

CADTH Reimbursement Recommendation

Cariprazine (Vraylar)

Indication: As monotherapy for:

- bipolar mania: acute management of manic or mixed episodes associated with bipolar I disorder in adults, and
- bipolar depression: acute management of depressive episodes associated with bipolar I disorder in adults.

Sponsor: Allergan (an AbbVie Company)

Final recommendation: Do not reimburse

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What Is the CADTH Reimbursement Recommendation for Vraylar?

CADTH recommends that Vraylar should not be reimbursed by public drug plans for use as monotherapy for the acute management of manic or mixed episodes associated with bipolar I disorder (bipolar mania), and acute management of depressive episodes associated with bipolar I disorder (bipolar depression).

Why Did CADTH Make This Recommendation?

- Despite results from 6 clinical trials that showed treatment with Vraylar may improve manic and depressive symptoms associated with bipolar mania and bipolar depression, it is unclear if patients treated with Vraylar in clinical practice would experience the same magnitude of improvement, as patients in the cariprazine studies may not represent the population of patients who will use cariprazine in Canada.
- Although the results for the 1.5 mg dose of Vraylar suggested an improvement in depressive symptoms, the results for the 3 mg dose of Vraylar were inconsistent across studies; therefore, the CADTH Canadian Drug Expert Committee (CDEC) was not confident that Vraylar would fill a treatment gap.
- The potential benefit of Vraylar compared to other treatments for bipolar I disorder are unknown. There were no studies directly comparing Vraylar with any other treatments, and the indirect comparative evidence reviewed had many limitations.

Additional Information

What Is Bipolar I Disorder?

Bipolar I disorder is a condition defined by episodes of mania and depression. During these episodes, patients may experience severe changes in their mood, activity levels, energy, and ability to carry out everyday tasks. It is estimated that 0.87% of those living in Canada are living with bipolar I disorder.

Unmet Needs in Bipolar I Disorder

Patients expressed a need for treatments that control the symptoms of bipolar I disorder, provide an additional therapy for those who do not respond adequately to existing drugs, lower the frequency of administration, and minimize side effects.

How Much Does Vraylar Cost?

Treatment with Vraylar is expected to cost approximately \$1,790 per patient annually.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that cariprazine not be reimbursed for use as monotherapy for the acute management of manic or mixed episodes associated with bipolar I disorder (bipolar mania), and acute management of depressive episodes associated with bipolar I disorder (bipolar depression).

Rationale for the Recommendation

Six randomized, double-blind trials demonstrated that, compared with placebo, 3 to 6 weeks of treatment with cariprazine monotherapy resulted in a reduction in symptoms of either acute manic or mixed episodes (based on the Young Mania Rating Scale [YMRS] total score in studies RGH-MD-31, RGH-MD-32, and RGH-MD-33), or acute depressive episodes (based on the change in Montgomery-Åsberg Depression Rating Scale [MADRS] total score in studies RGH-MD-53, RGH-MD-54, and RGH-MD-56), in patients with bipolar I disorder. Regarding the latter trials, CDEC noted that reduction of depressive symptoms with cariprazine 3 mg was not demonstrated in 2 of the 3 trials for bipolar depression. CDEC was unable to ascertain whether results from the trials would be observed in patients with bipolar disease in Canada as generalizability to clinical practice was limited due to the inclusion of highly selected patients who may not represent the intended population for cariprazine and the short duration of the studies, which creates uncertainty regarding the duration of response and long-term safety of cariprazine. Moreover, results of cariprazine treatment on health-related quality of life (HRQoL), hospitalizations, cognitive impairment, and adherence or persistence with therapy remain unknown, as they were not evaluated in any of the trials. Acute episodes of bipolar I disorder are almost always treated with pharmacotherapy, and multiple drugs are currently available. As such, CDEC noted that comparison of effectiveness against placebo does not inform the anticipated place in therapy of cariprazine in this patient population. In the absence of direct comparative evidence, the results of 3 network meta-analyses (NMAs) were considered. However, conclusions regarding the results of the NMAs were limited by uncertainty, and therefore, how cariprazine compares to other treatments for bipolar I disorder remains unclear. Patients expressed a need for treatments that control the symptoms of bipolar I disorder, provide an additional therapy for those who do not respond adequately to existing drugs, lower the frequency of administration, and minimize adverse effects. CDEC concluded that there was insufficient evidence to demonstrate that these needs were met by cariprazine.

Discussion Points

- CDEC noted that it is common for clinical trials for bipolar mania or mixed episodes to be conducted in an inpatient setting, as was the case RGH-MD-31, RGH-MD-32, and RGH-MD-33. However, there is uncertainty regarding whether similar results would be observed in an outpatient treatment setting, where the majority of patients with bipolar disorder are managed. The committee also discussed the potential uncertainty of the generalizability of the trial results to patients often seen in clinical practice as patients with comorbidities, other diagnoses, substance use disorder, and elevated risk of suicide were excluded from

the trials. During the discussion of the request for reconsideration, CDEC deliberated on the challenges associated with conducting a trial in a complex patient population such as those living with bipolar I disorder. However, the generalizability of the cariprazine trials remains a limitation of the evidence, particularly when trying to determine the place in therapy for cariprazine, considering the availability of alternative treatments.

- CDEC noted that the overall mean daily dose in 2 of the acute mania trials, RGH-MD-31 and RGH-MD-32, was 8.8 mg per day and 7.5 mg per day, respectively. This exceeds the maximum daily dose of 6 mg set by Health Canada, and imparts uncertainty regarding the efficacy of cariprazine, particularly when used according to the approved indication in Canadian clinical practice. CDEC discussed this issue during the reconsideration of the recommendation for cariprazine, and noted that the dosing of cariprazine used in the trials was not a reason for the recommendation, although it adds to the uncertainty of the evidence supporting the efficacy and safety of the drug.
- Since no direct comparative evidence was identified, CDEC considered indirect evidence from 3 NMAs, 1 of which was submitted by the sponsor. The NMA submitted by the sponsor [REDACTED] a benefit for treatment with cariprazine relative to other comparators of interest for the treatment of acute manic or mixed episodes or acute depressive episodes. The results of the NMAs were considered highly uncertain due to limitations that include potential heterogeneity, lack of precision, and bias resulting from a small number of events. The 2 published NMAs were limited by insufficiently reported methodology, but the results were generally consistent with the sponsor-submitted NMA. As part of the reconsideration discussion, CDEC considered the indirect evidence included in the review of cariprazine. Given the limitations of the NMAs that have been described, the committee indicated that the indirect evidence does not permit the ability to draw conclusions about the comparison between cariprazine and other treatments for bipolar I disorder. Given the other available treatments for bipolar I disorder that are available, the absence of robust evidence comparing cariprazine to other treatments such as quetiapine or lurasidone remains a key gap in the evidence.
- CDEC discussed the evidence in support of cariprazine for patients with acute mania with mixed features associated with bipolar I disorder. The bipolar mania studies included a subgroup analysis of the primary outcome (change in YMRS score) by patients with mania and patients with mixed mania (mixed features). The results were reported descriptively and based on a small sample size of patients with mixed features, ranging from 15 to 23 patients per treatment group. Overall, the result of the primary outcome assessment in the subgroup of patients with mixed features was consistent with the primary analysis in 2 of the 3 studies. Due to the limitations of the data available for patients with mixed features and the availability of other agents for this population (e.g., asenapine and ziprasidone), there is uncertainty regarding whether cariprazine fulfills an unmet need in this patient population.
- CDEC noted that extrapyramidal symptoms, headache, and akathisia were the most common adverse events (AEs) among those who received cariprazine. Additionally, a dose-response relationship was observed with the frequency of AEs. The short duration of the trials limited the ability to sufficiently evaluate some outcomes (e.g., weight gain) as well as longer-term efficacy and safety. Given these issues and the need for treatments for bipolar I disorder that are well-tolerated by patients, particularly in terms of sedation, weight gain, and metabolic effects, CDEC indicated that it is unclear if cariprazine addresses this need.

