CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Cariprazine (Vraylar)

Indication: For the treatment of schizophrenia in adults

Sponsor: Allergan (an AbbVie company)

Recommendation: Do Not Reimburse

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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 CADTH Canadian Drug Expert Committee (CDEC) recommends that cariprazine not be reimbursed for the treatment of schizophrenia in adults.

Rationale for the Recommendation

Evidence from three 6-week double blind randomized controlled trials (RCTs) in adults experiencing an acute exacerbation of schizophrenia showed that cariprazine was associated with modest improvements in schizophrenia symptoms and overall severity at 6 weeks relative to placebo that were statistically significant but of uncertain clinical relevance. Although one randomized withdrawal design study showed that patients who continued with cariprazine had a longer time to relapse than those who were switched to placebo, this study enrolled an enriched population and included only patients who tolerated and showed a good response to cariprazine. Additionally, a large proportion of patients discontinued the trial, which challenges the generalizability of the results. No comparative data versus other antipsychotics were available. Further, in a 26-week RCT in adults with schizophrenia and predominant negative symptoms, treatment with cariprazine led to a greater improvement in 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 since the minimally important difference to show a clinical effect is unknown (for negative symptoms scores) or was not exceeded (for functional status).

Patients expressed a need for treatments which minimize the negative and cognitive symptoms of schizophrenia, provide an additional therapy for those who do not respond, or respond well, to existing drugs, and which minimize adverse effects. CDEC concluded that there was insufficient evidence to demonstrate that these needs were met by cariprazine. Furthermore, conclusions could not be drawn on the impact of cariprazine on functional status, hospitalization, or persistence with therapy due to study limitations (such as lack of control for multiplicity of testing) or lack of data.

Discussion Points

- CDEC discussed the comparison of cariprazine with placebo and the reported magnitude of effects in the acute trials. CDEC highlighted the uncertainty with defining a minimally important between-group difference based on the PANSS total score. CDEC noted that the differences in CGI-S between cariprazine and placebo did not exceed the minimally important difference threshold. In light of these findings, CDEC considered cariprazine treatment effects to be modest and of uncertain clinical relevance.
- 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 agents. As such, comparison of effectiveness against placebo has limited meaning in clinical practice. While 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 to aripiprazole or risperidone in patients with acute schizophrenia.
- CDEC acknowledged that management of negative symptoms of schizophrenia is an important unmet need in the current treatment paradigm. Negative symptoms of schizophrenia are challenging to treat and may be predominant only in a subset of patients that are difficult to identify during the acute phase. Although statistically significant differences were detected between cariprazine and risperidone in terms of negative symptoms or functional status, those differences were considered small, and substantial uncertainty remains regarding the clinical relevance and importance of the effects observed.
- CDEC noted that 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.
- CDEC noted that evidence from the network meta-analysis submitted by the sponsor for the treatment of acute schizophrenia and prevention of relapse was 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.

Background

Schizophrenia is a chronic mental illness that affects the way a person interacts with and understands the world. The condition, when active, is characterized by delusions, hallucinations, disorganized speech, disorganized behavior and impaired cognitive ability. The symptoms associated with schizophrenia are categorized as being 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 (2016-2017), 1 out of 100 Canadians 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 has been approved by Health Canada for the treatment of schizophrenia in adults. Cariprazine is an atypical antipsychotic drug. 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.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A systematic review of 5 double-blind randomized controlled trials (RCTs) in adults with schizophrenia.
- Patients' perspectives gathered by patient groups, 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 comprising of Canadian psychiatrists with experience in the management of schizophrenia.
- Indirect evidence from 3 indirect treatment comparisons (ITCs).
- Additional data from two open-label extension studies.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

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

The patient input was based on two 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 impacts their ability to access treatment and support. This can cause significant strains in their relationships with their support network, ultimately leading to social isolation.

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 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.

