptoms, and do not reliably improve psychosocial function. Moreover, existing treatments have burdensome adverse effects which, in some cases, are life-threatening (diabetes, neuroleptic malignant syndrome) or irreversible (tardive dyskinesia).

According to the clinical expert, cariprazine could be suitable for most adult patients with schizophrenia, but the clinical expert also suggested it could be reserved as a second-line treatment. Cariprazine will be relatively expensive and, for many patients, medications that have well-established efficacy and risk profiles will be appropriate for first-line treatment. Cariprazine may play a role when tolerability or lack of efficacy occur with existing and less expensive treatments. The expert indicated that cariprazine could be an option for patients in whom metabolic effects, weight gain, or sexual dysfunction are of great concern, and it may be selected for patients who have chronic negative symptoms causing functional impairment.

In clinical practice, a routine mental status examination that thoroughly assesses hallucinations, delusions, and disorganized thought and behaviour, and that shows documented improvement over an 8-week course of therapy, would indicate a response to treatment, including collateral input from caregivers, when available, indicating reduced behavioural signs of psychosis. The expert noted that evaluating negative symptoms is not as well established in many clinical programs and may be under-reported and, because negative symptoms are not the primary target of antipsychotic therapy, they may go unnoticed until positive symptoms are controlled. Adherence to treatment and concurrent substance use

must also be assessed especially when treatment response is poor. Ongoing therapy for 2 or more years is often required, and a switch in therapies may be needed if patients experience significant adverse effects.

The expert stated that psychiatrists are most often involved in diagnosing schizophrenia and initiating therapy, which may occur in hospital settings. Once a patient is stable on a regular treatment regimen and there are few or no psychiatric comorbidities, such as substance use or mood disorder, a family physician can manage the patient with some consultative support from a psychiatrist.

Clinician Group Input

Two clinician groups provided input to the submission: CCEIP and a national advisory board composed of psychiatrists in Canada with experience in the management of schizophrenia. Three clinicians with CCEIP and 8 with the national advisory board contributed to these submissions. CCEIP noted the unmet need in young adults in the early phase of psychosis, in whom the current treatments may not optimize their long-term outcomes. Both groups agreed there is a need for treatments that improve negative symptoms and treatments for patients who do not respond to current drugs. Both groups advocated for cariprazine as a first-line antipsychotic for patients with schizophrenia, including those with early phase of psychosis or negative symptoms.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for cariprazine:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

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

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Five double-blind RCTs met the inclusion criteria for the systematic review, including 3 short-term studies (MD-16, MD-04, and MD-05), 1 randomized withdrawal study (MD-06), and 1 study in patients with PNS (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 PANSS is a 30-item rating scale that assesses the presence and severity of psychopathology. It is scored from 30 to 210, with higher scores indicating more severe symptoms and psychopathology.

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 the majority of patients were categorized as markedly ill based on the CGI-S score.

The objective of Study MD-06 was to evaluate the efficacy and safety of cariprazine compared with placebo in the prevention of relapse of symptoms of schizophrenia. Adults with acute schizophrenia were enrolled and received open-label cariprazine (3 mg to 9 mg daily) for up to 20 weeks. Those who were able to tolerate cariprazine and 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 stage and were randomized to a treatment group 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 PNS 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 in the PANSS factor score for negative symptoms from baseline to week 26.

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 █% of patients classified as moderately ill and █% 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 mg to 6 mg group in Study MD-05 to -10.4 (95% CI, -14.6 to -6.2; $P < 0.0001$) for the cariprazine 4.5 mg group in Study MD-16. No statistical testing was performed comparing cariprazine to risperidone or aripiprazole.

The change in CGI-S score from baseline to week 6 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 favoured 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 ($\geq 30\%$ improvement in the PANSS total score) favoured 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%) than placebo (19.5%; $P = 0.013$), but there was no difference for the cariprazine 3 mg group versus placebo (24.5%, $P = 0.28$). There was no difference in the proportion of responders between the cariprazine 3 mg to 6 mg (28.6%) group or the 6 mg to 9 mg (34.7%) group and 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 HRQoL measured using the Schizophrenia Quality of Life Scale Revision 4 instrument. The between-group differences favoured the cariprazine 3 mg to 6 mg dosage groups versus placebo in Study MD-04 and Study MD-05, but no differences were detected between the cariprazine 6 mg to 9 mg dosage group and placebo in Study MD-05. For this outcome, the type I error rate was not controlled for, and the clinical relevance of the differences is unclear because the MID is not known.

Withdrawal Design Trial

Time to relapse was the primary outcome in Study MD-06. Relapse was defined as a composite end point that included clinical outcomes (hospitalization, self-harm or violent behaviour, suicidal or homicidal ideation) as well as criteria based on standardized symptom and disease severity rating scales (e.g., $\geq 30\%$ increase in PANSS total score; increase in CGI-S score of ≥ 2 points, 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% experienced a relapse after being switched to placebo compared with 24.8% of patients who remained on cariprazine therapy. The between-group differences favoured cariprazine versus placebo with a hazard ratio 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 factor score for negative symptoms (scored from 7 to 49 with a lower score indicating fewer symptoms). Both treatment groups showed an improvement over time with an 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) favouring 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 factors score for negative symptoms at week 26 was 69.2% and 58.1% in the cariprazine and risperidone groups, respectively, with an

odds ratio 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), favouring 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 █%) and the longer-term studies (54% to 80%) reported 1 or more adverse events, with a frequency that was generally similar between groups within trials. Insomnia, akathisia, and headache were the most commonly reported adverse events in the cariprazine groups.