- CDEC noted that uncertainties remain regarding the use of cariprazine in combination with other agents. Clinical experts indicated that cariprazine would likely be used in monotherapy and in combination with either lithium or anticonvulsants, which is a standard approach with the use of second generation antipsychotic drugs in bipolar disorder. CDEC noted that combination therapy is not part of the Health Canada–approved indication for cariprazine. Additionally, the clinical experts suggested that the lack of evidence for the use of cariprazine as maintenance therapy is a limitation of its use.
- CDEC discussed each of the issues identified by the sponsor in their request for reconsideration. The issues indicate that the sponsor does not agree that the original recommendation is supported by the evidence due to the committee’s interpretation of the needs of patients addressed by cariprazine, the generalizability of the results of the cariprazine trials, and how the results of the evidence included in the CADTH review of cariprazine were reported. Due to the limitations of the available evidence from the cariprazine trials, CDEC remained uncertain whether cariprazine meets important therapeutic needs for patients experiencing bipolar mania and bipolar depression.

Background

Bipolar I disorder is a mood disorder characterized by episodes of mania, hypomania, and major depression. The estimated average age of onset in Canada is 22.5 years, and the estimated lifetime prevalence of bipolar I disorder in Canada is 0.87%. Episodes of mania and depression present with significant changes in mood, energy, behaviour, sleep, and cognition. Mania also presents with change in activity. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) patients that present with mixed features experience at least 3 non-overlapping symptoms from the opposing pole (mania or depression) during the majority of the days of their current episode. Quality of life and psychosocial functioning – including the ability to maintain proper work – are severely impacted by bipolar disorder and are more pronounced in those living with depressive symptoms, those with multiple previous episodes, those with a longer duration of illness, and in those with cognitive decline.

There are no disease-modifying treatments for bipolar disorder. Bipolar disorder is treated with the combination of pharmacological, non-pharmacological (e.g., electroconvulsotherapy), and psychosocial (e.g., psychotherapy) treatments. Medications include mood stabilizers (which include agents from a variety of classes, such as second generation antipsychotic drugs, anticonvulsants, and lithium), and antidepressants. The clinical experts stated that overall, there are many different pharmacological options, and the choice of treatment is usually guided by evidence of efficacy and tolerability, and tailored to the patient’s needs. A limitation of treatment is there are fewer treatments available for the management of depressive episodes, and they are associated with relatively high rates of treatment failure due to non-response or poor tolerability.

Cariprazine has been approved by Health Canada for treatment as monotherapy for:

- bipolar mania: acute management of manic or mixed episodes associated with bipolar I disorder in adults
- bipolar depression: acute management of depressive episodes associated with bipolar I disorder in adults.

Cariprazine is a second generation antipsychotic drug. It is available as 1.5 mg, 3 mg, 4.5 mg, and 6 mg oral capsules. The dosage recommended in the product monograph is 1.5 mg to 6 mg once daily for bipolar mania, and 1.5 mg once daily for bipolar depression.

Sources of Information Used by the Committee

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

- a systematic review of 6 randomized, double-blind, placebo-controlled trials in adult patients with a primary diagnosis of bipolar I disorder
- a review of 1 sponsor-submitted NMA and 2 published NMAs
- a review of 1 long-term, open-label study examining the long-term safety and tolerability of cariprazine in patients with bipolar mania and 1 post hoc analysis of the efficacy of cariprazine in a subpopulation of patients with bipolar mania with mixed features
- patient perspectives gathered by 2 patient groups, the Institute for Advancements in Mental Health (IAM) and the Mood Disorders Society of Canada (MDSC)
- input from public drug plans that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with bipolar disorder
- input from 2 clinician groups, the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Western Canadian Clinical Advisory Network (WC-CAN)
- 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

This section was prepared by CADTH staff based on the input provided by patient groups.

Two responses to CADTH's call for patient input were received for this review: a submission from IAM and a submission from MDSC. IAM and MDSC are organizations that support individuals living with mental illness such as bipolar disorder, including patients, their families, and service providers.

The information used to inform the IAM submission was based on 2 online surveys, conducted in 2018 and February 2022. Potential respondents to these online surveys included members of the IAM and Hope and Me – Mood Disorders Association of Ontario client networks. 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. Among the respondents of the 2022 survey, 33% identified as an individual living with symptoms of bipolar disorder, 58% were relatives, 8% were caregivers of someone with lived experience, and 1% did not specify. MDSC drew information from interviews with patients and family members, 2 national mental health surveys conducted in March 2018 and September 2021, and shared experiences that have

been posted on the MDSC online discussion forum. The interviews were conducted with 5 patients with bipolar disorder, including semi-structured phone interviews with adults living with bipolar disorder in January 2021, and 3 family members.

Respondents indicated that living with bipolar disorder has impacted their mental health, social relationships, and day-to-day functioning at work and school. Patients can also experience a lack of insight into their illness, which impacts their ability and motivation to seek treatment and causes significant strain in relationships. Survey respondents described the advantages of taking medications for bipolar disorder, which include managing symptoms of bipolar disorder, experiencing fewer episodes of mental illness, and avoiding visits to the hospital. They also described disadvantages of taking medications for bipolar disorder, which include requiring frequent follow-ups with health care providers; needing to take the medication daily; and their symptoms, including bipolar depression, not being well controlled. Further, respondents described the benefits of an injectable formulation, which include convenience and not needing to remember to take it daily, while the difficulties were pain at injection site and frequent travel to clinics. The most common side effects of medications for bipolar disorder identified by respondents were drowsiness, dry mouth, restlessness, and weight gain. Respondents also identified the cost of medications as a significant barrier to access.

Survey respondents reported that treatment of bipolar disorder is individualized, as not every patient will respond to 1 medication. To find the right medication that enables the highest degree of functioning while minimizing side effects, patients with bipolar disorder often have to go through a trial and error process. This process involves taking a number of different medications and at different dosages until their goals of therapy have been achieved. This process can make it challenging for patients to adhere to their prescribed regimen and can be exacerbated by additional challenges such as waiting to be approved for coverage by public drug programs and experiencing relapse. As a result, patients feel that outcomes can be improved by increasing equitable access to and the selection of medications that are reimbursable. According to respondents, antipsychotic medications can be improved by increasing its ability to control the symptoms of bipolar disorder, improving the side effect profile, and providing a greater range of strengths and dosages to lower the frequency of administration.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts indicated numerous challenges with addressing treatment goals for patients living with bipolar I disorder using currently available treatments. Insufficient response to treatment was noted as being very common, particularly in bipolar depression. There are no disease-modifying treatments, and long-term effectiveness of current treatments is unclear. Bipolar disorder is typically a lifelong, persistent, and/or highly recurrent condition. Some key outcomes are not adequately addressed by current treatments. For example, the extent to which current treatments address cognition directly, instead of indirectly through mood symptoms, is unclear. Tolerability is a problem, particularly in bipolar depression, where the most effective agents — like quetiapine and olanzapine — have well-known metabolic side effects, which is particularly concerning given the elevated and independent risk of metabolic and cardiovascular conditions in this population. Finally, adherence is also an issue; poor compliance is very common in real-world settings.

