# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 204370Orig1s006

| | |
|---|---|
| ***Trade Name:*** | VRAYLAR |
| ***Generic or Proper Name:*** | (cariprazine hydrochloride) |
| ***Sponsor:*** | AbbVie Inc. |
| ***Approval Date:*** | May 24, 2019 |
| ***Indication:*** | VRAYLAR is an atypical antipsychotic indicated for the:<br>• Treatment of schizophrenia in adults.<br>• Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.<br>• Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 204370Orig1s006

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# APPROVAL LETTER

NDA 204370/S-006

**SUPPLEMENT APPROVAL**

Allergan Sales, LLC
Attention: Nicola Walters, MBA, MPH
Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Ms. Walters:

Please refer to your supplemental new drug application (sNDA) dated July 24, 2018, received July 24, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vraylar (cariprazine) capsules 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg.

This Prior Approval supplemental new drug application provides for a new indication of treatment of depressive episodes associated with bipolar I disorder (bipolar depression).

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

We note that your May 22, 2019, and May 23, 2019, submissions include final printed labeling (FPL) for your Medication Guide and Prescribing Information respectively. We have not reviewed this FPL. You are responsible for assuring that the wording in this FPL is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years because necessary studies are impossible or highly impracticable. This is because it is extremely difficult to make a diagnosis of bipolar disorder in children younger than 10 years. Therefore, studies in children younger than 10 years would be highly impractical.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3619-1 Deferred pediatric study under PREA (ages 10 to 17) with a diagnosis of acute bipolar depression associated with bipolar I disorder. A study of the efficacy and safety of cariprazine in the relevant pediatric population.

Final Protocol Submission: 06/2020
Study/Trial Completion: 01/2024
Final Report Submission: 07/2024

Submit the protocol to your IND 077726, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Danbi Lee, Regulatory Project Manager, at danbi.lee@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Tiffany R. Farchione, MD
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# LABELING

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use VRAYLAR safely and effectively. See full prescribing information for VRAYLAR.**

**VRAYLAR® (cariprazine) capsules, for oral use**
**Initial U.S. Approval: 2015**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS**
***See** full prescribing information **for complete boxed warning.***

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis. (*5.1*)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of VRAYLAR have not been established in pediatric patients (5.2, 8.4)**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Boxed Warning | 5/2019 |
| Indications and Usage (1) | 5/2019 |
| Dosage and Administration (2.4) | 5/2019 |
| Warnings and Precautions (5.2, 5.7) | 5/2019 |

**----------INDICATIONS AND USAGE----------**
VRAYLAR is an atypical antipsychotic indicated for the:
- Treatment of schizophrenia in adults (*1*)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults (*1*)
- Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (*1*)

**----------DOSAGE AND ADMINISTRATION----------**
- Administer VRAYLAR once daily with or without food (*2*)

| | Starting Dose | Recommended Dose |
|---|---|---|
| Schizophrenia (*2.2*) | 1.5 mg daily | 1.5 mg to 6 mg daily |
| Bipolar Mania (*2.3*) | 1.5 mg daily | 3 mg to 6 mg daily |
| Bipolar Depression (*2.4*) | 1.5 mg daily | 1.5 mg or 3 mg daily |

- Schizophrenia and Bipolar Mania: Dosages above 6 mg daily do not confer significant benefit but increase the risk of dose-related adverse reactions (2.2, 2.3)
- Bipolar Depression: The maximum recommended daily dosage is 3 mg (2.4)

**----------DOSAGE FORMS AND STRENGTHS----------**
Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg (*3*)

**----------CONTRAINDICATIONS----------**
Known hypersensitivity to VRAYLAR (*4*)

**----------WARNINGS AND PRECAUTIONS----------**
- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (*5.3*)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (*5.4*)
- *Tardive Dyskinesia*: Discontinue if appropriate (*5.5*)
- *Late-Occurring Adverse Reactions:* Because of VRAYLAR's long half-life, monitor for adverse reactions and patient response for several weeks after starting VRAYLAR and with each dosage change (*5.6*)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (*5.7*)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell counts (WBC) or history of leukopenia or neutropenia. Consider discontinuing VRAYLAR if a clinically significant decline in WBC occurs in absence of other causative factors (*5.8*)
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (*5.9*)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (*5.11*)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (*5.12*)

**----------ADVERSE REACTIONS----------**
Most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) were (*6.1*):
- Schizophrenia: extrapyramidal symptoms and akathisia
- Bipolar mania: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness
- Bipolar depression: nausea, akathisia, restlessness, and extrapyramidal symptoms

**To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**----------DRUG INTERACTIONS----------**
- Strong CYP3A4 inhibitors: Reduce VRAYLAR dosage by half (2.5, 7.1)
- CYP3A4 inducers: Concomitant use is not recommended (2.5, 7.1)

**----------USE IN SPECIFIC POPULATIONS----------**
- *Pregnancy:* Based on animal data, may cause fetal harm (8.1)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 05/2019**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

**FULL PRESCRIBING INFORMATION**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.**

**Suicidal Thoughts and Behaviors**

**Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for the emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.2)]*. The safety and effectiveness of VRAYLAR have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.**

## 1. INDICATIONS AND USAGE

VRAYLAR® is indicated for the:

- Treatment of schizophrenia in adults *[see Clinical Studies (14.1)]*
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults *[see Clinical Studies (14.2)]*.
- Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults *[see Clinical Studies (14.3)]*

## 2. DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Information

VRAYLAR is given orally once daily and can be taken with or without food.

Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Prescribers should monitor patients for adverse reactions and treatment response for several weeks after starting VRAYLAR and after each dosage change *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

### 2.2 Schizophrenia

The recommended dosage range is 1.5 mg to 6 mg once daily. The starting dosage of VRAYLAR is 1.5 mg daily. The dosage can be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily. In short-term controlled trials, dosages above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions [*see Adverse Reactions (6.1), Clinical Studies (14.1)*].

### 2.3 Manic or Mixed Episodes Associated with Bipolar I Disorder

The recommended dosage range is 3 mg to 6 mg once daily. The starting dose of VRAYLAR is 1.5 mg and should be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily.

In short-term controlled trials, dosages above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions [*see Adverse Reactions (6.1), Clinical Studies (14.2)*].

### 2.4 Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The starting dose of VRAYLAR is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. Maximum recommended dosage is 3 mg once daily.

### 2.5 Dosage Adjustments for CYP3A4 Inhibitors and Inducers

CYP3A4 is responsible for the formation and elimination of the major active metabolites of cariprazine.

*Dosage recommendation for patients initiating a strong CYP3A4 inhibitor while on a stable dose of VRAYLAR*: If a strong CYP3A4 inhibitor is initiated, reduce the current dosage of VRAYLAR by half. For patients taking 4.5 mg daily, the dosage should be reduced to 1.5 mg or 3 mg daily. For patients taking 1.5 mg daily, the dosing regimen should be adjusted to every other day. When the CYP3A4 inhibitor is withdrawn, VRAYLAR dosage may need to be increased *[see Drug Interactions (7.1)]*.

*Dosage recommendation for patients initiating VRAYLAR therapy while already on a strong CYP3A4 inhibitor:* Patients should be administered 1.5 mg of VRAYLAR on Day 1 and on Day 3 with no dose administered on Day 2. From Day 4 onward, the dose should be administered at 1.5 mg daily, then increased to a maximum dose of 3 mg daily. When the CYP3A4 inhibitor is withdrawn, VRAYLAR dosage may need to be increased *[see Drug Interactions (7.1)]*.

*Dosage recommendation for patients concomitantly taking VRAYLAR with CYP3A4 inducers:*
Concomitant use of VRAYLAR and a CYP3A4 inducer has not been evaluated and is not recommended because the net effect on active drug and metabolites is unclear *[see Dosage and Administration (2.1), Warnings and Precautions (5.6), Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

### 2.6 Treatment Discontinuation

Following discontinuation of VRAYLAR, the decline in plasma concentrations of active drug and metabolites may not be immediately reflected in patients' clinical symptoms; the plasma concentration of cariprazine and its active metabolites will decline by 50% in ~1 week [*see Clinical Pharmacology (12.3)]*. There are no systematically collected data to specifically address switching patients from VRAYLAR to other antipsychotics or concerning concomitant administration with other antipsychotics.

## 3. DOSAGE FORMS AND STRENGTHS

**VRAYLAR (cariprazine) capsules are available in four strengths.**

- 1.5 mg capsules: White cap and body imprinted with "FL 1.5"
- 3 mg capsules: Green to blue-green cap and white body imprinted with "FL 3"
- 4.5 mg capsules: Green to blue-green cap and body imprinted with "FL 4.5"
- 6 mg capsules: Purple cap and white body imprinted with "FL 6"

## 4. CONTRAINDICATIONS

VRAYLAR is contraindicated in patients with history of a hypersensitivity reaction to cariprazine. Reactions have ranged from rash, pruritus, urticaria, and events suggestive of angioedema (e.g., swollen tongue, lip swelling, face edema, pharyngeal edema, and swelling face).

## 5. WARNINGS AND PRECAUTIONS

### 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

### 5.2 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

**Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients**

| Age Range | Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated |
|---|---|
| | **Increases Compared to Placebo** |
| <18 years old | 14 additional patients |
| 18-24 years old | 5 additional patients |
| | **Decreases Compared to Placebo** |
| 25-64 years old | 1 fewer patient |
| ≥65 years old | 6 fewer patients |

* Vraylar is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing VRAYLAR, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

### 5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

### 5.4 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue VRAYLAR and provide intensive symptomatic treatment and monitoring.

### 5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs, including VRAYLAR. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, VRAYLAR should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on VRAYLAR, drug discontinuation should be considered. However, some patients may require treatment with VRAYLAR despite the presence of the syndrome.

### 5.6 Late-Occurring Adverse Reactions

Adverse events may first appear several weeks after the initiation of VRAYLAR treatment, probably because plasma levels of cariprazine and its major metabolites accumulate over time. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after longer term exposures *[see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*.

Monitor for adverse reactions, including extrapyramidal symptoms (EPS) or akathisia, and patient response for several weeks after a patient has begun VRAYLAR and after each dosage increase. Consider reducing the dose or discontinuing the drug.

### 5.7 Metabolic Changes

Atypical antipsychotic drugs, including VRAYLAR, have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all of the drugs in the class to date have been shown to produce some metabolic changes, each drug has its own specific risk profile.

*Hyperglycemia and Diabetes Mellitus*

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication, and monitor periodically during long-term treatment.

Schizophrenia

In the 6-week, placebo-controlled trials of adult patients with schizophrenia, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with VRAYLAR and placebo. In the long-term, open-label schizophrenia studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥6.5%).

Bipolar Disorder

In six placebo-controlled trials up to 8-weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with VRAYLAR and placebo. In the long-term, open-label bipolar disorder studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥6.5%).

*Dyslipidemia*

Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Schizophrenia

In the 6-week, placebo-controlled trials of adult patients with schizophrenia, the proportion of patients with shifts in fasting total cholesterol, LDL, HDL and triglycerides were similar in patients treated with VRAYLAR and placebo.

Bipolar Disorder

In six placebo-controlled trials up to 8-weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting total cholesterol, LDL, HDL and triglycerides were similar in patients treated with VRAYLAR and placebo.

*Weight Gain*

Weight gain has been observed with use of atypical antipsychotics, including VRAYLAR. Monitor weight at baseline and frequently thereafter. Tables 2, 3, and 4 show the change in body weight occurring from baseline to endpoint in 6-week schizophrenia, 3-week bipolar mania, and 6-week and 8-week bipolar depression trials, respectively.

**Table 2. Change in Body Weight (kg) in 6-Week Schizophrenia Trials**

| | | VRAYLAR* | | |
|---|---|---|---|---|
| | Placebo (N=573) | 1.5 - 3 mg/day (N=512) | 4.5 - 6 mg/day (N=570) | 9 - 12◦ mg/day (N=203) |
| Mean Change at Endpoint | +0.3 | +0.8 | +1 | +1 |
| Proportion of Patients with Weight Increase (≥7%) | 5% | 8% | 8% | 17% |

*Data shown by modal daily dose, defined as most frequently administered dose per patient
◦The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In long-term, uncontrolled trials with VRAYLAR in schizophrenia, the mean changes from baseline in weight at 12, 24, and 48 weeks were 1.2 kg, 1.7 kg, and 2.5 kg, respectively.