The frequency of serious adverse events ranged from 1% to 9% of patients in the placebo groups, 3% to 6% of patients in the cariprazine groups, and 3% to █% of patients in the active control groups of the acute schizophrenia trials. In the longer-term studies, serious adverse events were reported in 7% and 14% of patients in the open-label and double-blind phases of Study 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 █% to 15% in the placebo groups, █% to 14% in the cariprazine groups, and 9% to 12% in the active control groups. Schizophrenia and psychotic disorders were the most frequently reported serious adverse events or adverse event 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 extrapyramidal symptoms were reported by █% to █% of patients in the placebo groups, █% to █% of patients in the cariprazine groups, and █% and █% of patients in the aripiprazole and risperidone groups, respectively. The frequency of extrapyramidal symptoms was similar in the cariprazine and risperidone groups of Study 188-05 (14% versus 13%). In Study MD-06, extrapyramidal symptoms were reported in 40% of patients receiving open-label cariprazine, in 21% of patients who remained on cariprazine, and in 7% who switched to placebo during the double-blind phase. The frequency of discontinuation due to extrapyramidal symptoms adverse events was low, ranging from █% to █% 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, █% to █% of patients reported suicidal ideation and █% to █% reported suicidal behaviour across treatment groups. One completed suicide and 1 suicide attempt was reported among patients receiving cariprazine, as well as █ suicide attempt in a patient on risperidone.

In the 6-week studies, █% to █% of patients who received cariprazine reported a clinically important increase in body weight (defined as ≥ 7%), versus █% to █% in the placebo group, █% in the aripiprazole group, and █% in the risperidone group. In Study MD-06, █%

of patients reported a 7% or greater increase in body weight during the open-label cariprazine phase, and in █% to █% 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 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 there were 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 end point measurements reported in these trials had to be estimated by imputation, which may have introduced 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 in several outcomes of interest, such as the responder analyses and change in HRQoL scores.

In the study that enrolled patients with PNS, the use of risperidone as a comparator is a potential limitation because of 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.

Regarding 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 has the potential to affect the external validity because 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 (PNS). Although 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 effect of treatment on HRQoL was assessed in 2 studies, but the type I error rate was not controlled for in these analyses. Only the PNS 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 adverse events.

Indirect Comparisons

Description of Studies

One unpublished 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 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) from week 4 to week 8. For the maintenance therapy model, the primary outcome was the proportion who relapsed between week 26 and 72.

The published ITCs focused on short-term efficacy and safety (Huhn et al. [2019]), or metabolic effects (Pillinger et al. [2020]) of antipsychotic drugs 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 2 published ITCs [redacted] and 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 and high uncertainty. Considering these limitations, the results of this ITC may not be representative of the true effect of cariprazine compared with placebo or other comparators.

Comparative evidence for HRQoL or functional status, both of which were identified as important end points by patients, is lacking because 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 1 of the 6-week pivotal studies and had responded to treatment (CGI-S score \leq 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 49% 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 of therapy.

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 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 Study MD-17 and Study MD-11. Adverse events 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% or greater increase in body weight was reported by 26% and 33% of patients in Study MD-11 and Study MD-17, respectively. In both studies, 10% to 13% of patients discontinued the study due to adverse events or experienced a serious adverse event. 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. Because only descriptive statistics were published, and did not include comparator groups, the interpretation of the results is limited. Moreover, there is potential for selection bias because 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 recommended by Health Canada.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model