Based on the currently available clinical evidence, the clinical experts felt it was very unlikely that cariprazine would cause a shift in treatment paradigm, despite having a somewhat distinct pharmacological profile. Mechanistically, cariprazine was described as very similar to currently available treatments, and therefore very much within the current paradigm of symptomatic management. However, the experts noted that the combination of efficacy for both acute mania and depression, as well as an acceptable tolerability profile, may eventually result in cariprazine as a first-line treatment. The experts did not identify any reason to recommend that patients try other treatments before cariprazine. The clinical experts suggested cariprazine will probably be used in monotherapy and in combination with either lithium or anticonvulsants, which is a standard approach with second generation antipsychotic drugs in bipolar disorder.

The experts indicated that it is challenging to identify and diagnose patients with bipolar disorder, and that misdiagnosis and/or delayed diagnosis are relatively common. Relatedly, they stated that there are no diagnostic tools or tests that are useful, and the diagnosis is based on clinical assessment.

At this time, the clinical experts stated that it is not possible to identify patients who are most likely to exhibit a response to treatment with cariprazine. They noted that reliable prediction of response has not been achieved, even with sophisticated research methods (e.g., genomics, neuroimaging), and certainly cannot be done reliably with the most widely available clinical tools. Other than polarity of mood episode, there are no other validated indices to predict response to any given agent, according to the clinical experts. The clinical experts stated that pre-symptomatic patients should not be treated with cariprazine, or any other agent, mostly due to the low predictive power of current assessment tools. The clinical experts did not identify any patients that would be least suited for treatment with cariprazine, noting that within the population of adults with bipolar I disorder, there were no major contraindications unique to cariprazine.

The clinical experts identified YMRS, MADRS, and Hamilton Depression Rating Scale (HAMD-17) as the most commonly used outcomes to assess response to treatment in research settings, but in the real world, patient-rated questionnaires such as the Patient Health Questionnaire and the Beck Depression Inventory are more common. The experts also noted that all of these outcomes, however, have very good concurrent validity. A reduction in the frequency or severity of symptoms, improvement in symptoms, stabilization (no deterioration) of symptoms, ability to perform activities of daily living, and improved survival were all clinically meaningful, according to the clinical experts. They described a reduction in the severity (e.g., controlling physical agitation) and frequency of symptoms as the usual first goal of treatment. Subsequently, the experts stated that treatment aims to restore functioning, including improving cognitive functioning and coping skills, with a return to work, school, and daily activities being an important benchmark. The experts identified long-term goals, such as the prevention of relapses and recurrences, as well the onset and progression of psychiatric (e.g., anxiety disorders, substance abuse) and medical comorbidities (e.g., obesity or diabetes).

Regarding how often treatment response should be assessed, the clinical experts suggested that in the acute phase, response is usually assessed between 2 and 4 weeks, depending on the severity. In the maintenance phase, it is recommended that patients are assessed at least every 2 to 3 months. The clinical experts indicated that treatment discontinuation is determined by either lack of response or poor tolerability, noting that most guidelines recommend discontinuing a treatment if there is no response to very poor response within

4 to 6 weeks. Further, they indicated that discontinuation due to tolerability depends on the severity and progression of specific side effects, particularly extrapyramidal side effects (EPS) and akathisia, which are the most common side effects of cariprazine and similar drugs. These can be time dependent, which tend to be worse in initial titration phases but improve with time. If side effects are moderate to severe and/or do not meaningfully improve in 1 to 2 weeks, treatment should be discontinued.

The clinical experts reported that family physicians can and frequently do make a diagnosis of bipolar disorder, and regularly prescribe similar agents. The experts also noted that there are no special tests required for diagnosis of bipolar disorder, nor for the prescription and monitoring of cariprazine. Given the high prevalence of bipolar disorder and the relative lack of psychiatrists in Canada, a significant proportion of patients are treated by family physicians, therefore requiring the involvement of specialists would significantly restrict the use of this medication.

Clinician Group Input

Two clinician groups provided input to this review: CANMAT and WC-CAN. One clinician on behalf of CANMAT and 6 clinicians with WC-CAN contributed to these submissions. Both clinician groups recognized the unmet need for a medication that is effective in multiple phases of bipolar disorder, including bipolar depression, with low rates of AEs, to minimize polypharmacy and improve adherence. The clinical experts consulted by CADTH identified additional unmet needs, which include the absence of disease-modifying agents, the uncertainty regarding the long-term effectiveness and the direct effects on cognition of currently available treatments, and the lack of depot alternatives for commonly used first-line pharmacologic options. Both clinician groups advocated for cariprazine as a first-line treatment option for patients with bipolar disorder in the treatment of acute mania and depression, and to be used as monotherapy and possibly as combination therapy with other mood stabilizers.

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
- generalizability of trial populations to the broader populations in the jurisdictions.

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

The systematic review of cariprazine included a total of 6 multi-centre, randomized, double-blind, placebo-controlled, parallel-group studies in adults with a primary diagnosis of bipolar

I disorder. Of the 6 included RCTs, 3 evaluated cariprazine 3 mg to 12 mg (flexible dose) for the treatment of acute manic or mixed episodes (RGH-MD-31, N = 238; RGH-MD-32, N = 312; and RGH-MD-33, N = 497) and 3 evaluated cariprazine 1.5 mg and 3 mg (fixed dose) for the treatment of acute depressive episodes (RGH-MD-56, N = 578; RGH-MD-53, N = 493; and RGH-MD-54, N = 488). The flexible-dosing regimen in the bipolar mania studies involved dose adjustments based on treatment response assessed by the investigator (RGH-MD-31) or using the YMRS (RGH-MD-32 and RGH-MD-33) and tolerability at the discretion of the investigator. The objective of each of the studies was similar: to evaluate the efficacy, safety, and tolerability of cariprazine monotherapy versus placebo for the treatment of acute manic or mixed episodes, or acute depressive episodes, associated with bipolar I disorder. The primary end point in all studies was the change in symptoms, measured using the YMRS total score in the studies of acute manic or mixed episodes, and MADRS total score in the studies of acute depressive episodes. The secondary end point was the change in CGI-S and was consistent across studies. Primary and secondary outcomes were assessed at week 3 in the acute mania studies and at week 6 in the acute depression studies. Other measures of changes in symptom severity (CGI-I, PANSS, HAMD-17, HAM-A, QIDS-SR16), functioning (Functioning Assessment Short Test [FAST]), suicidal ideation (Columbia Suicide Severity Rating Scale), response rate, and remission rate were also reported.

The mean age of patients enrolled in the included studies ranged between 36 years (SD = 11) and 45 years (SD = 12), and the mean weight of patients ranged from 70 kg (SD = 20) to 87 kg (SD = 25). The population in the acute mania studies was slightly younger and had a lower body weight than patients in the acute depression studies. More patients in the acute mania studies were male (54% and 68%) and more patients in the acute depression studies were female (57% and 65%). The mean duration of bipolar I disorder was 10 years (SD = 9) to 16 years (SD = 10), and the age of onset ranged from 23 years (SD = 8) to 28 years (SD = 11). The duration and age of onset of bipolar I disorder was not reported in the RGH-MD-53 and RGH-MD-54 studies. During the trials for acute mania or mixed episodes, between 81% and █% of patients were currently experiencing a manic episode and between █% and 20% were experiencing a mixed episode. Between █% and █% of patients were diagnosed with a moderate episode, █% to █% with a severe episode without psychotic features, and █% to █% with a severe episode with psychotic features. During the RGH-MD-53 and RGH-MD-54 studies (not reported in the RGH-MD-56 study), between █% and █% of patients were currently experiencing a severe depressive episode and between █% and █% were experiencing a moderate depressive episode, and the mean duration of the current episode was 3.3 months (SD = 2.3) to 3.9 months (SD = 2.6).