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

Clinician input

Input from clinical experts 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 suggested it may 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 exam which thoroughly assesses hallucinations, delusions and disorganized thought and behavior and that shows documented improvement over an 8 week course of therapy would indicate a response to treatment, along with collateral input from caregivers when available indicating reduced behavioral 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 as 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 regime 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: the Canadian Consortium for Early Intervention in Psychosis group (CCEIP), and a national advisory board comprising of Canadian psychiatrists with experience in the management of schizophrenia. Three clinicians with the 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 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, 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 Positive and Negative Syndrome Scale (PANSS) total score. The PANSS is a 30-item rating scale that assess 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 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.

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 assess 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 versus placebo (24.5%, P = 0.28). 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. The between group differences favored cariprazine versus placebo with a hazard ration (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 factor score for negative symptoms (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 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 (OR) of 2.1 ([redacted] 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 78%) and the longer-term studies (54% to 80%) reported one 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 those in the cariprazine groups and 3% to 4% 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 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 9% to 15% in the placebo groups, 6% 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 events 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 [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. 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 7% who switched to placebo during the double-blind phase. The frequency of discontinuation due to extrapyramidal symptoms adverse events was low, ranging from 0% to 2% 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 [redacted] was reported among patients receiving cariprazine, [redacted].

In the 6-week studies, 5% to 11% of patients who received cariprazine reported a clinically important increase in body weight (defined as ≥7%), versus 2% to 4% in the placebo group, 6% in the aripiprazole group and 17% in the risperidone group. In study MD-06, 11% of patients reported a ≥7% increase in body weight during the open label cariprazine phase, and in 27% to 32% 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 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 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 has 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 adverse events.

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. 201917), or metabolic effects (Pillinger et al. 202016) of antipsychotics in patients with acute schizophrenia.

Results

For the acute treatment of schizophrenia, the results of the unpublished NMA favored cariprazine versus placebo for the proportion of responders, but with no differences detected compared with other atypical antipsychotics. The indirect evidence suggests that cariprazine may have a higher risk of all-cause discontinuation but lower risk of sedation or somnolence versus some, but not all active comparators. No differences were detected between cariprazine and other antipsychotics in the risk of extrapyramidal symptoms or weight gain based on the unpublished NMA.

The results of the two published ITCs were generally consistent with the unpublished ITC 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 (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 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.

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 (standard error [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. 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% increase in body weight was reported by 26% and 33% of patients in study MD-11 and MD-17, respectively. In both studies, 10% to 13% of patients discontinued 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. 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.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	• Patients with schizophrenia experiencing predominant negative symptoms (PNS) • Patients with acute schizophrenia requiring both acute and long-term maintenance therapy with oral atypical antipsychotics (AAPs)
Treatment	Cariprazine
Submitted price	Cariprazine: $4.90 per capsule, regardless of strength
Treatment cost	The cost for cariprazine is $1,789 per year
Comparators	• PNS patients: risperidone • Acute patients: aripiprazole, asenapine, brexpiprazole, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	2 years
Key data source	• 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 three short-term trials (RGH-MD-16, RGH-MD-04, and RGH-MD-05) for cariprazine.

Key limitations	• Based on CADTH's Clinical Review:
	  ○ For the PNS population – based on the pivotal trial and clinical expert feedback, it is unknown whether the difference in PANSS mean score between cariprazine and risperidone is clinically relevant, because the minimally important difference in negative symptom scores is unknown. 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 NMA, no differences were observed in the efficacy of cariprazine compared to other oral AAPs. Long-term data regarding relapse 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 to 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, potentially biasing cost-effectiveness in favour of cariprazine.
	• Transition probabilities in the PNS model were derived partly from clinical expert elicitation due to 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	• 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

Component	Description
	(and the meaningfulness of observed changes) for cariprazine and relevant comparators. Use of 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. • The $4.90 daily cost of cariprazine is more expensive than all generic oral AAPs 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 AAP, olanzapine, at upper and lower recommended doses, respectively.

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 three-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, in addition to the limitations with the sponsor's estimation of comparator capture rates.

Canadian Drug Expert Committee (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.

Meeting Date: March 23, 2022

Regrets

None

Conflicts of Interest

None