**Table 3. Change in Body Weight (kg) in 3-Week Bipolar Mania Trials**

| | | VRAYLAR* | |
|---|---|---|---|
| | Placebo (N=439) | 3 - 6 mg/day (N=259) | 9 - 12◦ mg/day (N=360) |
| Mean Change at Endpoint | +0.2 | +0.5 | +0.6 |
| Proportion of Patients with Weight Increase (≥7%) | 2% | 1% | 3% |

*Data shown by modal daily dose, defined as most frequently administered dose per patient
◦The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

**Table 4. Change in Body Weight (kg) in two 6-Week and one 8-Week Bipolar Depression Trials**

| | | VRAYLAR | |
|---|---|---|---|
| | Placebo (N=463) | 1.5 mg/day (N=467) | 3 mg/day (N=465) |
| Mean Change at Endpoint | -0.1 | +0.7 | +0.4 |
| Proportion of Patients with Weight Increase (≥7%) | 1% | 3% | 3% |

### 5.8 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including VRAYLAR. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of VRAYLAR at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue VRAYLAR in patients with absolute neutrophil count < 1000/mm$^3$ and follow their WBC until recovery.

### 5.9 Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. Symptomatic orthostatic hypotension was infrequent in trials of VRAYLAR and was not more frequent on VRAYLAR than placebo. Syncope was not observed.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. VRAYLAR has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

### 5.10 Falls

Antipsychotics, including VRAYLAR, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

### 5.11 Seizures

Like other antipsychotic drugs, VRAYLAR may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

### 5.12 Potential for Cognitive and Motor Impairment

VRAYLAR, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills.

In 6-week schizophrenia trials, somnolence (hypersomnia, sedation, and somnolence) was reported in 7% of VRAYLAR-treated patients compared to 6% of placebo-treated patients. In 3-week bipolar mania trials, somnolence was reported in 8% of VRAYLAR-treated patients compared to 4% of placebo-treated patients.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with VRAYLAR does not affect them adversely.

### 5.13 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use VRAYLAR with caution in patient who may experience these conditions.

### 5.14 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia has been reported with VRAYLAR. VRAYLAR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Late Occurring Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Metabolic Changes *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Falls *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.13)]*
- Dysphagia *[see Warnings and Precautions (5.14)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The information below is derived from an integrated clinical study database for VRAYLAR consisting of 4753 adult patients exposed to one or more doses of VRAYLAR for the treatment of schizophrenia, manic or mixed episodes associated with bipolar I disorder, and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 940.3 patient-years. A total of 2568 VRAYLAR-treated patients had at least 6 weeks and 296 VRAYLAR-treated patients had at least 48 weeks of exposure.

*Patients with Schizophrenia*

The following findings are based on four placebo-controlled, 6-week schizophrenia trials with VRAYLAR doses ranging from 1.5 to 12 mg once daily. The maximum recommended dosage is 6 mg daily.

Adverse Reactions Associated with Discontinuation of Treatment: There was no single adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms and akathisia.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo, at any dose are shown in Table 5.

**Table 5. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 6-Week Schizophrenia Trials**

| System Organ Class / Preferred Term | Placebo (N= 584) (%) | VRAYLAR* 1.5 - 3 mg/day (N=539) (%) | VRAYLAR* 4.5 - 6 mg/day (N=575) (%) | VRAYLAR* 9 - 12 mg/day° (N=203) (%) |
|---|---|---|---|---|
| **Cardiac Disorders** | | | | |
| Tachycardia[a] | 1 | 2 | 2 | 3 |
| **Gastrointestinal Disorders** | | | | |
| Abdominal pain[b] | 5 | 3 | 4 | 7 |
| Constipation | 5 | 6 | 7 | 10 |
| Diarrhea[c] | 3 | 1 | 4 | 5 |
| Dry Mouth | 2 | 1 | 2 | 3 |
| Dyspepsia | 4 | 4 | 5 | 5 |
| Nausea | 5 | 5 | 7 | 8 |
| Toothache | 4 | 3 | 3 | 6 |
| Vomiting | 3 | 4 | 5 | 5 |
| **General Disorders/Administration Site Conditions** | | | | |
| Fatigue[d] | 1 | 1 | 3 | 2 |
| **Infections and infestations** | | | | |
| Nasopharyngitis | 1 | 1 | 1 | 2 |
| Urinary tract infection | 1 | 1 | <1 | 2 |
| **Investigations** | | | | |
| Blood creatine phosphokinase increased | 1 | 1 | 2 | 3 |
| Hepatic enzyme increased[e] | <1 | 1 | 1 | 2 |
| Weight increased | 1 | 3 | 2 | 3 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 2 | 1 | 3 | 2 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Arthralgia | 1 | 2 | 1 | 2 |
| Back pain | 2 | 3 | 3 | 1 |
| Pain in extremity | 3 | 2 | 2 | 4 |
| **Nervous System Disorders** | | | | |
| Akathisia | 4 | 9 | 13 | 14 |
| Extrapyramidal Symptoms[f] | 8 | 15 | 19 | 20 |
| Headache[g] | 13 | 9 | 11 | 18 |
| Somnolence[h] | 5 | 5 | 8 | 10 |
| Dizziness | 2 | 3 | 5 | 5 |
| **Psychiatric Disorders** | | | | |
| Agitation | 4 | 3 | 5 | 3 |
| Insomnia[i] | 11 | 12 | 13 | 11 |
| Restlessness | 3 | 4 | 6 | 5 |
| Anxiety | 4 | 6 | 5 | 3 |

**Table 5. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 6-Week Schizophrenia Trials**

| System Organ Class / Preferred Term | Placebo (N= 584) (%) | VRAYLAR* 1.5 - 3 mg/day (N=539) (%) | VRAYLAR* 4.5 - 6 mg/day (N=575) (%) | VRAYLAR* 9 - 12 mg/day◦ (N=203) (%) |
|---|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 2 | 1 | 2 | 4 |
| **Skin and subcutaneous disorders** | | | | |
| Rash | 1 | <1 | 1 | 2 |
| **Vascular Disorders** | | | | |
| Hypertension[j] | 1 | 2 | 3 | 6 |

Note: Figures rounded to the nearest integer

* Data shown by modal daily dose, defined as most frequently administered dose per patient

[a] **Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia

[b] **Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain

[c] **Diarrhea terms**: diarrhea, frequent bowel movements

[d] **Fatigue terms:** asthenia, fatigue

[e] **Hepatic enzyme increase terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased

[f] **Extrapyramidal Symptoms terms:** bradykinesia, cogwheel rigidity, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, Musculoskeletal stiffness, oculogyric crisis, oromandibular dystonia, parkinsonism, salivary hypersecretion, tardive dyskinesia, torticollis, tremor, trismus

[g] **Headache terms:** headache, tension headache

[h] **Somnolence terms:** hypersomnia, sedation, somnolence

[i] **Insomnia terms:** initial insomnia, insomnia, middle insomnia, terminal insomnia

[j] **Hypertension terms:** blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension

◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

*Patients with Bipolar Mania*

The following findings are based on three placebo-controlled, 3-week bipolar mania trials with VRAYLAR doses ranging from 3 to 12 mg once daily. The maximum recommended dosage is 6 mg daily.

Adverse Reactions Associated with Discontinuation of Treatment: The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo was akathisia (2%). Overall, 12% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 7% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at any dose are shown in Table 6.

**Table 6. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials**

| System Organ Class / Preferred Term | Placebo (N= 442) (%) | VRAYLAR* | |
|---|---|---|---|
| | | 3 - 6 mg/day (N=263) (%) | 9 - 12 mg/day° (N=360) (%) |
| **Cardiac Disorders** | | | |
| Tachycardia[a] | 1 | 2 | 1 |
| **Eye Disorders** | | | |
| Vision blurred | 1 | 4 | 4 |
| **Gastrointestinal Disorders** | | | |
| Nausea | 7 | 13 | 11 |
| Constipation | 5 | 6 | 11 |
| Vomiting | 4 | 10 | 8 |
| Dry mouth | 2 | 3 | 2 |
| Dyspepsia | 4 | 7 | 9 |
| Abdominal pain[b] | 5 | 6 | 8 |
| Diarrhea[c] | 5 | 5 | 6 |
| Toothache | 2 | 4 | 3 |
| **General Disorders/Administration Site Conditions** | | | |
| Fatigue[d] | 2 | 4 | 5 |
| Pyrexia[e] | 2 | 1 | 4 |
| **Investigations** | | | |
| Blood creatine phosphokinase increased | 2 | 2 | 3 |
| Hepatic enzymes increased[f] | <1 | 1 | 3 |
| Weight increased | 2 | 2 | 3 |
| **Metabolism and Nutrition Disorders** | | | |
| Decreased appetite | 3 | 3 | 4 |
| **Musculoskeletal and Connective Tissue Disorders** | | | |
| Pain in extremity | 2 | 4 | 2 |
| Back pain | 1 | 1 | 3 |
| **Nervous System Disorders** | | | |
| Akathisia | 5 | 20 | 21 |
| Extrapyramidal Symptoms[g] | 12 | 26 | 29 |
| Headache[h] | 13 | 14 | 13 |
| Dizziness | 4 | 7 | 6 |
| Somnolence[i] | 4 | 7 | 8 |
| **Psychiatric Disorders** | | | |
| Insomnia[j] | 7 | 9 | 8 |
| Restlessness | 2 | 7 | 7 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Oropharyngeal pain | 2 | 1 | 3 |
| **Vascular Disorders** | | | |
| Hypertension[k] | 1 | 5 | 4 |

Note: Figures rounded to the nearest integer
*Data shown by modal daily dose, defined as most frequently administered dose per patient
[a]**Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia
[b]**Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness,
[c]**Diarrhea:** diarrhea, frequent bowel movements
[d]**Fatigue terms:** asthenia, fatigue
[e]**Pyrexia terms:** body temperature increased, pyrexia
[f]**Hepatic enzymes increased terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased
[g]**Extrapyramidal Symptoms terms:** bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism, salivary hypersecretion, tremor
[h]**Headache terms:** headache, tension headache
[i]**Somnolence terms:** hypersomnia, sedation, somnolence
[j]**Insomnia terms:** initial insomnia, insomnia, middle insomnia
[k]**Hypertension terms:** blood pressure diastolic increased, blood pressure increased, hypertension
◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

*Patients with Bipolar Depression*

The following findings are based on three placebo-controlled, two 6-week and one 8-week bipolar depression trials with VRAYLAR doses of 1.5 mg and 3 mg once daily.

Adverse Reactions Associated with Discontinuation of Treatment: There were no adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo. Overall, 6% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 5% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): nausea, akathisia, restlessness, and extrapyramidal symptoms.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 7.

**Table 7. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in two 6-week trials and one 8-week trial**

| | Placebo(N=468) (%) | VRAYLAR | |
|---|---|---|---|
| | | 1.5 mg/day (N=470) (%) | 3 mg/day (N=469) (%) |
| Restlessness | 3 | 2 | 7 |
| Akathisia | 2 | 6 | 10 |
| Extrapyramidal symptoms[a] | 2 | 4 | 6 |
| Dizziness | 2 | 4 | 3 |
| Somnolence[b] | 4 | 7 | 6 |
| Nausea | 3 | 7 | 7 |

| | | | |
|---|---|---|---|
| Increased appetite | 1 | 3 | 3 |
| Weight increase | <1 | 2 | 2 |
| Fatigue[c] | 2 | 4 | 3 |
| Insomnia[d] | 7 | 7 | 10 |

[a]**Extrapyramidal symptoms terms**: akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle tightness, musculoskeletal stiffness, myoclonus, oculogyric crisis, salivary hypersecretion, tardive dyskinesia, tremor
[b]**Somnolence terms**: hypersomnia, sedation, somnolence
[c]**Fatigue terms**: asthenia, fatigue, malaise
[d]**Insomnia terms**: initial insomnia, insomnia, insomnia related to another mental condition, middle insomnia, sleep disorder terminal insomnia

*Dystonia*

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

*Extrapyramidal Symptoms (EPS) and Akathisia*

In schizophrenia, bipolar mania, and bipolar depression trials, data were objectively collected using the Simpson Angus Scale (SAS) for treatment-emergent EPS (parkinsonism) (SAS total score ≤ 3 at baseline and > 3 post-baseline) and the Barnes Akathisia Rating Scale (BARS) for treatment-emergent akathisia (BARS total score ≤ 2 at baseline and > 2 post-baseline).