Efficacy Results

The bipolar studies used a flexible dose regimen for cariprazine. The overall mean daily dose in the RGH-MD-31 and RGH-MD-32 studies was 8.8 mg (SD = █) and 7.5 mg (SD = █) per day, respectively. The overall mean daily dose in RGH-MD-33 was 4.8 mg (SD = █). The overall mean daily dose was not reported in the bipolar depression studies.

All 3 studies of acute mania demonstrated that treatment with flexible dosing of cariprazine was associated with a greater reduction of symptoms of acute mania relative to placebo, based on the YMRS total score at week 3. This was based on a difference in score between cariprazine (3 mg to 12 mg) and placebo of -6.1 (95% CI, -8.9 to -3.3; $P < 0.0001$) in the RGH-MD-31 study, and -4.3 (95% CI, -6.7 to -1.9; $P = 0.0004$) in the RGH-MD-32 study. In the RGH-MD-33 study, the difference in score between cariprazine (3 mg to 6 mg) and placebo was -6.1 (95% CI, -8.4 to -3.8; $P < 0.001$). The within-group change in YMRS

score was clinically meaningful for both the cariprazine and placebo treatment groups, based on a within-group minimally important difference (MID) of 6.6 points. All sensitivity analyses supported the results of the primary efficacy analyses. Subgroup analyses based on the pivotal trials did not suggest a difference in efficacy between patients experiencing a manic episode and patients experiencing a mixed episode. In the studies of acute bipolar depression, treatment with cariprazine 1.5 mg was associated with a greater reduction of symptoms of depression relative to placebo, based on a LSMD in the MADRS total score at week 6 of -2.5 (95% CI, -4.6 to -0.4 ; $P = 0.0417$) in the RGH-MD-53 study, -2.5 (95% CI, -4.6 to -0.4 ; $P = 0.0331$) in the RGH-MD-54 study, and -4.0 (95% CI, -6.3 to -1.6 ; $P = 0.0030$) in the RGH-MD-56 study. The comparison of cariprazine 3 mg to placebo did not consistently demonstrate a benefit with treatment. In the RGH-MD-54 study, the LSMD was in favour of cariprazine 3 mg relative to placebo (LSMD = -3.0 ; 95% CI, -5.1 to -0.9 ; $P = 0.0103$). The LSMD in the RGH-MD-53 and RGH-MD-56 studies was -1.8 (95% CI, -3.9 to 0.4 ; $P = 0.1051$) and -2.5 (95% CI, -4.9 to -0.1 ; $P = 0.1122$), respectively. A between-groups MID of at least 2 points was identified for the MADRS total score.^{8,9} Comparisons that were statistically significant were also clinically meaningful as per the MID, with the exception of cariprazine 3 mg in the RGH-MD-56 study, which was not statistically significant.

The secondary end point in all studies was the change in CGI-S, which is an outcome based on a global assessment of symptom severity relative to other patients the assessor has observed. The CGI-S has been validated through a comparison to the PANSS in patients with schizophrenia, but evidence of reliability and responsiveness were not identified. In the acute mania studies, the cariprazine treatment groups exhibited a greater change in overall severity based on the CGI-S at week 3 than the placebo treatment groups, which is consistent with the primary analysis. This was based on a difference in score between cariprazine (3 mg to 12 mg) and placebo of -0.6 (95% CI, -1.0 to -0.3 ; $P = 0.0001$) in the RGH-MD-31 study, and -0.4 (95% CI, -0.7 to -0.1 ; $P = 0.0027$) in the RGH-MD-32 study. In the RGH-MD-33 study, the difference in score between cariprazine (3 mg to 6 mg) and placebo was -0.6 (95% CI, -0.9 to -0.4 ; $P < 0.001$). In the acute depression studies, a benefit in terms of the change from baseline to week 6 in the CGI-S was demonstrated for comparisons of cariprazine 1.5 mg to placebo in the RGH-MD-53 (LSMD = -0.3 ; 95% CI, -0.6 to -0.1 ; $P = 0.0417$) and RGH-MD-56 (LSMD = -0.4 ; 95% CI, -0.6 to -0.1 ; $P = 0.0132$) studies. The LSMD of the change from baseline in CGI-S at week 6 was -0.2 (95% CI, -0.4 to 0.1 ; $P = 0.1370$), -0.3 (95% CI, -0.5 to -0.0 ; $P = 0.0662$), and -0.3 (95% CI, -0.5 to -0.0 ; $P = 0.1122$) for the RGH-MD-53, RGH-MD-54, and RGH-MD-56 studies, respectively. Similar to the primary analysis, cariprazine 3 mg did not demonstrate a benefit relative to placebo, nor did the 1.5 mg treatment group in RGH-MD-54 study (LSMD = -0.2 ; 95% CI, -0.5 to 0.0 ; $P = 0.0714$). The suggested MID for the CGI-S is a difference of 1 point for both within-group and between-group analyses. Based on this threshold, a clinically meaningful within-group difference was observed for all treatment groups (except placebo in the RGH-MD-31 study); however, the between-group differences were not clinically meaningful.

Other assessments of the change in symptoms were reported in the included studies; however, a lack of control for multiplicity of testing renders additional efficacy outcomes as supportive only.

In the studies of acute mania, overall improvement of symptoms using the CGI-I, change in symptoms of depression using the MADRS total score, and the change in severity of psychotic symptoms using the PANSS were assessed. The results of the CGI-I at week 3 were supportive of the primary and secondary analyses. The LSMD of the change from baseline in CGI-I at week 3 for cariprazine compared to placebo was -0.8 (95% CI, -1.2

to -0.5 ; $P < 0.0001$), -0.5 (95% CI, $-0.7, -0.2$; $P = 0.0004$), and -0.7 (95% CI, -0.9 to -0.4 ; $P < 0.001$) in the RGH-MD-31, RGH-MD-32, and RGH-MD-33 studies, respectively. An MID was not identified for the CGI-I, which made it difficult to interpret this outcome further. The results of the change in MADRS total score at week 3 were consistent with a small reduction of depressive symptoms, with no apparent difference between cariprazine and placebo. The clinical experts consulted by CADTH did not expect to see a change in depressive symptoms for patients experiencing an acute manic episode, but also suggested that not observing an increase in symptoms of depression is notable. A numerical reduction in the PANSS total score was observed at week 3 in all treatment groups (cariprazine and placebo) in the bipolar mania studies; however, limitations of the PANSS outcome led to difficulty with the interpretation of the results in the context of short-term treatment for acute mania associated with bipolar disorder.

The bipolar depression studies also assessed changes in severity of symptoms of depression using the HAMD-17 and QIDS-SR16, and symptoms of anxiety using the HAM-A. A clinically significant difference of 2 or 3 points in the HAMD-17 has been suggested in the literature, although justification for this threshold was unclear and likely opinion-based. The difference in the change of depressive symptoms based on the HAMD-17 at week 6 was inconsistent across studies, although a numerical decrease in HAMD-17 score (reduction of symptoms) was observed for all treatment groups. Also, the RGH-MD-56 study reported similar results at week 6 and week 8. Neither cariprazine 1.5 mg nor 3 mg demonstrated a benefit relative to placebo based on the change in depressive symptoms at week 6 as per the QIDS-SR16. A numerical reduction in the HAM-A score at week 6, indicating an improvement of symptoms of anxiety, was observed in all treatment groups, with no difference observed between cariprazine 3 mg and placebo. The clinical relevance of these changes is unknown. Overall, the evidence in support of changes in the severity of symptoms associated with a depressive episode of bipolar disorder was inconsistent with respect to the difference between cariprazine 1.5 mg and placebo, and did not support a benefit with cariprazine 3 mg relative to placebo.