Component	Description
Target populations	<ul style="list-style-type: none"> • Patients with schizophrenia experiencing PNS • Patients with acute schizophrenia requiring both acute and long-term maintenance therapy with oral atypical antipsychotic drugs
Treatment	Cariprazine
Submitted price	Cariprazine: \$4.90 per capsule, regardless of strength
Treatment cost	The cost for cariprazine is \$1,789 per year
Comparators	<ul style="list-style-type: none"> • PNS patients: risperidone • Acute patients: aripiprazole, asenapine, brexpiprazole, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life-years, life-years
Time horizon	2 years
Key data source	<ul style="list-style-type: none"> • PNS model: efficacy data were based on the head-to-head RGH-188-005 trial • Acute model: efficacy data were obtained from a network meta-analysis, which included 3 short-term trials (RGH-MD-16, RGH-MD-04, and RGH-MD-05) for cariprazine
Key limitations	<ul style="list-style-type: none"> • Based on CADTH's Clinical Review: <ul style="list-style-type: none"> ◦ For the PNS population: Based on the pivotal trial and clinical expert feedback, it is unknown whether the difference in PANSS mean score between cariprazine and risperidone is clinically relevant because the minimal important difference in negative symptom scores is unknown. The sponsor's model relies on improvements in PANSS score to inform treatment efficacy, and its estimates of cost-effectiveness are therefore highly uncertain. ◦ For the acute population: Based on the sponsor's submitted network meta-analysis, [REDACTED] was also severely limited by heterogeneity. Any conclusions about the incremental cost-effectiveness are highly uncertain. • In the PNS model, the sponsor did not adequately model all relevant comparators when they excluded olanzapine and clozapine. Furthermore, clinical expert feedback suggested that risperidone may have minimal impacts on PNS and may not be the most relevant choice of comparator. Therefore, the clinical effectiveness and cost-effectiveness of cariprazine compared with other comparators for PNS is unknown. • High structural uncertainty is present in the PNS model. The sponsor's model does not reflect treatment of PNS due to limited relevance of the chosen comparator, improper modelling of treatment-resistant patients, and incomplete modelling of treatment sequence by exclusion of third-line therapy. • The utility values used in the sponsor's model are not appropriate and should instead be derived using indirect methods of measurement. The utility values for specific health states did not meet face validity and are key drivers in the sponsor's model, which potentially biases cost-effectiveness in favour of cariprazine. • Transition probabilities in the PNS model were derived partly from clinical expert elicitation because of a lack of clinical data. The transition from specific "worse" health states to "better" health states did not meet face validity and were derived from an inappropriate sample size. These likely biased cost-effectiveness in favour of cariprazine.
CADTH reanalysis results	<ul style="list-style-type: none"> • Given CADTH could not address the limitations found in the submitted models, and the overall uncertainty of the clinical data, CADTH could not derive a base case in the acute or PNS models. There is a high degree of uncertainty regarding the comparative clinical effects (and the meaningfulness of observed changes) for cariprazine and relevant comparators. Use of

Component	Description
	<p>the sponsor’s models to examine the impact of uncertainty was of limited value given issues regarding the model structure. Consequently, CADTH conducted a cost comparison between cariprazine and its comparators to highlight the differences in drug costs.</p> <ul style="list-style-type: none"> • The \$4.90 daily cost of cariprazine is more expensive than all generic oral atypical antipsychotic drugs available in Canada, which range from \$0.35 to \$3.16 daily. There is no clinical evidence to justify a price premium for cariprazine. • A price reduction of 71% to 93% for the submitted price of cariprazine is necessary to be equivalent to the lowest-priced generic atypical antipsychotic drug, olanzapine, at the upper and lower recommended doses, respectively.

PANSS = Positive and Negative Syndrome Scale; PNS = predominant negative symptoms.

Budget Impact

CADTH identified key limitations with the sponsor’s analysis related to the underestimation of market shares for cariprazine, the inappropriate exclusion of relevant comparators for the treatment of PNS in the estimation of capture rates, and uncertainty with a claims-based approach to assessing the budget impact. CADTH reanalysis increased the market shares for cariprazine. In the CADTH base case, the anticipated budget impact of reimbursing cariprazine for the treatment of schizophrenia in adults is \$1,535,742 in year 1, \$5,437,489 in year 2, and \$11,695,629 in year 3, for a 3-year total of \$18,668,860. Uncertainty remains in this estimate due to a lack of technical information about the claims-based approach and data sources used as well as the limitations with the sponsor’s estimation of comparator capture rates.

Request for Reconsideration

The sponsor filed a Request for Reconsideration of the draft recommendation for cariprazine for the treatment of adult patients with schizophrenia. In their request, the sponsor identified the following issues:

- The recommendation and cited reasons of “uncertain clinical relevance” are not supported by the submitted evidence. The sponsor maintained that there is sufficient evidence to conclude that cariprazine will have clinically relevant treatment effects.
- The sponsor is of the view that the CDEC recommendation for cariprazine is inconsistent with recommendations previously issued by CDEC for antipsychotic treatments for schizophrenia, specifically those recommending reimbursement.
 - CDEC discussed the issue raised in the Request for Reconsideration regarding consistency in recommendations for drugs to treat schizophrenia. Each submission or resubmission that is filed for review through the drug reimbursement process is evaluated independently of previous submissions based on the procedures and processes in effect at the time of the review.
- The recommendation fails to recognize that the submitted clinical evidence package for cariprazine addresses specific treatment gaps that were raised by patient and clinician groups via the stakeholder input process.

In the meeting to discuss the sponsor's Request for Reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in the diagnosis and management of schizophrenia
- feedback from the public drug plans
- feedback from 3 clinician groups: the CCEIP, the Atlantic Psychiatrists group, and the National Advisory Panel; as well as 2 individual clinicians who submitted input on the draft recommendation
- feedback from 3 patient groups: the Institute for Advancement in Mental Health, the SSC, and the CMHA Alberta Division.

All stakeholder feedback received in response to the draft recommendation from patient and clinician groups and the public drug programs is available on the CADTH website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Initial meeting date: March 23, 2022

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: July 27, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None