In 6-week schizophrenia trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness was 17% for VRAYLAR-treated patients versus 8% for placebo-treated patients. These events led to discontinuation in 0.3% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 11% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These events led to discontinuation in 0.5% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of EPS is shown in Table 8.

**Table 8. Incidence of EPS Compared to Placebo in 6-Week Schizophrenia Studies**

| | | **VRAYLAR*** | | |
|---|---|---|---|---|
| **Adverse Event Term** | Placebo (N= 584) (%) | 1.5 - 3 mg/day (N=539) (%) | 4.5 - 6 mg/day (N=575) (%) | 9-12 mg/day° (N=203) (%) |
| **All EPS events** | 14 | 24 | 32 | 33 |
| **All EPS events, excluding Akathisia/Restlessness** | 8 | 15 | 19 | 20 |
| Akathisia | 4 | 9 | 13 | 14 |
| Dystonia** | <1 | 2 | 2 | 2 |
| Parkinsonism§ | 7 | 13 | 16 | 18 |
| Restlessness | 3 | 4 | 6 | 5 |
| Musculoskeletal stiffness | 1 | 1 | 3 | 1 |

Note: Figures rounded to the nearest integer
*Data shown by modal daily dose, defined as most frequently administered dose per patient
** **Dystonia includes adverse event terms:** dystonia, oculogyric crisis, oromandibular dystonia, trismus, torticollis
§ **Parkinsonism includes adverse event terms:** bradykinesia, cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, parkinsonism, tremor, salivary hypersecretion
◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In 3-week bipolar mania trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for VRAYLAR-treated patients versus 12% for placebo-treated patients. These events led to a discontinuation in 1% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 20% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These events led to discontinuation in 2% of VRAYLAR-treated patients versus 0% of placebo-treated patients. The incidence of EPS is provided in Table 9.

**Table 9. Incidence of EPS Compared to Placebo in 3-Week Bipolar Mania Trials**

| | | VRAYLAR* | |
|---|---|---|---|
| **Adverse Event Term** | Placebo (N= 442) (%) | 3 - 6 mg/day (N=263) (%) | 9 - 12 mg/day◦ (N=360) (%) |
| **All EPS events** | 18 | 41 | 45 |
| **All EPS events, excluding Akathisia/Restlessness** | 12 | 26 | 29 |
| Akathisia | 5 | 20 | 21 |
| Dystonia** | 1 | 5 | 3 |
| Parkinsonism§ | 10 | 21 | 26 |
| Restlessness | 2 | 7 | 7 |
| Musculoskeletal stiffness | 1 | 2 | 2 |

Note: Figures rounded to the nearest integer
*Data shown by modal daily dose, defined as most frequently administered dose per patient
** **Dystonia includes adverse event terms:** dystonia, oromandibular dystonia
§ **Parkinsonism includes adverse event terms:** bradykinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, parkinsonism, salivary hypersecretion, tremor
◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In the two 6-week and one 8-week bipolar depression trials, the incidence of reported events related to EPS, excluding akathisia and restlessness was 4% for VRAYLAR-treated patients versus 2% for placebo-treated patients. These events led to discontinuation in 0.4% of VRAYLAR-treated patients versus 0% of placebo-treated patients. The incidence of akathisia was 8% for VRAYLAR-treated patients versus 2% for placebo-treated patients. These events led to discontinuation in 1.5% of VRAYLAR-treated patients versus 0% of placebo-treated patients. The incidence of EPS is shown in Table 10.

**Table 10. Incidence of EPS Compared to Placebo in two 6-Week and one 8-Week Bipolar Depression Trials**

| | | VRAYLAR* | |
|---|---|---|---|
| **Adverse Event Term** | Placebo (N=468) (%) | 1.5 mg/day (N=470) | 3 mg/day (N=469) |

| | | (%) | (%) |
|---|---|---|---|
| **All EPS events** | 7 | 10 | 19 |
| **All EPS events, excluding Akathisia/Restlessness** | 2 | 4 | 6 |
| Akathisia | 2 | 6 | 10 |
| Dystonia* | <1 | <1 | <1 |
| Parkinsonism§ | 2 | 3 | 4 |
| Restlessness | 3 | 2 | 7 |
| Musculoskeletal stiffness | <1 | <1 | 1 |
| Tardive Dyskinesia | 0 | 0 | <1 |

Note: Figures rounded to the nearest integer
* **Dystonia includes adverse event terms:** dystonia, myoclonus, oculogyric crisis
§ **Parkinsonism includes adverse event terms:** akinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle tightness, salivary hypersecretion, and tremor.

*Cataracts*

In the long-term uncontrolled schizophrenia (48-week) and bipolar mania (16-week) trials, the incidence of cataracts was 0.1% and 0.2%, respectively. The development of cataracts was observed in nonclinical studies *[see Nonclinical Toxicology (13.2)]*. The possibility of lenticular changes or cataracts cannot be excluded at this time.

*Vital Signs Changes*

There were no clinically meaningful differences between VRAYLAR-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine blood pressure parameters except for an increase in supine diastolic blood pressure in the 9 - 12 mg/day VRAYLAR-treated patients with schizophrenia.

Pooled data from 6-week schizophrenia trials are shown in Table 11 and from 3-week bipolar mania trials are shown in Table 12.

**Table 11. Mean Change in Blood Pressure at Endpoint in 6-Week Schizophrenia Trials**

| | | **VRAYLAR*** | | |
|---|---|---|---|---|
| | Placebo (N=574) | 1.5 - 3 mg/day (N=512) | 4.5 - 6 mg/day (N=570) | 9- 12 mg/day° (N=203) |
| Supine Systolic Blood Pressure (mmHg) | +0.9 | +0.6 | +1.3 | +2.1 |
| Supine Diastolic Blood Pressure (mmHg) | +0.4 | +0.2 | +1.6 | +3.4 |

* Data shown by modal daily dose, defined as most frequently administered dose per patient
° The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

**Table 12. Mean Change in Blood Pressure at Endpoint in 3-Week Bipolar Mania Trials**

| | Placebo (N=439) | VRAYLAR* 3 - 6 mg/day (N=259) | VRAYLAR* 9 – 12 mg/day° (N=360) |
|---|---|---|---|
| Supine Systolic Blood Pressure (mmHg) | -0.5 | +0.8 | +1.8 |
| Supine Diastolic Blood Pressure (mmHg) | +0.9 | +1.5 | +1.9 |

* Data shown by modal daily dose, defined as most frequently administered dose per patient
° The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In the two 6-week and one 8-week bipolar depression trials, there were no clinically meaningful differences between VRAYLAR-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine systolic and diastolic blood pressure.

Pooled data from two 6-week and one 8-week bipolar depression trials are shown in Table 13**.**

**Table 13. Mean Change in Blood Pressure at Endpoint in two 6-Week and one 8-Week Bipolar Depression Trials**

| | Placebo (N=468) | VRAYLAR* 1.5 mg/day (N=572) | VRAYLAR* 3 mg/day (N=426) |
|---|---|---|---|
| Supine Systolic Blood Pressure (mmHg) | -0.2 | 0.2 | -0.1 |
| Supine Diastolic Blood Pressure (mmHg) | 0.2 | 0.1 | -0.3 |

*Changes in Laboratory Tests*

The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week schizophrenia trials ranged between 1% and 2% for VRAYLAR-treated patients, increasing with dose, and was 1% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 3-week bipolar mania trials ranged between 2% and 4% for VRAYLAR-treated patients depending on dose group administered and 2% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week and 8-week bipolar depression trials ranged between 0% and 0.5% for VRAYLAR-treated patients depending on dose group administered and 0.4% for placebo-treated patients.

The proportions of patients with elevations of creatine phosphokinase (CPK) greater than 1000 U/L in 6-week schizophrenia trials ranged between 4% and 6% for VRAYLAR-treated patients, increasing with dose, and was 4% for placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 3-week bipolar mania trials was about 4% in VRAYLAR and placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 6-week and 8-week bipolar

depression trials ranged between 0.2% and 1% for VRAYLAR-treated patients versus 0.2% for placebo-treated patients.

*Other Adverse Reactions Observed During the Pre-marketing Evaluation of VRAYLAR*

Adverse reactions listed below were reported by patients treated with VRAYLAR at doses of ≥ 1.5 mg once daily within the premarketing database of 3988 VRAYLAR-treated patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions that appear elsewhere in the VRAYLAR label are not included.

Reactions are further categorized by organ class and listed in order of decreasing frequency, according to the following definition: those occurring in at least 1/100 patients (frequent) [only those not already listed in the tabulated results from placebo-controlled studies appear in this listing]; those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

*Gastrointestinal Disorders:* ***Infrequent****: gastroesophageal reflux disease, gastritis*
*Hepatobiliary Disorders:* ***Rare:*** *hepatitis*
*Metabolism and Nutrition Disorders:* ***Frequent****: decreased appetite;* ***Infrequent****: hyponatremia*
*Musculoskeletal and Connective Tissue Disorders:* ***Rare****: rhabdomyolysis*
*Nervous System Disorders:* ***Rare****: ischemic stroke*
*Psychiatric Disorders:* ***Infrequent:*** *suicide attempts, suicide ideation;* ***Rare****: completed suicide*
*Renal and Urinary Disorders:* ***Infrequent****: pollakiuria*
*Skin and Subcutaneous Tissue Disorders:* ***Infrequent:*** *hyperhidrosis*

### 6.2 Postmarketing Experience

The following adverse reaction has been identified during post approval use of VRAYLAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

*Skin and Subcutaneous Tissue Disorders* – Stevens-Johnson syndrome

# 7 DRUG INTERACTIONS

## 7.1 Drugs Having Clinically Important Interactions with VRAYLAR

**Table 14. Clinically Important Drug Interactions with VRAYLAR**

| **Strong CYP3A4 Inhibitors** | |
|---|---|
| *Clinical Impact:* | Concomitant use of VRAYLAR with a strong CYP3A4 inhibitor increases the exposures of cariprazine and its major active metabolite, didesmethylcariprazine (DDCAR), compared to use of VRAYLAR alone *[see Clinical Pharmacology (12.3)]*. |
| *Intervention:* | If VRAYLAR is used with a strong CYP3A4 inhibitor, reduce VRAYLAR dosage *[see Dosage and Administration (2.5)]*. |
| *Examples:* | itraconazole, ketoconazole |
| **CYP3A4 Inducers** | |
| *Clinical Impact:* | CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the exposure of VRAYLAR has not been evaluated, and the net effect is unclear *[see Clinical Pharmacology (12.3)]*. |
| *Intervention:* | Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended *[see Dosage and Administration (2.1, 2.5)]*. |
| *Examples:* | rifampin, carbamazepine |

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

*Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VRAYLAR during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

*Risk Summary*

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. There are no available data on VRAYLAR use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DDCAR, has been detected in adult patients up to 12 weeks after discontinuation of VRAYLAR *[see Clinical Pharmacology (12.3)]*. Based on animal data, VRAYLAR may cause fetal harm.

Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dose (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

*Clinical Considerations*

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

*Data*

Animal Data

Administration of cariprazine to pregnant rats during the period of organogenesis at oral doses of 0.5, 2.5, and 7.5 mg/kg/day which are 0.2 to 3.5 times the maximum recommended human dose (MRHD) of 6 mg/day based on AUC of total cariprazine (i.e. sum of cariprazine, DCAR, and DDCAR) caused fetal developmental toxicity at all doses which included reduced body weight, decreased male anogenital distance and skeletal malformations of bent limb bones, scapula and humerus. These effects occurred in the absence or presence of maternal toxicity. Maternal toxicity, observed as a reduction in body weight and food consumption, occurred at doses 1.2 and 3.5-times the MRHD of 6 mg/day based on AUC of total cariprazine. At these doses, cariprazine caused fetal external malformations (localized fetal thoracic edema), visceral variations (undeveloped/underdeveloped renal papillae and/or distended urethrae), and skeletal developmental variations (bent ribs, unossified sternebrae). Cariprazine had no effect on fetal survival.