The incidence of most severe suicidal ideation and most severe suicidal behaviour per the Columbia Suicide Severity Rating Scale (C-SSRS) was reported in all studies except RGH-MD-31. In all treatment groups for the bipolar mania studies, suicidal ideation was reported in 1% to 3% of patients. In the bipolar depression studies, suicidal ideation was reported in 3% to 11% of patients. The incidence by dose of cariprazine varied between studies. None of the patients were reported as exhibiting suicidal behaviour in any of the included studies.

Daily functioning was also identified as an outcome of interest to patients and by clinicians.

Functioning was not assessed in any of the other included studies.

Response rate and remission rate based on reductions in the YMRS total score (acute mania studies) and MADRS total score (depressive studies) were also reported. These outcomes were also not controlled for multiplicity, and therefore considered supportive only. In the acute mania studies, a response was observed in 48% to 61% of patients receiving cariprazine and 25% to 44% of patients receiving placebo. Remission was observed in 42% to 52% of patients receiving cariprazine and 23% to 35% of patients receiving placebo. The clinical experts indicated that a trial duration of 3 weeks is likely too short to observe full remission, which may take up to 4 to 6 weeks for an acute manic or mixed episode. In the acute depressive studies, 41% to 50% and 43% to 52% of patients receiving cariprazine 1.5 mg and 3 mg,

respectively, were considered responders as per the MADRS definition. The response rate among patients receiving placebo ranged from 32% to 40% across the trials. The benefit of treatment with cariprazine (1.5 mg and 3 mg) was inconsistently demonstrated across the studies based on this outcome. Similar results were reported for the analysis of MADRS remitters, where 26% to 37% and 26% to 32% of patients receiving cariprazine 1.5 mg and 3 mg, respectively, and 20% to 23% of patients receiving placebo, were considered to have a remission of depressive symptoms.

Outcomes related to HRQoL, hospitalization, cognitive impairment, and persistence with therapy were included in the CADTH systematic review protocol but not identified in the included studies.

Harms Results

In the bipolar mania studies, the percentage of patients that reported a treatment-emergent adverse event (AE) ranged from 78% to 86% for patients randomized to cariprazine (3 mg to 12 mg, or 3 mg to 6 mg) and 61% to 79% for patients randomized to placebo. In the bipolar depression studies, the percentage of patients that reported an AE ranged from 50% to 62% for patients randomized to cariprazine 1.5 mg, 49% to 62% for patients randomized to cariprazine 3 mg, and 46% to 55% for patients randomized to placebo. The overall rate of AEs was higher in the acute mania trials than acute depression trials, despite a shorter duration of treatment. This may be due to the use of a higher dose of cariprazine. Whether AEs were more likely to be detected in an inpatient setting, or the result of the higher dose of cariprazine in the acute mania trials, or both, is unknown.

In all included studies, serious adverse events (SAEs) were infrequently reported, and 1 death was reported in all of the included trials. In the bipolar mania studies, SAEs were reported by 3.2% to 4.2% of patients randomized to cariprazine (3 mg to 12 mg, or 3 to 6 mg) and 1.9% to 4.2% of patients randomized to placebo. In the bipolar depression studies, the percentage of patients that reported at least 1 SAE in the cariprazine 1.5 mg and cariprazine 3 mg treatment groups ranged from 0.6% to 1.4% and 0 to 1.4%, respectively. In the placebo groups, the percentage of patients who reported at least 1 SAE ranged from 1.3% to 3.4%. In the bipolar mania studies, patients who stopped treatment due to AEs (withdrawal due to AEs [WDAEs]) ranged from 9% to 14% of patients randomized to cariprazine and 5% to 10% of patients randomized to placebo. In the bipolar depression studies, WDAEs were reported by 3% to 8% of patients randomized to cariprazine 1.5 mg, 6% to 12% of patients randomized to cariprazine 3 mg, and 3% to 10% of patients randomized to placebo. The most common reasons for WDAEs were mania, akathisia, restlessness, and agitation. WDAEs tended to be slightly more frequent among patients randomized to cariprazine compared to placebo, but this was inconsistent across studies.

Of the notable harms identified in the CADTH systematic review protocol, hyperglycemia, weight gain, sexual dysfunction, tardive dyskinesia, and neuroleptic malignant syndrome were infrequently reported in all trials. Additionally, vomiting and EPS were infrequently reported in the bipolar depression studies. In the acute mania studies, the following notable harms were reported more frequently with cariprazine versus placebo: EPS (10% to 25% versus 2% to 10%), akathisia (17% to 22% versus 4% to 6%), vomiting (8% to 10% versus 3% to 5%), and restlessness (6% to 8% versus 1% to 5%). Similarly, in the bipolar depression studies, akathisia (5% to 14% versus 1% to 3%) and restlessness (2% to 7% versus 3% to 4%) were more common in the cariprazine versus placebo groups and occurred more frequently with cariprazine 3 mg than cariprazine 1.5 mg (akathisia: 5% to 6% versus 6% to 14%, and

restlessness: 1% to 3% versus 6% to 7%, for 1.5 mg versus 3 mg dose, respectively). The frequency of AEs during a short treatment period of 3 weeks in the acute mania studies and up to 8 weeks in the acute depression studies, and with the high discontinuation rates in the studies, is notable, although comparable to other treatments for bipolar disorder as indicated by the clinical experts consulted by CADTH.

Weight gain (increase in body weight of at least 7%) was captured in the safety assessment of vital signs. While the duration of the trials may not have been long enough to sufficiently assess the impact of treatment of cariprazine on weight gain, this outcome was still observed in the trials. However, there was only a slight difference in weight gain between the cariprazine and placebo treatment groups.

Critical Appraisal

Appropriate methods of randomization were used, although there was potential for unblinding or knowledge of treatment received due to AEs, most notably EPS and akathisia, which were more common in the cariprazine treatment groups relative to placebo. Treatment groups were well balanced in terms of baseline characteristics. Discontinuation rates were high in all included studies, but generally aligned with expectations for clinical trials for acute episodes of bipolar disorder. Overall discontinuation rates were balanced between treatment groups in most studies, except the RGH-MD-54 and RGH-MD-56 studies, where discontinuation was notably higher among the cariprazine 3 mg group. Discontinuation was also higher for patients in the placebo treatment group compared to cariprazine 1.5 mg in the RGH-MD-56 study. The imbalance in discontinuation rates in RGH-MD-56 appears to be driven by discontinuation due to AEs and withdrawal of consent. In the bipolar mania studies, there was an imbalance in the reason for discontinuation due to AEs (more frequent with cariprazine) and insufficient therapeutic response (more frequent with placebo), which may have biased the safety and efficacy results in favour of cariprazine. Missing data were handled using the last observation carried forward (LOCF) (RGH-MD-31) and mixed models for repeated measures (MMRM) approach (all other studies). Both methods rely on the assumption that data are missing at random, which is likely not the case given the imbalance in reasons for discontinuation that have been described. However, the sponsor conducted a pattern mixture model analysis that relies on the assumption that data are not missing at random. The results of the pattern mixture model analysis were consistent with the results of the primary analysis. All studies implemented methods to control for multiplicity up to the secondary end point, which was the change from baseline in the CGI-S at week 3 (bipolar mania studies) and week 6 (bipolar depression studies). The RGH-MD-31 and RGH-MD-32 studies used a closed testing procedure to control for the type I error rate; the RGH-MD-33 study and the 3 bipolar depression studies used a matched parallel gatekeeping procedure. The analyses of the primary and secondary outcomes were the only outcomes controlled for multiplicity; therefore, all other efficacy outcome are at risk of type I error and viewed as supportive evidence only.