Administration of cariprazine to pregnant rats during pregnancy and lactation at oral doses of 0.1, 0.3, and 1 mg/kg/day which are 0.03 to 0.4 times the MRHD of 6 mg/day based on AUC of total cariprazine caused a decrease in postnatal survival, birth weight, and post-weaning body weight of first generation pups at the dose that is 0.4 times the MRHD of 6 mg/day based on AUC of total cariprazine in absence of maternal toxicity. First generation pups also had pale, cold bodies and developmental delays (renal papillae not developed or underdeveloped and decreased auditory startle response in males). Reproductive performance of the first generation pups was unaffected; however, the second generation pups had clinical signs and lower body weight similar to those of the first generation pups.

Administration of cariprazine to pregnant rabbits during the period of organogenesis at oral doses of 0.1, 1, and 5 mg/kg/day, which are 0.02 to 4.6 times the MRHD of 6 mg/day based on AUC of total cariprazine was not teratogenic. Maternal body weight and food consumption were decreased at 4.6 times the MRHD of 6 mg/day based on AUC of total cariprazine; however, no adverse effects were observed on pregnancy parameters or reproductive organs.

### 8.2 Lactation

*Risk Summary*

Lactation studies have not been conducted to assess the presence of cariprazine in human milk, the effects on the breastfed infant, or the effects on milk production. Cariprazine is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for VRAYLAR and any potential adverse effects on the breastfed infant from VRAYLAR or from the underlying maternal condition.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric studies of VRAYLAR have not been conducted. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

### 8.5 Geriatric Use

Clinical trials of VRAYLAR in the treatment of schizophrenia and bipolar mania did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Elderly patients with dementia-related psychosis treated with VRAYLAR are at an increased risk of death compared to placebo. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1, 5.3)]*.

### 8.6 Hepatic Impairment

No dosage adjustment for VRAYLAR is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5 and 9) [*see Clinical Pharmacology (12.3)*]. Usage of VRAYLAR is not recommended in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). VRAYLAR has not been evaluated in this patient population.

### 8.7 Renal Impairment

No dosage adjustment for VRAYLAR is required in patients with mild to moderate (CrCL ≥ 30 mL/minute) renal impairment [*see Clinical Pharmacology (12.3)*].

Usage of VRAYLAR is not recommended in patients with severe renal impairment (CrCL < 30 mL/minute). VRAYLAR has not been evaluated in this patient population.

### 8.8 Smoking

No dosage adjustment for VRAYLAR is needed for patients who smoke. VRAYLAR is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of VRAYLAR.

### 8.9 Other Specific Populations

No dosage adjustment is required based on patient's age, sex, or race. These factors do not affect the pharmacokinetics of VRAYLAR [*see Clinical Pharmacology (12.3)*].

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

VRAYLAR is not a controlled substance.

### 9.2 Abuse

VRAYLAR has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance.

### 9.3 Dependence

VRAYLAR has not been systematically studied in animals or humans for its potential for physical dependence.

## 10 OVERDOSAGE

### 10.1 Human Experience

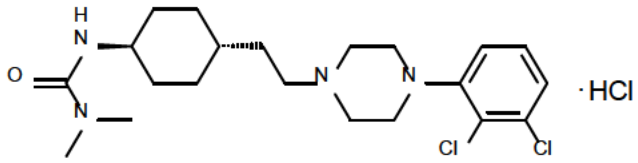
In pre-marketing clinical trials involving VRAYLAR in approximately 5000 patients or healthy subjects, accidental acute overdosage (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

### 10.2 Management of Overdosage

No specific antidotes for VRAYLAR are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. In case of an overdose, consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

## 11 DESCRIPTION

The active ingredient of VRAYLAR is cariprazine HCl, an atypical antipsychotic. The chemical name is *trans*-N-{4-[2-[4-(2,3-dichlorophenyl)piperazine-1-yl]ethyl]cyclohexyl}-N',N'-dimethylurea hydrochloride; its empirical formula is $C_{21}H_{33}Cl_3N_4O$ and its molecular weight is 463.9 g/mol. The chemical structure is:




VRAYLAR capsules are intended for oral administration only. Each hard gelatin capsule contains a white to off-white powder of cariprazine HCl, which is equivalent to 1.5, 3, 4.5, or 6 mg of cariprazine base. In addition, capsules include the following inactive ingredients: gelatin, magnesium stearate, pregelatinized starch, shellac, and titanium dioxide. Colorants include black iron oxide (1.5, 3, and 6 mg), FD&C Blue 1 (3, 4.5, and 6 mg), FD&C Red 3 (6 mg), FD&C Red 40 (3 and 4.5 mg), or yellow iron oxide (3 and 4.5 mg).

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

The mechanism of action of cariprazine in schizophrenia and bipolar I disorder is unknown. However, the efficacy of cariprazine could be mediated through a combination of partial agonist activity at central dopamine $D_2$ and serotonin 5-$HT_{1A}$ receptors and antagonist activity at serotonin 5-$HT_{2A}$ receptors. Cariprazine forms two major metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), that have *in vitro* receptor binding profiles similar to the parent drug.

## 12.2 Pharmacodynamics

Cariprazine acts as a partial agonist at the dopamine $D_3$ and $D_2$ receptors with high binding affinity ($K_i$ values 0.085 nM, and 0.49 nM ($D_{2L}$) and 0.69 nM ($D_{2S}$), respectively) and at the serotonin 5-$HT_{1A}$ receptors ($K_i$ value 2.6 nM). Cariprazine acts as an antagonist at 5-$HT_{2B}$ and 5-$HT_{2A}$ receptors with high and moderate binding affinity (Ki values 0.58 nM and 18.8 nM respectively) as well as it binds to the histamine $H_1$ receptors ($K_i$ value 23.2 nM). Cariprazine shows lower binding affinity to the serotonin 5-$HT_{2C}$ and $\alpha_{1A}$- adrenergic receptors ($K_i$ values 134 nM and 155 nM, respectively) and has no appreciable affinity for cholinergic muscarinic receptors ($IC_{50}$>1000 nM).

*Effect on QTc Interval*

At a dose three-times the maximum recommended dose, cariprazine does not prolong the QTc interval to clinically relevant extent.

## 12.3 Pharmacokinetics

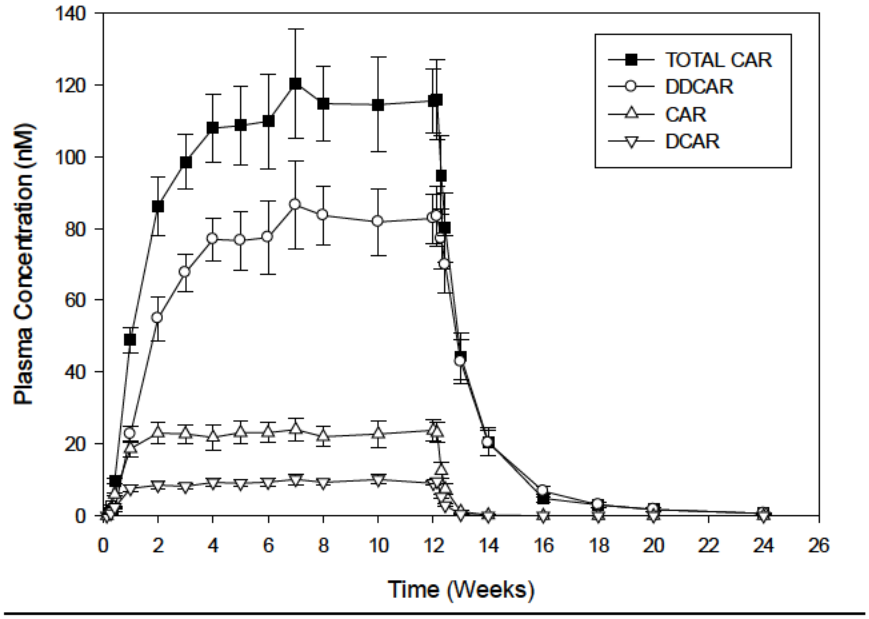
VRAYLAR activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

After multiple dose administration of VRAYLAR, mean cariprazine and DCAR concentrations reached steady state at around Week 1 to Week 2 and mean DDCAR concentrations appeared to be approaching steady state at around Week 4 to Week 8 in a 12-week study (Figure 1). The half-lives based on time to reach steady state, estimated from the mean concentration-time curves, are 2 to 4 days for cariprazine, about 1 to 2 days for DCAR, and approximately 1 to 3 weeks for DDCAR. The time to reach steady state for the major active metabolite DDCAR was variable across patients, with some patients not achieving steady state at the end of the 12 week treatment *[see Dosage and Administration (2.1), Warnings and Precautions (5.6)]*. Mean concentrations of DCAR and DDCAR are approximately 30% and 400%, respectively, of cariprazine concentrations by the end of 12-week treatment.

After discontinuation of VRAYLAR, cariprazine, DCAR, and DDCAR plasma concentrations declined in a multi-exponential manner. Mean plasma concentrations of DDCAR decreased by about 50%, 1 week after the last dose and mean cariprazine and DCAR concentration dropped by about 50% in about 1 day. There was an approximately 90% decline in plasma exposure within 1 week for cariprazine and DCAR, and at about 4 weeks for DDCAR. Following a single dose of 1 mg of cariprazine administration, DDCAR remained detectable 8 weeks post-dose.

After multiple dosing of VRAYLAR, plasma exposure of cariprazine, DCAR, and DDCAR, increases approximately proportionally over the therapeutic dose range.

**Figure 1. Plasma Concentration (Mean ± SE)-Time Profile During and Following 12-weeks of Treatment with Cariprazine 6 mg/day[a]**




[a] Trough concentrations shown during treatment with cariprazine 6 mg/day.
SE: standard error; TOTAL CAR: sum concentration of cariprazine, DCAR and DDCAR; CAR: cariprazine

*Absorption*

After single dose administration of VRAYLAR, the peak plasma cariprazine concentration occurred in approximately 3-6 hours.

Administration of a single dose of 1.5 mg VRAYLAR capsule with a high-fat meal did not significantly affect the $C_{max}$ and AUC of cariprazine or DCAR.

*Distribution*

Cariprazine and its major active metabolites are highly bound (91 to 97%) to plasma proteins.

*Elimination*

Metabolism
Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to DCAR and DDCAR. DCAR is further metabolized into DDCAR by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite.

Excretion
Following administration of 12.5 mg/day cariprazine to patients with schizophrenia for 27 days, about 21% of the daily dose was found in urine, with approximately 1.2% of the daily dose was excreted in urine as unchanged cariprazine.

*Studies in Specific Populations*

Hepatic Impairment
Compared to healthy subjects, exposure ($C_{max}$ and AUC) in patients with either mild or moderate hepatic impairment (Child-Pugh score between 5 and 9) was approximately 25% higher for cariprazine and 20% to 30% lower for the major metabolites (DCAR and DDCAR) following daily doses of 0.5 mg cariprazine for 14 days *[see Use in Specific Populations (8.6)]*.

Renal Impairment
Cariprazine and its major active metabolites are minimally excreted in urine. Pharmacokinetic analyses indicated no significant relationship between plasma clearance and creatinine clearance *[see Use in Specific Populations (8.7)]*.

CYP2D6 Poor Metabolizers
CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

Age, Sex, Race
Age, sex, or race does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

*Drug Interaction Studies*

*In vitro* studies
Cariprazine and its major active metabolites did not induce CYP1A2 and CYP3A4 enzymes and were weak inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 *in vitro*. Cariprazine was also a weak inhibitor of CYP2C19, CYP2A6, and CYP2E1 *in vitro.*

Cariprazine and its major active metabolites are not substrates of P-glycoprotein (P-gp), the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), or the breast cancer resistance protein (BCRP).

Cariprazine and its major active metabolites were poor or non-inhibitors of transporters OATP1B1, OATP1B3, BCRP, organic cation transporter 2 (OCT2), and organic anion transporters 1 and 3 (OAT1 and OAT3) *in vitro*. The major active metabolites were also poor or non-inhibitors of transporter P-gp although cariprazine was probably a P-gp inhibitor based on the theoretical GI concentrations at high doses *in vitro*.

Based on in vitro studies, VRAYLAR is unlikely to cause clinically significant pharmacokinetic drug interactions with substrates of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E, and CYP3A4, or OATP1B1, OATP1B3, BCRP, OCT2, OAT1 and OAT3

*In vivo* studies

CYP 3A4 inhibitors
Co-administration of ketoconazole (400 mg/day), a strong CYP3A4 inhibitor, with VRAYLAR (0.5 mg/day) increased cariprazine $C_{max}$ and $AUC_{0-24h}$ by about 3.5-fold and 4-fold, respectively; increased DDCAR $C_{max}$ and $AUC_{0-24h}$ by about 1.5-fold; and decreased DCAR $C_{max}$ and $AUC_{0-24h}$ by about one-third. The impact of moderate CYP3A4 inhibitors has not been studied.

CYP3A4 inducers

CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the plasma exposure of cariprazine and its major active metabolites has not been evaluated, and the net effect is unclear.

CYP2D6 inhibitors

CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.

Proton pump inhibitors

Co-administration of pantoprazole (40 mg/day), a proton pump inhibitor, with VRAYLAR (6 mg/day) in patients with schizophrenia for 15 days did not affect cariprazine exposure at steady-state, based on $C_{max}$ and $AUC_{0-24}$. Similarly, no significant change in exposure to DCAR and DDCAR was observed.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenesis*

There was no increase in the incidence of tumors following daily oral administration of cariprazine to rats for 2 years and to Tg.rasH2 mice for 6 months at doses which are up to 4 and 19 times respectively, the MRHD of 6 mg/day based on AUC of total cariprazine, (i.e. sum of AUC values of cariprazine, DCAR and DDCAR).

Rats were administered cariprazine at oral doses of 0.25, 0.75, and 2.5 (males)/1, 2.5, and 7.5 mg/kg/day (females) which are 0.2 to 1.8 (males)/ 0.8 to 4.1 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine.

Tg.rasH2 mice were administered cariprazine at oral doses of 1, 5, and 15 (males)/5, 15, and 50 mg/kg/day (females) which are 0.2 to 7.9 (males)/2.6 to 19 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine.

*Mutagenesis*

Cariprazine was not mutagenic in the *in vitro* bacterial reverse mutation assay, nor clastogenic in the in vitro human lymphocyte chromosomal aberration assay or in the *in vivo* mouse bone marrow micronucleus assay. However, cariprazine increased the mutation frequency in the in vitro mouse lymphoma assay under conditions of metabolic activation. The major human metabolite DDCAR was not mutagenic in the *in vitro* bacterial reverse mutation assay, however, it was clastogenic and induced structural chromosomal aberration in the *in vitro* human lymphocyte chromosomal aberration assay.

*Impairment of Fertility*

Cariprazine was administered orally to male and female rats before mating, through mating and up to day 7 of gestation at doses of 1, 3, and 10 mg/kg/day which are 1.6 to 16 times the MRHD of 6 mg/day based on $mg/m^2$. In female rats, lower fertility and conception indices were observed at all dose levels which are equal to or higher than 1.6 times the MRHD of 6 mg/day based on $mg/m^2$. No effects on male fertility were noted at any dose up to 4.3 times the MRHD of 6 mg/day based on AUC of total cariprazine.

### 13.2 Animal Toxicology and/or Pharmacology

Cariprazine caused bilateral cataract and cystic degeneration of the retina in the dog following oral daily administration for 13 weeks and/or 1 year and retinal degeneration/atrophy in the rat following oral daily administration for 2 years. Cataract in the dog was observed at 4 mg/kg/day which is 7.1 (male) and 7.7 (female) times the MRHD of 6 mg/day based on AUC of total cariprazine. The NOEL for cataract and retinal toxicity in the dog is 2 mg/kg/day which is 5 (males) to 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. Increased incidence and severity of retinal degeneration/atrophy in the rat occurred at all doses tested, including the low dose of 0.75 mg/kg/day, at total cariprazine plasma levels less than clinical exposure (AUC) at the MRHD of 6 mg/day. Cataract was not observed in other repeat dose studies in pigmented mice or albino rats.

Phospholipidosis was observed in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures (AUC) of total cariprazine. Phospholipidosis was not reversible at the end of the 1-2 month drug-free periods. Inflammation was observed in the lungs of dogs dosed daily for 1 year with a NOEL of 1 mg/kg/day which is 2.7 (males) and 1.7 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. No inflammation was observed at the end of 2-month drug free period following administration of 2 mg/kg/day which is 5 (males) and 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine; however, inflammation was still present at higher doses.

Hypertrophy of the adrenal gland cortex was observed at clinically relevant total cariprazine plasma concentrations in rats (females only) and mice following daily oral administration of cariprazine for 2 years and 6 months, respectively. Reversible hypertrophy/hyperplasia and vacuolation/vesiculation of the adrenal gland cortex were observed following daily oral administration of cariprazine to dogs for 1 year. The NOEL was 2 mg/kg/day which is 5 (males) and 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. The relevance of these findings to human risk is unknown.

## 14 CLINICAL STUDIES

### 14.1 Schizophrenia

The efficacy of VRAYLAR for the treatment of schizophrenia was established in three, 6-week, randomized, double-blind, placebo-controlled trials in patients (aged 18 to 60 years) who met Diagnostic and Statistical Manual of Mental Disorders 4$^{th}$ edition, Text Revision (DSM-IV-TR) criteria for schizophrenia. An active control arm (risperidone or aripiprazole) was included in two trials to assess assay sensitivity. In all three trials, VRAYLAR was superior to placebo.

Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) rating scales were used as the primary and secondary efficacy measures, respectively, for assessing psychiatric signs and symptoms in each trial:

- PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme). The PANSS total score may range from 30 to 210 with the higher score reflecting greater severity.

- The CGI-S is a validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In each study, the primary endpoint was change from baseline in PANSS total score at the end of week 6. The change from baseline for VRAYLAR and active control groups was compared to placebo. The results of the trials are shown in Table 15. The time course of efficacy results of Study 2 is shown in Figure 2.

Study 1: In a 6-week, placebo-controlled trial (N = 711) involving three fixed doses of VRAYLAR (1.5, 3, or 4.5 mg/day) and an active control (risperidone), all VRAYLAR doses and the active control were superior to placebo on the PANSS total score and the CGI-S.

Study 2: In a 6-week, placebo-controlled trial (N = 604) involving two fixed doses of VRAYLAR (3 or 6 mg/day) and an active control (aripiprazole), both VRAYLAR doses and the active control were superior to placebo on the PANSS total score and the CGI-S.

Study 3: In a 6-week, placebo-controlled trial (N = 439) involving two flexible-dose range groups of VRAYLAR (3 to 6 mg/day or 6 to 9 mg/day), both VRAYLAR groups were superior to placebo on the PANSS total score and the CGI-S.

The efficacy of VRAYLAR was demonstrated at doses ranging from 1.5 to 9 mg/day compared to placebo. There was, however, a dose-related increase in certain adverse reactions, particularly above 6 mg. Therefore, the maximum recommended dose is 6 mg/day.

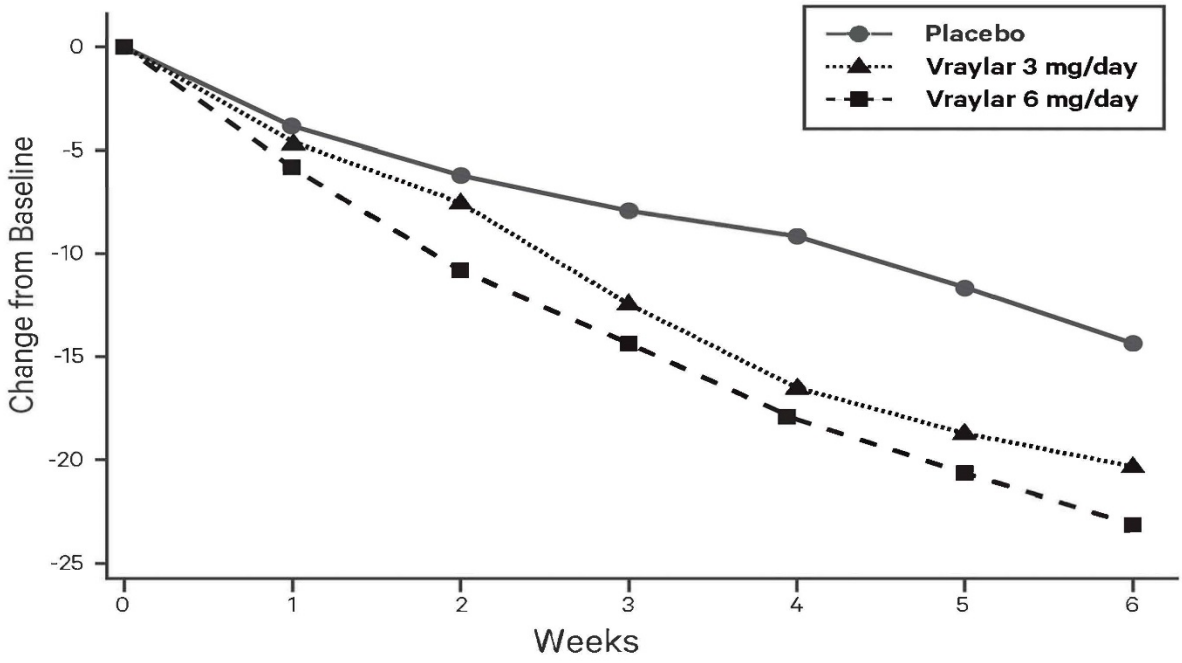
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

**Table 15. Primary Analysis Results from Schizophrenia Trials**

| Study Number | Treatment Group (# ITT patients) | Primary Efficacy Endpoint: PANSS Total | | |
|---|---|---|---|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
| Study 1 | VRAYLAR (1.5 mg/day)* (n=140) | 97.1 (9.1) | -19.4 (1.6) | -7.6 (-11.8, -3.3) |
| | VRAYLAR (3 mg/day)* (n=140) | 97.2 (8.7) | -20.7 (1.6) | -8.8 (-13.1, -4.6) |
| | VRAYLAR (4.5 mg/day)* (n=145) | 96.7 (9.0) | -22.3 (1.6) | -10.4 (-14.6, -6.2) |
| | Placebo (n=148) | 97.3 (9.2) | -11.8 (1.5) | -- |
| Study 2 | VRAYLAR (3 mg/day)* (n=151) | 96.1 (8.7) | -20.2 (1.5) | -6.0 (-10.1, -1.9) |
| | VRAYLAR (6 mg/day)* (n=154) | 95.7 (9.4) | -23.0 (1.5) | -8.8 (-12.9, -4.7) |
| | Placebo (n=149) | 96.5 (9.1) | -14.3 (1.5) | -- |
| Study 3 | VRAYLAR (3-6 mg/day)* (n=147) | 96.3 (9.3) | -22.8 (1.6) | -6.8 (-11.3, -2.4) |
| | VRAYLAR (6-9 mg/day)*[b] (n=147) | 96.3 (9.0) | -25.9 (1.7) | -9.9 (-14.5, -5.3) |
| | Placebo (n=145) | 96.6 (9.3) | -16.0 (1.6) | -- |

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo
[b]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