The clinical experts described the patient population included in the trials for cariprazine as typical for clinical trials, but lacking characteristics that are often seen in clinical practice, such as the presence of comorbidities, rapid cycling, other diagnoses, comorbid substance use disorder, and elevated risk of suicide. The exclusion criteria can lead to a less severe and less complex sample relative to clinical practice. The clinical experts indicated that the baseline characteristics were suggestive of a patient population with bipolar I disorder of moderate severity. In the RGH-MD-31 and RGH-MD-32 studies, the permitted dose of cariprazine ranged from 3 mg to 12 mg daily, which extends beyond the Health Canada–approved dose

of up to 6 mg cariprazine daily. As such, specific conclusions regarding the effects of the Health Canada–approved dosing cannot be drawn based on these 2 studies. However, the RGH-MD-33 study provided evidence for cariprazine at a dose that was consistent with the Health Canada indication (in the 3 mg to 6 mg treatment group), which demonstrated a similar treatment effect to the higher doses used in the RGH-MD-31 and RGH-MD-32 studies. Dosing was consistent with the approved indication in all other studies included in this review. The studies for bipolar mania involved rapid titration that is inconsistent with how this drug is expected to be used by most patients treated in an outpatient setting. Generalizing the efficacy, safety, and tolerability outcomes observed in the trials to an outpatient setting for the treatment of acute mania is associated with some uncertainty. Another consideration for the intervention is that the clinical experts indicated that it is unlikely for cariprazine to be used only for acute management of episodes associated with bipolar I disorder. While the duration of the trials was considered adequate to observe a treatment effect on an acute episode, they were too short to properly assess safety and tolerability or efficacy beyond 3 weeks (bipolar mania studies) and 6 to 8 weeks (bipolar depression studies). Lastly, all of the outcomes used in the studies are commonly used in clinical trials or research settings for bipolar I disorder. None of the included outcomes are designed for or typically used in clinical practice, as per feedback from the clinical experts.

Indirect Comparisons

Description of Studies

One NMA submitted by the sponsor and 2 published NMAs that examined the comparative efficacy, safety, and tolerability of acute treatments for bipolar I disorder were included in this report. All of the NMAs conducted a systematic review of RCTs in adults either with acute bipolar mania (Kishi et al.), acute bipolar depression (Kadokia et al.), or both populations (sponsor-submitted NMA). The sponsor-submitted NMA performed separate analyses for the bipolar mania and depression populations. All included NMAs specified treatments for acute episodes of bipolar I disorder that were administered orally or sublingually as monotherapy. This included second generation antipsychotic drugs and other treatments, such as lithium, divalproex, and carbamazepine. Note that the NMA by Kadokia et al. was limited to atypical antipsychotic drugs and recent publications (since May 2015). The sponsor-submitted NMA was conducted using a Bayesian approach, the publication by Kishi et al. performed both pairwise and frequentist NMAs using a random effects (RE) model, and the NMA by Kadokia et al. used a Bayesian approach where the base case was based on an RE model.

Efficacy Results

A total of 65 studies were included in the sponsor-submitted NMA: 43 studies in the population of patients with manic or mixed bipolar I disorder and 22 studies in the population of patients with depressive bipolar I disorder. Fourteen treatments were represented in the manic or mixed studies: aripiprazole, asenapine, carbamazepine, cariprazine, divalproex, haloperidol, lamotrigine, lithium, olanzapine, paliperidone, placebo, quetiapine, risperidone, and ziprasidone. Thirteen treatments were represented in the depressive studies: aripiprazole, cariprazine, divalproex, fluoxetine, lamotrigine, lithium, lurasidone, olanzapine, olanzapine plus fluoxetine, paroxetine, placebo, quetiapine, and ziprasidone. The sponsor-submitted NMA reported the following outcomes: YMRS and MADRS response, YMRS and MADRS remission, change from baseline in YMRS and MADRS, weight gain, EPS, sedation or somnolence, all-cause discontinuation, and discontinuation due to AEs.

For the acute mania NMAs, YMRS response and YMRS remission [REDACTED] in treatment effect for comparisons between cariprazine and active comparators. The analysis of change from baseline in YMRS score suggested [REDACTED] but this network was associated with evidence of inconsistency, statistical heterogeneity, and imprecision of the results, and therefore uncertainty about any conclusions that can be drawn.

For the acute depression NMAs, MADRS response [REDACTED] in treatment effect for comparisons between cariprazine 1.5 mg or 3 mg and active comparators. The analysis of MADRS remission [REDACTED] Of note, the presence of inconsistency for this network is unknown, as inconsistency was not formally assessed. Additionally, it is unknown whether variability in baseline MADRS score influenced the results of the NMA. The analysis of change from baseline in MADRS suggested cariprazine 1.5 mg and 3 mg were [REDACTED] The NMA suggested [REDACTED]

The results suggest weight gain [REDACTED] in the NMA of treatments for bipolar mania [REDACTED] in the NMA of treatments for bipolar depression [REDACTED] However, these results were considered highly uncertain due to potential heterogeneity, lack of precision (mania NMA), and bias resulting from a small number of events. Therefore, there is uncertainty about the conclusion of potential benefit in terms of weight gain.

Overall, the sponsor-submitted NMA [REDACTED] for treatment with cariprazine relative to other comparators of interest for the treatment of acute manic or mixed episodes, or acute depressive episodes.

Harms Results

In the bipolar mania NMAs, the analysis of the rate of EPS and sedation or somnolence [REDACTED] In the bipolar depression NMAs, [REDACTED] This comparison was limited to aripiprazole and lurasidone as comparators. The analysis of the rate of sedation or somnolence suggested [REDACTED] in the rate of sedation or somnolence was reported for other comparisons of cariprazine 1.5 mg or cariprazine 3 mg and other treatments.

In the bipolar mania NMAs, all-cause discontinuation and discontinuation due to AEs were limited by evidence of inconsistency and substantial statistical heterogeneity. The results of the analysis suggest cariprazine [REDACTED]

Critical Appraisal

Studies that included patients with a dual diagnosis of substance use disorder or that investigated an intervention not used as monotherapy were excluded from the systematic

review, which may have resulted in missing potentially relevant patients and interventions. The study design was limited to double-blind RCTs, and quality of the studies was assessed using the NICE checklist and Jadad rubric. It is unclear how the quality assessment was used, and the Jadad rubric is not considered to be a reliable tool for assessing study quality. An insufficient quality assessment may have resulted in the inclusion of poor quality trials. Additionally, a sensitivity analysis for the quality of data was not performed.

Variation in the health care setting — particularly among the studies for manic or mixed episodes — and publication year, which ranged from 1991 to 2019, are potential sources of heterogeneity among the included studies. Baseline patient characteristics including age, sex, race, HAM-D score, MADRS score, YMRS score, CGI-S score, and time since diagnosis lacked important details and were subject to a large amount of missing data, hindering the ability to conduct a robust assessment of heterogeneity in the study populations. As a result, no studies were excluded based on outliers in the baseline characteristics, and it is unknown if the NMA was impacted by heterogeneity among the included patient populations. Inconsistency was assessed using a node-splitting approach, which is an appropriate statistical assessment of inconsistency, although it does not incorporate information from the entire network in the analysis. Evidence of inconsistency was identified in the following networks of the manic or mixed episode studies: change from baseline in YMRS, all-cause discontinuation, and discontinuation due to AEs. For the NMAs of outcomes in depressive studies, the author reported that inconsistency could not be assessed for the following networks: MADRS remission, weight gain, EPS, and all-cause discontinuation. The author reported that evidence of inconsistency was not identified for the remaining outcomes in the networks; however, a very wide 95% credible interval for the inconsistency factor (IF) of comparisons in the NMA for the following outcomes may suggest otherwise: sedation or somnolence (manic or mixed, and depressive), all-cause discontinuation (manic or mixed), and discontinuations due to AEs (manic or mixed, and depressive).

Missing data were an issue for certain outcomes, in part due to a small number of studies in the NMAs. This issue was compounded by few events per study for some outcomes, which was the case for the analysis of EPS (both the manic or mixed network and the depressive network) and weight gain (depressive network).

The 2 published NMAs summarized for this review^{18,19} were limited by insufficiently reported data and details about the methodology used, as well as low quality of evidence informing the networks. As a result, this summary has focused on the sponsor-submitted NMA. Briefly, the results of the published NMAs were generally consistent with the sponsor-submitted NMA, although subject to similar and additional limitations.

Other Relevant Evidence

Two studies were included as other relevant evidence for the review of cariprazine: 1 long-term, open-label study (RGH-MD-36) that examined the long-term safety and tolerability of cariprazine (3 mg to 12 mg daily) in patients with bipolar mania, and 1 post hoc analysis (McIntyre et al.) that provided additional efficacy data on cariprazine in the subpopulation of patients with bipolar mania with mixed features.

RGH-MD-36 Study

Description of Study

Patients were eligible to enrol into the RGH-MD-36 study if they were not currently taking any treatment or had a documented history of intolerance or inadequate response to their current therapy. They were treated with a flexible dose of cariprazine for up to 16 weeks of treatment. During the screening period, and for the first 2 weeks and up to 3 weeks of open-label treatment, all patients were hospitalized. At the end of week 3, all patients were discharged and followed as outpatients. Patients were discontinued from the study if they presented with clinical instability (by end of week 3), tolerability concerns, worsening of symptoms, inadequate response, or at the discretion of the investigator at any time.

All patients were required to have a total score of at least 18 on the YMRS and a total score below 18 on the MADRS. Further, a body mass index between █ kg/m² and █ kg/m², inclusive, was required. In comparison to the inclusion criterion regarding YMRS total score, the pivotal trials in bipolar mania (RGH-MD-31, RGH-MD-32, and RGH-MD-33) used a YMRS total score of at least 20, and a score of at least 4, on 2 of the following YMRS items: irritability, speech, content, and disruptive/aggressive behaviour.

Of the 403 patients who enrolled into the long-term, open-label study, 402 patients received at least 1 dose of open-label cariprazine (safety population). The mean age of patients in the study was 41.4 years (SD = 10.5). The majority of patients were male (57.2%) and White (51.2%). At baseline, the mean weight and body mass index were 86.5 kg (SD = 17.8) and 29.2 kg/m² (SD = 5.3), respectively. The mean age at onset and the known duration of bipolar I disorder were 27.9 (SD = 11.3) years and █ (SD = █) months, respectively. The duration of the current manic episode for the majority of patients (53.2%) was greater than 21 days.

Efficacy Results

A total of 132 patients (32.8%) completed the study and █ patients entered safety follow-up. The most frequently reported reason for discontinuation during the open-label treatment period was withdrawal of consent (19.7%), followed by AE (16.4%) and protocol violation (13.7%).

The mean change from baseline to week 16 in YMRS total score was -15.2 (SD = 9.2), and the mean change from baseline to week 16 in MADRS total score was -1.6 (SD = 7.5). At week 16, YMRS response criteria (≥ 50% reduction from baseline) was met by 64.2% of patients, and YMRS remission criteria (total score ≤ 12) was met by 63.4% of patients.

Harms Results

Treatment-emergent AEs were reported in 335 patients (83.3%) during the open-label treatment. The most commonly reported AEs (frequency ≥ 10%) were akathisia (32.6%), headache (16.7%), constipation (10.7%), and nausea (10.4%). SAEs were reported in 30 (7.5%) patients (7.5%). The following SAEs were reported in more than 1 patient: worsening of mania in 9 patients (2.2%), depression in 5 patients (1.2%), akathisia in 3 patients (0.7%), suicidal ideation in 2 patients (0.5%), and suicide attempt in 2 patients (0.5%). The most severe suicidal ideation and suicidal behaviour per the C-SSRS were reported in 35 patients (8.8%) and 3 patients (0.8%), respectively. No deaths were reported in the safety population. Premature discontinuation due to at least 1 AE was reported in 66 patients (16.4%) during the open-label treatment. The most frequently cited reason was akathisia in 19 patients (4.7%) and depression in 6 patients (1.5%).

The most commonly reported notable harms (frequency $\geq 5\%$) include akathisia in 131 patients (32.6%), insomnia in 28 patients (7.0%), EPS in 27 patients (6.7%), restlessness in 26 patients (6.5%), vomiting in 24 patients (6.0%), sedation in 23 patients (5.7%), and increase in weight in 23 patients (5.7%). A total of [REDACTED] patients had at least 1 AE related to extrapyramidal symptoms during open-label treatment. During the open-label treatment, 129 patients (32.1%) required treatment for extrapyramidal symptoms, of which 74 patients (18.4%) used a beta blocking agent (propranolol or propranolol hydrochloride), 64 patients (15.9%) used an anti-Parkinson drug (benztropine mesylate or biperiden), and [REDACTED] patients used a psycholeptic agent (diphenhydramine hydrochloride, diphenhydramine, or zolpidem tartrate).

Critical Appraisal

In the absence of an active comparator or placebo group, the interpretation of the efficacy results from the long-term, open-label study, RGH-MD-36, is limited. This is compounded by the use of descriptive statistics only. The use of an LOCF approach could overestimate or underestimate the overall long-term treatment benefits, particularly given the very high rates of discontinuation in the open-label study. Patients were discontinued from the study if they presented with clinical instability by the end of week 3, any tolerability concerns, worsening of symptoms, or inadequate response, or at the discretion of the investigator at any time. Consequently, the resultant population may be more tolerant of cariprazine, which could potentially lead to an underreporting of AEs and a response bias, as patients with an inadequate response (defined as an increase in the YMRS or MADRS total score by 30% or more at the end of week 2 or thereafter) were prematurely discontinued from the study.

The clinical experts consulted by CADTH stated that the exclusion of patients with, for example, rapid cycling and active substance use disorder, can lead to patients with complex cases who are seen in clinical practice being missed in the study. However, the clinical experts recognized that clinical trials will typically use said exclusion criteria to avoid confounding variables. There was a notable discontinuation rate of greater than 50%, which decreases the certainty and generalizability of the efficacy and safety results. According to the clinical experts, a discontinuation rate of approximately 35% is typically anticipated for clinical trials in bipolar mania. Further, some patients in the study received a dose higher than the Health Canada recommended daily dose of cariprazine, which is up to 6 mg per day.

Post Hoc Analysis

Description of Study

Data from 3 pivotal trials of cariprazine in adult patients with acute manic or mixed episodes associated with bipolar I disorder were pooled and used for the post hoc analysis. The objective of the post hoc analysis was to determine the effect of cariprazine on manic and depressive symptoms versus placebo in the subpopulation of patients with mania and subsyndromal depressive features.