**Figure 2. Change from Baseline in PANSS total score by weekly visits (Study 2)**

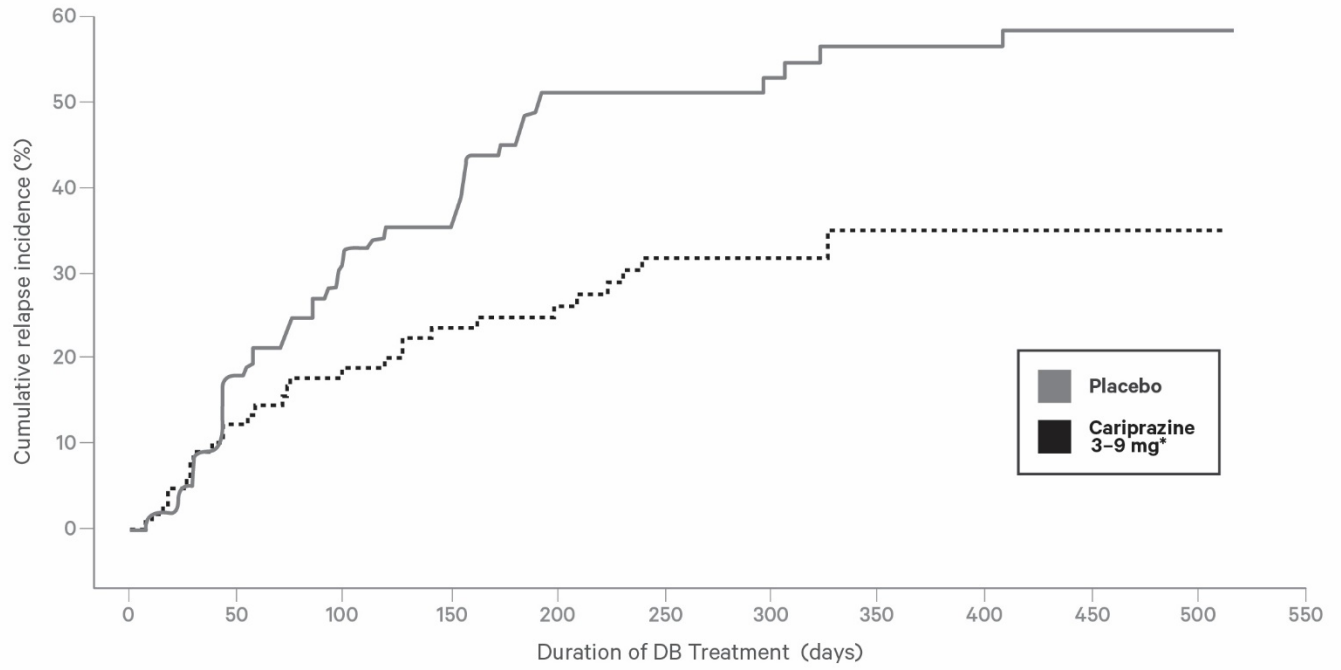



The safety and efficacy of VRAYLAR as maintenance treatment in adults with schizophrenia were demonstrated in a randomized withdrawal trial that included 200 patients meeting DSM-IV criteria for schizophrenia who were clinically stable following 20 weeks of open-label cariprazine at doses of 3 to 9 mg/day. Patients were randomized to receive either placebo or cariprazine at the same dose for up to 72 weeks for observation of relapse. The primary endpoint was time to relapse. Relapse during the double-blind phase (DBP) was defined as meeting any one of the following criteria: hospitalization due to worsening of schizophrenia, increase in the PANSS total score by ≥ 30%, increase in CGI-S score by ≥ 2 points, deliberate self-injury, aggressive or violent behavior, clinically significant suicidal or homicidal ideation, or score >4 on one or more of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucination (P3), suspiciousness or persecution (P6), hostility (P7), uncooperativeness (G8), or poor impulse control (G14).

The efficacy of VRAYLAR was demonstrated at doses ranging from 3 to 9 mg/day compared to placebo. There was, however, a dose-related increase in certain adverse reactions, particularly above 6 mg. Therefore, the maximum recommended dose is 6 mg/day.

The Kaplan-Meier curves of the time to relapse during the double-blind, placebo-controlled, randomized withdrawal phase of the long-term trial are shown in Figure 3. Time to relapse was statistically significantly longer in the VRAYLAR-treated group compared to the placebo group.

**Figure 3. Kaplan-Meier Curves of Cumulative Rate of Relapse During the Double-Blind Treatment Period**




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| At Risk | Cariprazine 3-9 mg* | 101 | 81 | 72 | 64 | 54 | 48 | 44 | 38 | 32 | 26 | 18 | 0 |
| | Placebo | 99 | 75 | 58 | 54 | 38 | 32 | 28 | 23 | 23 | 21 | 16 | 0 |
| Event | Cariprazine 3-9 mg* | 0 | 12 | 18 | 22 | 24 | 28 | 28 | 30 | 30 | 30 | 30 | 30 |
| | Placebo | 0 | 17 | 30 | 32 | 45 | 45 | 46 | 48 | 48 | 49 | 49 | 49 |

DB = double-blind
*The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

### 14.2 Manic or Mixed Episodes Associated with Bipolar I Disorder

The efficacy of VRAYLAR in the acute treatment of bipolar mania was established in three, 3-week placebo-controlled trials in patients (mean age of 39 years, range 18 to 65 years) who met DSM-IV-TR criteria for bipolar 1 disorder with manic or mixed episodes with or without psychotic features. In all three trials, VRAYLAR was superior to placebo.

Young Mania Rating Scale (YMRS) and Clinical Global Impressions-Severity scale (CGI-S) were used as the primary and secondary efficacy measures, respectively, for assessing psychiatric signs and symptoms in each trial:

- The YMRS is an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology. YMRS total score may range from 0 to 60 with a higher score reflecting greater severity.

- The CGI-S is validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In each study, the primary endpoint was decrease from baseline in YMRS total score at the end of week 3. The change from baseline for each VRAYLAR dose group was compared to placebo. The results of the trials are shown in Table 16. The time course of efficacy results is shown in Figure 4.

Study 4: In a 3-week, placebo-controlled trial (N = 492) involving two flexible-dose range groups of VRAYLAR (3 to 6 mg/day or 6 to 12 mg/day), both VRAYLAR dose groups were superior to placebo on the YMRS total score and the CGI-S. The 6 to 12 mg/day dose group showed no additional advantage.

Study 5: In a 3-week, placebo-controlled trial (N = 235) involving a flexible-dose range of VRAYLAR (3 to 12 mg/day), VRAYLAR was superior to placebo on the YMRS total score and the CGI-S.

Study 6: In a 3-week, placebo-controlled trial (N = 310) involving a flexible-dose range of VRAYLAR (3 to 12 mg/day), VRAYLAR was superior to placebo on the YMRS total score and the CGI-S.

The efficacy of VRAYLAR was established at doses ranging from 3 to 12 mg/day. Doses above 6 mg did not appear to have additional benefit over lower doses (Table 16) and there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

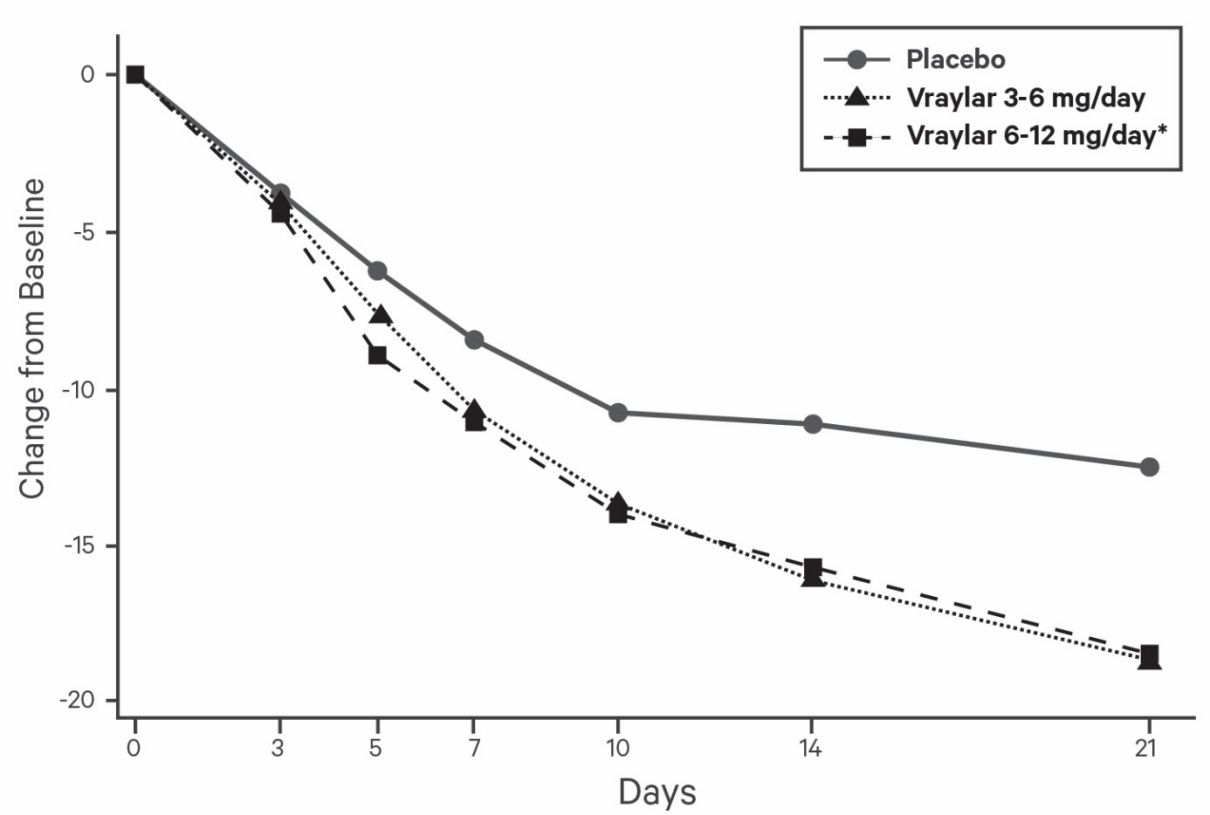
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

**Table 16. Primary Analysis Results from Manic or Mixed Episodes Associated with Bipolar I Disorder Trials**

| Study Number | Treatment Group (# ITT patients) | Primary Efficacy Endpoint: YMRS Total | | |
|---|---|---|---|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
| Study 4 | VRAYLAR (3-6 mg/day)* (n=165) | 33.2 (5.6) | -18.6 (0.8) | -6.1 (-8.4, -3.8) |
| | VRAYLAR (6-12 mg/day)*[b] (n=167) | 32.9 (4.7) | -18.5 (0.8) | -5.9 (-8.2, -3.6) |
| | Placebo (n=160) | 32.6 (5.8) | -12.5 (0.8) | -- |
| Study 5 | VRAYLAR (3-12 mg/day)*[b] (n=118) | 30.6 (5.0) | -15.0 (1.1) | -6.1 (-8.9, -3.3) |
| | Placebo (n=117) | 30.2 (5.2) | -8.9 (1.1) | -- |
| Study 6 | VRAYLAR (3-12 mg/day)*[b] (n=158) | 32.3 (5.8) | -19.6 (0.9) | -4.3 (-6.7, -1.9) |
| | Placebo (n=152) | 32.1 (5.6) | -15.3 (0.9) | -- |

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo
[b]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

**Figure 4. Change from Baseline in YMRS total score by study visit (Study 4)**




* The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

### 14.3 Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The efficacy of VRAYLAR in the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) was established in one 8-week and two 6-week placebo-controlled trials in patients (mean age of 41.6 years, range 18 to 65 years) who met DSM-IV-TR or DSM-5 criteria for depressive episodes associated with bipolar I disorder.

In each study, the primary endpoint was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of Week 6. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The MADRS total score change from baseline for VRAYLAR compared to placebo is shown in Table 17. The time course of efficacy results of Study 8 is shown in Figure 5. In each study, the VRAYLAR 1.5 mg dose demonstrated statistical significance over placebo. The secondary endpoint was change from baseline to Week 6 in CGI-S. The CGI-S is validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

Study 7: In an 8-week, placebo-controlled trial (N = 571) involving three-fixed doses of VRAYLAR (0.75 mg/day, 1.5 mg/day, and 3 mg/day), VRAYLAR 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S.

Study 8: In a 6-week, placebo-controlled trial (N = 474) involving two-fixed doses of VRAYLAR (1.5 mg/day and 3 mg/day), VRAYLAR 1.5 mg and 3 mg were superior to placebo at end of Week 6 on the MADRS total score.

Study 9: In a 6-week, placebo-controlled trial (N = 478) involving two-fixed doses of VRAYLAR (1.5 mg/day and 3 mg/day), VRAYLAR 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S.

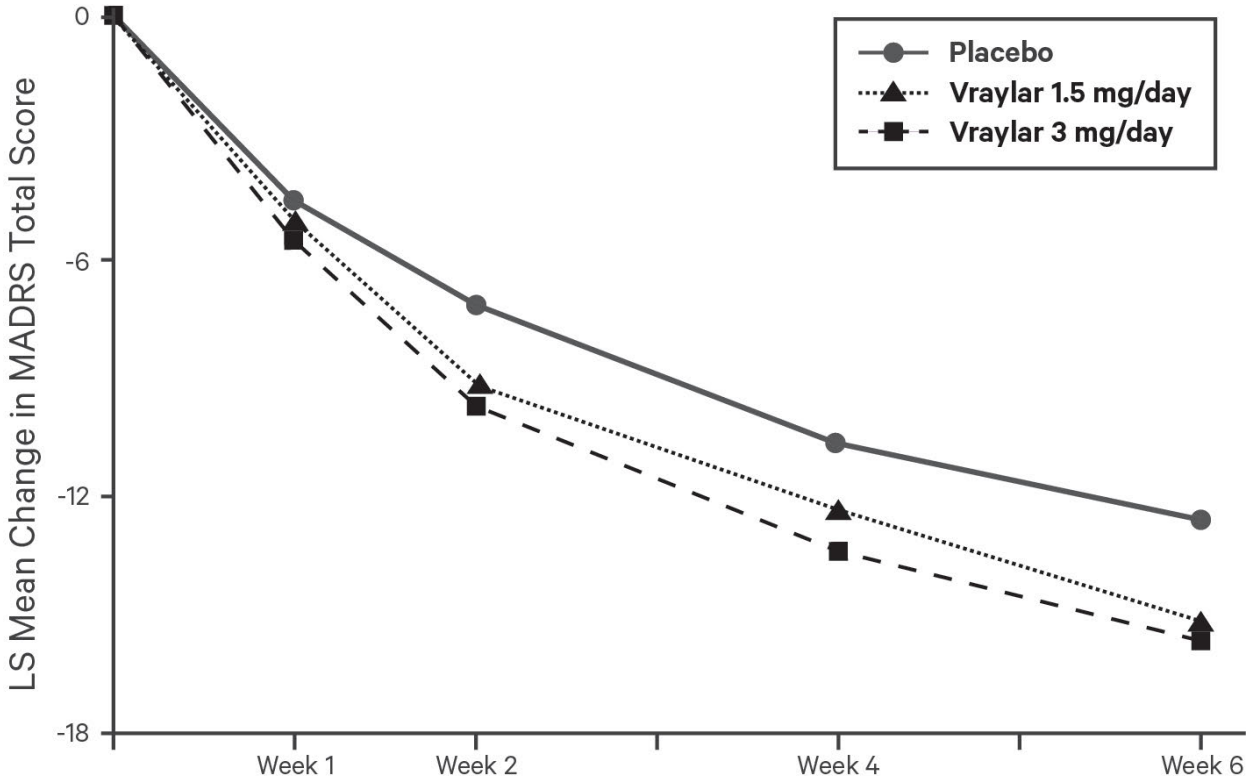
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

**Table 17. Primary Analysis Results from Bipolar Depression Trials**

| **Study Number** | **Treatment Group (# ITT patients)** | **Primary Efficacy Endpoint: MADRS Total** | | |
|---|---|---|---|---|
| | | **Mean Baseline Score (SD)** | **LS Mean Change from Baseline (SE)** | **Placebo-subtracted Difference[a] (95% CI)** |
| Study 7 | | | | |
| | VRAYLAR (1.5 mg/day)* (n=145) | 30.3 (4.4) | -15.1 (0.8) | -4.0 (-6.3, -1.6) |
| | VRAYLAR (3 mg/day) (n=145) | 30.6 (4.7) | -13.7 (0.9) | -2.5 (-4.9, -0.1) |
| | Placebo (n=141) | 30.4 (4.6) | -11.1 (0.9) | |
| Study 8 | VRAYLAR (1.5 mg/day)* (n=154) | 30.7 (4.3) | -15.1 (0.8) | -2.5 (-4.6, -0.4) |
| | VRAYLAR (3 mg/day)* (n=164) | 31.0 (4.9) | -15.6 (0.8) | -3.0 (-5.1, -0.9) |
| | Placebo (n=156) | 30.2 (4.4) | -12.6 (0.8) | |
| Study 9 | VRAYLAR (1.5 mg/day)* (n=162) | 31.5 (4.3) | -14.8 (0.8) | -2.5 (-4.6, -0.4) |
| | VRAYLAR (3 mg/day) (n=153) | 31.5 (4.8) | -14.1 (0.8) | -1.8 (-3.9, 0.4) |
| | Placebo (n=163) | 31.4 (4.5) | -12.4 (0.8) | |

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo

**Figure 5. LS Mean Change from Baseline in MADRS Total Score by Visits (Study 8)**




LS Mean: least-squares mean

## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

VRAYLAR capsules are supplied as follows:

| Capsule Strength | Imprint Codes | Package Configuration | NDC Code |
|---|---|---|---|
| 1.5 mg | FL 1.5 | Blister pack of 7 | 61874-115-17 |
| | | Bottle of 30 | 61874-115-30 |
| | | Bottle of 90 | 61874-115-90 |
| | | Box of 20 (Hospital Unit Dose) | 61874-115-20 |
| 3 mg | FL 3 | Bottle of 30 | 61874-130-30 |
| | | Bottle of 90 | 61874-130-90 |
| | | Box of 20 (Hospital Unit Dose) | 61874-130-20 |
| 4.5 mg | FL 4.5 | Bottle of 30 | 61874-145-30 |
| | | Bottle of 90 | 61874-145-90 |
| 6 mg | FL 6 | Bottle of 30 | 61874-160-30 |
| | | Bottle of 90 | 61874-160-90 |

| | | | |
|---|---|---|---|
| (1) 1.5 mg, (6) 3 mg | FL 1.5, FL 3 | Mixed Blister pack of 7 | 61874-170-08 |

### 16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*. Protect 3 mg and 4.5 mg capsules from light to prevent potential color fading.

## 17. PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide)

Physicians are advised to discuss with patients for whom they prescribe VRAYLAR all relevant safety information including, but not limited to, the following:

*Suicidal Thoughts and Behaviors*
Advise patients and caregivers to look for the emergence of suicidal thoughts and behaviors, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to their healthcare provider *[see Box Warning and Warnings and Precautions (5.2)]*.

*Dosage and Administration*
Advise patients that VRAYLAR can be taken with or without food. Counsel them on the importance of following dosage escalation instructions *[see Dosage and Administration (2)]*.

*Neuroleptic Malignant Syndrome (NMS)*
Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

*Tardive Dyskinesia*
Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

*Late-Occurring Adverse Reactions*
Counsel patients that adverse reactions may not appear until several weeks after the initiation of VRAYLAR treatment *[see Warnings and Precautions (5.6)]*.

*Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)*
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.7)]*.

*Leukopenia/Neutropenia*
Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while taking VRAYLAR *[see Warnings and Precautions (5.8)]*.

*Orthostatic Hypotension and Syncope*
Counsel patients on the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of re-initiating treatment or increases in dose *[see Warnings and Precautions (5.9)]*.

*Interference with Cognitive and Motor Performance*
Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that VRAYLAR therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

*Heat Exposure and Dehydration*
Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.13)]*.

*Concomitant Medications*
Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs since there is a potential for interactions *[see Drug Interactions (7.1)]*.

*Pregnancy*
Advise patients that third trimester use of VRAYLAR may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy [*see Use in Specific Populations (8.1)]*.

*Pregnancy Registry*
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VRAYLAR during pregnancy *[see Use in Specific Populations (8.1)]*.

Licensed from Gedeon Richter Plc.

Manufactured by:
Forest Laboratories Ireland Limited
Dublin, IE.

Distributed by:
Allergan USA, Inc.
Madison, NJ 07940

VRAYLAR® is a registered trademark of Forest Laboratories Holdings Ltd., an Allergan affiliate.


V4.0USPI115

**MEDICATION GUIDE**

VRAYLAR (VRAY-lar)
(cariprazine)
capsules

**What is the most important information I should know about VRAYLAR?**

**VRAYLAR may cause serious side effects, including**:

- **Increased risk of death in elderly people with dementia related psychosis.** Medicines like VRAYLAR can raise the risk of death in elderly who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). VRAYLAR is not approved for the treatment of patients with dementia-related psychosis.
- **Increased risk of suicidal thoughts or actions in children and young adults.** Antidepressant medicines may increase suicidal thoughts or actions in some children and young adults within the first few months of treatment and when the dose is changed.
  - **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or a history of suicidal thoughts or actions.

**How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- new or worse depression
- feeling very agitated or restless
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- an extreme increase in activity and talking (mania)
- attempts to commit suicide
- new or worse anxiety
- panic attacks
- new or worse irritability
- acting on dangerous impulses
- other unusual changes in behavior or mood

**What is VRAYLAR?**

VRAYLAR is a prescription medicine used in adults:

- to treat schizophrenia
- for short-term (acute) treatment of manic or mixed episodes that happen with bipolar I disorder
- to treat depressive episodes that happen with bipolar I disorder (bipolar depression)

It is not known if VRAYLAR is safe and effective in children.

**Do not take VRAYLAR if you are allergic to cariprazine.** See the end of this Medication Guide for a complete list of ingredients in VRAYLAR.

**Before taking VRAYLAR, tell your healthcare provider about all of your medical conditions, including if you:**

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar, or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start and during treatment with VRAYLAR.
- have or have had high levels of total cholesterol, LDL cholesterol, or triglycerides or low levels of HDL cholesterol.
- have or had seizures (convulsions)
- have or have had kidney or liver problems
- have or had a low white blood cell count
- are pregnant or plan to become pregnant. VRAYLAR may harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take VRAYLAR during pregnancy.
  - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with VRAYLAR.
  - If you become pregnant during treatment with VRAYLAR, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinicaland-researchprograms/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. It is not known if VRAYLAR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with VRAYLAR.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
VRAYLAR and other medicines may affect each other causing possible serious side effects. VRAYLAR may affect the way other medicines work, and other medicines may affect how VRAYLAR works.

Your healthcare provider can tell you if it is safe to take VRAYLAR with your other medicines. Do not start or stop any medicines while taking VRAYLAR without talking to your healthcare provider first.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

**How should I take VRAYLAR?**

- Take VRAYLAR exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking VRAYLAR without first talking to your healthcare provider.
- VRAYLAR can be taken with or without food.
- If you take too much VRAYLAR, call your healthcare provider or Poison Control Center or go to the nearest hospital emergency room, right away.

**What should I avoid while taking VRAYLAR?**

- Do not drive, operate machinery, or do other dangerous activities until you know how VRAYLAR affects you. VRAYLAR may make you drowsy.
- Do not become too hot or dehydrated during treatment with VRAYLAR.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

**What are the possible side effects of VRAYLAR?**

**VRAYLAR may cause serious side effects, including:**

- **See "What is the most important information I should know about VRAYLAR?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic malignant syndrome (NMS) is a serious condition that can lead to death.** Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - confusion
  - changes in your breathing, heart rate, and blood pressure
  - stiff muscles
  - increased sweating
- **Uncontrolled body movements (tardive dyskinesia).** VRAYLAR may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking VRAYLAR. Tardive dyskinesia may also start after you stop taking VRAYLAR.
- **Late occurring side effects**. VRAYLAR stays in your body for a long time. **Some side effects may not happen right away and can start a few weeks after you start taking VRAYLAR, or if your dose of VRAYLAR increases**. Your healthcare provider should monitor you for side effects for several weeks after you start and after any increase in your dose of VRAYLAR.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take VRAYLAR. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start, or soon after you start VRAYLAR, and then regularly during long-term treatment with VRAYLAR.

    **Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with VRAYLAR:**
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity
  - **increased fat levels (cholesterol and triglycerides) in your blood.** Your healthcare provider should check the fat levels in your blood before you start, or soon after you start VRAYLAR, and then periodically during treatment with VRAYLAR.
  - w**eight gain.** You and your healthcare provider should check your weight before you start and often during treatment with VRAYLAR.

- **Low white blood cell count**. Your healthcare provider may do blood tests during the first few months of treatment with VRAYLAR.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** VRAYLAR may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions).**
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking VRAYLAR?"
- **Difficulty swallowing** that can cause food or liquid to get into your lungs.

The most common side effects of VRAYLAR include: difficulty moving or slow movements, tremors, uncontrolled body movements, restlessness and feeling like you need to move around, sleepiness, nausea, vomiting, and indigestion.

These are not all the possible side effects of VRAYLAR.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store VRAYLAR?**

- Store VRAYLAR at room temperature, between 68°F to 77°F (20°C to 25°C).

**Keep VRAYLAR and all medicines out of the reach of children.**

**General information about the safe and effective use of VRAYLAR**.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VRAYLAR for a condition for which it was not prescribed. Do not give VRAYLAR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VRAYLAR that is written for healthcare professionals.

**What are the ingredients in VRAYLAR?**

**Active ingredient:** cariprazine hydrochloride

**Inactive ingredients:** gelatin, magnesium stearate, pregelatinized starch, shellac, and titanium dioxide.

Colorants include: black iron oxide, FD&C Blue I, FD&C Red 3, FD&C Red 40, or yellow iron oxide.