A total of 1,037 patients were pooled from the pivotal trials. The number of patients who met the DSM-5 criteria for mixed state (≥ 3 depressive symptoms) and the 2 proxy definitions for mixed episode (≥ 2 depressive symptoms and a MADRS total score ≥ 10) were 141 (13.6%), 269 (25.9%), and 453 (43.7%), respectively.

Results

The pooled placebo and active treatment groups showed an improvement in the mean YMRS total score at week 3 relative to baseline. The difference between cariprazine and placebo

in change in mean YMRS total score were -3.79 (SE = NR; $P = 0.0248$), -2.91 (SE = NR; $P = 0.0207$), and -5.49 (SE = NR; $P < 0.0001$) in patients with mixed features as defined by at least 3 depressive symptoms, at least 2 depressive symptoms, and a MADRS total score of at least 10, respectively, in favour of cariprazine.

The results of the change in mean MADRS total score at week 3 relative to baseline were inconsistent, based on the definition used for patients with mixed features. There was a benefit with cariprazine based on the MADRS total score of at least 10, and no difference was observed using the other 2 definitions. The difference between cariprazine and placebo in change in mean MADRS total score was -1.59 (SE = NR; $P < 0.0082$) in patients with mixed features as defined by a MADRS total score of at least 10, in favour of cariprazine.

The proportion of responders ($\geq 50\%$ improvement from baseline in the YMRS total score) was higher for cariprazine in the group of patients with at least 2 depressive symptoms (47%; $P = 0.0483$) and the group of patients with a MADRS total score of at least 10 (57%; $P < 0.0001$) than placebo (34% and 31%, respectively). There was no difference between the cariprazine and placebo treatment groups ($P = 0.2608$) based on the definition of at least 3 depressive symptoms for patients with mixed features.

The proportion of remitters (YMRS total score ≤ 12) was higher for cariprazine in the group of patients with at least 2 depressive symptoms (39%; $P = 0.0462$) and the group of patients with a MADRS total score of at least 10 (44%; $P < 0.0001$) than placebo (27% and 23%, respectively). There was no difference between cariprazine and placebo treatment groups ($P = 0.1224$) based on the definition of at least 3 depressive symptoms for patients with mixed features.

Critical Appraisal

The pooled post hoc analysis was summarized to supplement the evidence for patients experiencing mixed episodes associated with bipolar I disorder. The pooled analysis is subject to the same limitations of the bipolar mania studies included in the systematic review, in addition to a small sample size and lack of power to detect a difference between treatment groups. Moreover, given that the subgroups of interest were not included as stratification variables at randomization, differences in baseline characteristics between the groups would be expected to introduce bias into the results observed. Overall, the results of this analysis should be considered exploratory.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree + Markov model
Target populations	Adults with manic or mixed episodes and depressive episodes associated with bipolar I disorder
Treatment	Cariprazine
Submitted price	Cariprazine, 1.5 mg, 3 mg, 4.5 mg, or 6 mg: \$4.90 per capsule
Treatment cost	Cariprazine has a 28-day cost of \$137 and an annual cost of \$1,790
Comparators	Manic or mixed episodes: <ul style="list-style-type: none"> • quetiapine • asenapine • aripiprazole • paliperidone • risperidone Depressive episodes: <ul style="list-style-type: none"> • quetiapine • lurasidone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	5 years
Key data source	Comparative clinical efficacy data were derived from a sponsor-submitted network meta-analysis (NMA), which was used to determine transition probabilities, discontinuation rates, and rates of adverse events (AEs).
Key limitations	<ul style="list-style-type: none"> • The sponsor’s approach to modelling only a single episode of mania or depression separately does not accurately represent the disease pathway or the expected use of cariprazine in clinical practice. • The sponsor-submitted NMA [REDACTED] cariprazine over other comparators in terms of response rate, discontinuation, rate of AEs, or weight gain. While there is uncertainty associated with the findings, cariprazine [REDACTED] when compared with other treatments (as per the sponsor’s own analysis). Given the challenges with the face validity of the model, a cost minimization analysis may be more relevant. • The sponsor included haloperidol, clonazepam, and chlorpromazine as subsequent therapies, which are mainly used for agitation control and rarely as a treatment for bipolar disorder. • The sponsor’s model contained programming errors which led to incorrect drug acquisition costs for aripiprazole and risperidone.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH revised the economic evaluation to take the form of a cost minimization analysis, given the results of the sponsor’s NMA and the issues with the designs of the models. In addition, CADTH fixed the programming errors and also excluded haloperidol, clonazepam, and chlorpromazine in the base case. • In the CADTH reanalysis, the total costs for cariprazine are \$3,947 in the manic or mixed phase, and \$7,935 in the depressive phase, per patient over the 5-year time horizon. In the absence of data to support a price premium, price reductions would be required to ensure similar treatment costs when

Component	Description
	compared with the least costly comparators. In the manic or mixed setting, a price reduction of 83% would be required compared to risperidone; and in the depressive setting, a price reduction of 75% would be required compared to quetiapine.

Budget Impact

The sponsor's use of a claims-based approach to the BIA was associated with uncertainty and was difficult to validate. CADTH undertook a complete revision of the BIA from an epidemiologic perspective, using input from published literature and feedback from clinical experts. Based on the CADTH BIA, the estimated budget impact of funding cariprazine for the treatment of bipolar I disorder is expected to be \$28,632,545 over 3 years. CADTH notes that given the considerations of the flat pricing and dose titration with cariprazine the true budget impact for cariprazine may be higher than the CADTH base case.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for cariprazine (Vraylar) for use as monotherapy for the acute management of manic or mixed episodes associated with bipolar I disorder (bipolar mania), and acute management of depressive episodes associated with bipolar I disorder (bipolar depression). In their request, the sponsor identified 5 issues:

- Cariprazine addresses key gaps in therapy identified by patient groups, CADTH's clinical experts, and clinician groups.
- The evidence demonstrates that cariprazine's results are more generalizable to Canadian patients and clinical practice than suggested by the CDEC draft recommendation. The enrolled population and trial design is consistent with other atypical antipsychotic drugs for the treatment of bipolar I disorder.
- Contrary to CDEC's conclusions, evidence suggests that the 1.5 mg cariprazine dose demonstrated statistically significant and clinically meaningful reductions in depressive symptoms that were consistently reproduced across 3 studies.
- As concluded in the RGH-MD-33 study (acute mania study) and by Health Canada, the efficacy of the doses within the Health Canada-approved range is similar to that of doses beyond 6 mg, and as such, results from the 3 mg to 12 mg flexible dose arms of the RGH-MD-31 and RGH-MD-32 studies are generalizable to the Health Canada-approved dose range.
- The conclusions on the NMA were not reported in a fair and balanced manner in the draft CDEC recommendation. Specifically, CDEC's general conclusion that cariprazine is worse in terms of safety versus quetiapine is not supported by the totality of evidence.

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 2 clinical specialists with expertise in diagnosing and treating patients with bipolar disorder
- feedback from public drug plans that participate in the CADTH review process
- feedback on the draft recommendation from 2 clinician groups: the Ontario and Maritimes Key Opinion Clinicians and Western Canadian Clinical Advisory Network (WC-CAN)
- feedback on the draft recommendation from 3 patient groups: the Mood Disorders Society of Canada, the Institute for Advancements in Mental Health, and the Canadian Mental Health Association, Alberta Division

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

CDEC Information

Initial Meeting Date: June 23, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, 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.

Regrets: None

Conflicts of interest: None

Reconsideration Meeting Date: October 27, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, 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.

Regrets: None

Conflicts of interest: None