Manufactured by: Forest Laboratories Ireland Limited, Dublin, IE. Distributed by: Allergan USA, Inc. Madison, NJ 07940



For more information, go to www.VRAYLAR.com or call 1-800-678-1605.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued May 2019

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Joint Supervisory Memo

| | |
|---|---|
| **Date** | *see electronic date* |
| **From** | Bernard Fischer, MD (Cross-Discipline Team Leader)<br>Tiffany R. Farchione, MD (Acting Division Director) |
| **Subject** | Joint Supervisory Memo |
| **NDA/BLA # and Supplement#** | NDA 204370, S-006 |
| **Applicant** | Forest Research Institute/Allergan |
| **Date of Submission** | 07/24/2018 |
| **PDUFA Goal Date** | 05/24/2019 |
| **Proprietary Name (code name)** | Vraylar |
| **Established or Proper Name** | Cariprazine |
| **Dosage Form(s) and strengths** | 1.5, 3 mg |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults |
| **Applicant Proposed Dosing Regimen(s)** | Start at 1.5 mg daily, recommended dose 1.5 or 3 mg daily |
| **Recommendation on Regulatory Action** | *Approve* |
| **Recommended Indication(s)/Population(s)** | *Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults* |
| **Recommended Dosing Regimen(s)** | *Start at 1.5 mg daily, recommended dose 1.5 or 3 mg daily; maximum recommended dose 3 mg daily* |

# 1. Benefit-Risk Assessment

**Benefit-Risk Assessment Framework**

| Benefit-Risk Integrated Assessment |
|---|
| This supplement was submitted to provide safety and effectiveness data on cariprazine for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults. Bipolar disorder type I is a serious psychiatric illness that typically continues throughout a patient's lifetime. The illness often has a significant and disabling impact on the patient's functioning and puts him or her at risk of suicide. Treatment generally requires long-term use of mood stabilizing medication—however, treatment of bipolar disorder's depressive episodes remains a poorly met need. The use of most approved antidepressants (including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants) carries the risk of triggering a manic or mixed episode if the patient is not on an adequate mood stabilizer. Of the four currently approved treatments for bipolar depression, three carry significant risk for weight gain and metabolic syndrome (i.e., Seroquel (quetiapine) immediate-release and extended-release, and Symbyax (olanzapine and fluoxetine combination)).<br>The data submitted from the Applicant's trials indicate that cariprazine is effective in decreasing symptoms in the depressive episodes of bipolar I disorder. Cariprazine's trials in bipolar depression did not reveal any new safety signals compared with the already marketed doses and indications. It appears that cariprazine has less weight-gain and metabolic derangement risk than other available antipsychotics. Thus, the risk-benefit ratio for cariprazine in the treatment of bipolar depression is considered favorable. |

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Bipolar disorder is characterized by manic (bipolar I) or hypomanic (bipolar II) episodes. However, major depressive episodes contribute to the substantial mortality (through suicide) and morbidity of the illness.<br>• Approximately 3% of the U.S. population will receive a diagnosis of bipolar disorder in their lifetime. | Bipolar depression substantially compromises academic and work performance and can impair social development and relationships without treatment. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Current Treatment Options** | • Currently approved medications include Seroquel (quetiapine), Symbyax (olanzapine and fluoxetine combination product), and Latuda (lurasidone).<br>• Electroconvulsive therapy (ECT) is also used to treat bipolar depression.<br>• Lithium, most atypical antipsychotics, and several anticonvulsants are approved for the treatment of manic and mixed episodes in bipolar disorder, but not for the depressive episodes of bipolar disorder.<br>• Oral antidepressants are often used off-label for the treatment of bipolar depression. | Of the currently approved medications, Seroquel and Symbyax include a significant risk of metabolic syndrome. ECT is associated with anesthesia risks and memory impairment. Data from drugs approved for the treatment of bipolar disorder more generally is largely restricted to manic episodes. Most oral antidepressants carry a risk of switching a patient into a manic or mixed episode. |
| **Benefit** | • Based on the Applicant's pre-specified analysis, Vraylar demonstrated statistically significant and clinically meaningful improvement over placebo in bipolar depression symptoms from baseline to 6 weeks. The 1.5 mg dose was superior in two of the three submitted studies while the 3 mg dose was superior in only one of the studies. The 3 mg dose was superior to placebo in a second study, but the result did not survive correction for multiple comparisons. A 0.75 mg dose was tested in one of the three studies but did not separate from placebo.<br>• The Agency's analysis supported the conclusion of efficacy. | Although the 3 mg dose was not consistently superior to placebo, the Division determined that there was enough supportive data for this dose to approve Vraylar for bipolar depression at both the 1.5 and 3 mg doses. |
| **Risk and Risk Management** | • (b) (4) (b) (4) (b) (4) severe akathisia and blood pressure and creatinine phosphokinase (CPK) elevations. These adverse events were less problematic at doses below 6 mg.<br>• A major active Vraylar metabolite, didesmethylcariprazine | There was no signal from the studies submitted for bipolar depression of any additional safety risks. As expected, rates of akathisia were slightly worse in the 8-week versus the 6-week studies and were dose-dependent. There was no meaningful signal for ocular adverse events in the submitted studies. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | (DDCAR), has a half-life of 3 weeks and is responsible for late-occurring adverse events such as extrapyramidal symptoms (EPS), somnolence, and akathisia.<br>• Nonclinical data (previously reviewed) indicated the potential for ocular adverse events (such as cataracts) and teratogenicity. | Labeling was revised to include a nonclinical teratogenicity risk identified during earlier reviews. |

# 2. Background

Vraylar (cariprazine) is an atypical antipsychotic initially approved on September 17, 2015, for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adult patients. Doses of 1.5, 3, 4.5, and 6 mg capsules are approved for oral ingestion once daily with or without food.

The Agency had issued a Complete Response (CR) letter on November 19, 2013 for Vraylar's initial submission (for the treatment of schizophrenia and bipolar mania). Issues cited in the CR included incomplete characterization of the pharmacokinetics (PK), dose-response, and safety as major deficiencies. This CR resulted in the revision of the maximum recommended dose to 6 mg in both proposed indications (schizophrenia and bipolar mania) (b) (4) (b) (4)

For the bipolar depression indication, specific regulatory milestones included:

- 10/19/2015: Type B End of Phase 2 Meeting held with Forest Research Institute to agree on Phase 3 trial design
- 07/06/2016: Agreement letter issued for Agreed Initial Pediatric Study Plan
- 01/02/2018: Change of sponsorship from Forest to Allergan Sales
- 05/10/2018: Type B, Pre-sNDA Meeting held with Allergan to agree that three studies were acceptable to support a supplemental NDA submission for the treatment of bipolar depression. The Meeting Minutes noted that the efficacy results for the 3 mg/day dosage appear less robust than those for the 1.5 mg/day dosage.

The Office of Scientific Investigations conducted inspections of Site 41 (RGH-MD-53) and Sites 1 and 15 (RGH-MD-54) and reported no issues.

# 3. Product Quality

The product quality review was performed by primary reviewer Lin Qi and secondary reviewer Branch Chief David Lewis. They conclude that the supplement did not provide for any changes to the chemistry, manufacturing, or controls of the drug product and there were no changes proposed to CMC labeling information. They recommend approval.

# 4. Nonclinical; Pharmacology/Toxicology

The Applicant did not submit any nonclinical data in this supplement.

# 5. Clinical Pharmacology

The primary Clinical Pharmacology reviewer was Huixia Zhang; the secondary reviewer was Team Leader Luning (Ada) Zhuang. This efficacy supplement contained a labeling change based on the Applicant's findings from Study RGH-PK-19; "Evaluation of the Effect of Pantoprazole, a Proton Pump Inhibitor, on Cariprazine Exposure in Patients with Schizophrenia." This study was reviewed separately from the efficacy supplement (archived in DARRTS 02/08/2019).

The study showed, and the Agency agreed, that coadministration of pantoprazole with cariprazine did not significantly affect the Cmax or AUC of cariprazine, or its two active metabolites: desmethylcariprazine and didesmethylcariprazine. Dosage adjustment of cariprazine is not deemed necessary when it is co-administered with a proton pump inhibitor.

The Clinical Pharmacology Team recommends approval with the addition of proton pump inhibitor pharmacokinetic data in labeling.

# 6. Clinical Microbiology

There were no clinical microbiology concerns with this supplement.

# 7. Clinical/Statistical Efficacy

The primary clinical reviewer was Nancy Dickinson; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer. The primary biometrics reviewer was Andrew Potter; the secondary reviewer was Team Leader Peiling Yang.

The Applicant submitted one phase 2b and two phase 3 studies (see Table 1). The primary efficacy endpoint in all three studies was the change from baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Inclusion and exclusion criteria were appropriate. Major inclusion criteria were:

- A current major depressive episode of at least 4 weeks
- A minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HAMD-17)
- A minimum score of 2 on item 1 of the HAMD-17 (depressed mood)
- A maximum score on the Young Mania Rating Scale (YMRS; 12 for RGH-MD-53 and -54, 10 for RGH-MD-56)

**Table 1. Studies Evaluated for Efficacy.**

| Study | Description | Study Length/Primary Endpoint | Doses |
|---|---|---|---|
| RGH-MD-53 | Phase 3<br>RCT | 6 weeks<br>MADRS | Placebo (n=163)<br>Cariprazine<br>1.5 mg (n=162)<br>3 mg (n=153) |
| RGH-MD-54 | Phase 3<br>RCT | 6 weeks<br>MADRS | Placebo (n=156)<br>Cariprazine<br>1.5 mg (n=154)<br>3 mg (n=164) |
| RGH-MD-56 | Phase 2b<br>RCT | 8 weeks<br>(primary analysis at 6 weeks)<br>MADRS | Placebo (n=141)<br>Cariprazine<br>0.75 mg (n=140)<br>1.5 mg (n=145)<br>3 mg (n=145) |

MADRS= Montgomery Åsberg Depression Rating Scale; RCT=Randomized, placebo-controlled, clinical trial.

Demographics and baseline characteristics for all three studies are presented in Table 2. There were no clinically important differences in study groups. (The statistically significant age difference in Study RGH-MD-56 (p = 0.0163) is not clinically meaningful.)

**Table 2. Demographic and Baseline Characteristics for Patients in Submitted Studies.**

| | Cariprazine | | | Placebo |
|---|---|---|---|---|
| | 0.75 mg | 1.5 mg | 3 mg | |
| **RGH-MD-53** | | | | |
| **Age**, years, M (SD) | - | 42 (12) | 44 (12) | 45 (12) |
| **Sex**, n (%)<br>Male<br>Female | - | <br>60 (36%)<br>107 (64%) | <br>55 (34%)<br>103 (65%) | <br>68 (41%)<br>97 (59%) |
| **Race Category**, n (%)<br>Black/African American<br>White<br>Other | - | <br>41 (25%)<br>120 (72%)<br>6 (3%) | <br>39 (24%)<br>117 (74%)<br>2 (1%) | <br>45 (27%)<br>120 (73%)<br>0 |
| **Ethnicity Category**, n (%)<br>Hispanic<br>Non-Hispanic | - | <br>21 (13%)<br>146 (87%) | <br>15 (10%)<br>143 (90%) | <br>18 (11%)<br>147 (89%) |
| **Duration Current Episode**, Mean Months (SD) | - | 3.6 (2.5) | 3.5 (2.5) | 3.7 (2.8) |
| **Previous Depressive Episodes**, Mean (SD) | - | 6.8 (7.2) | 6.7 (9.3) | 7.2 (8.2) |

Table 2. (continued)

| | | | | |
|---|---|---|---|---|
| **RGH-MD-54** | | | | |
| **Age**, years, M (SD) | - | 43 (12) | 42 (12) | 44 (13) |
| **Sex**, n (%) | | | | |
| Male | - | 59 (38%) | 71 (43%) | 66 (42%) |
| Female | | 98 (62%) | 94 (57%) | 92 (58%) |
| **Race Category**, n (%) | | | | |
| Black/African American | - | 29 (19%) | 37 (22%) | 37 (23%) |
| White | | 123 (78%) | 126 (76%) | 115 (73%) |
| Other | | 5 (3%) | 2 (2%) | 6 (4%) |
| **Ethnicity Category**, n (%) | | | | |
| Hispanic | - | 15 (10%) | 14 (9%) | 115 (73%) |
| Non-Hispanic | | 142 (90%) | 151 (91%) | 43 (27%) |
| **Duration Current Episode,** Mean Months (SD) | - | 3.9 (2.6) | 3.6 (2.2) | 3.8 (2.5) |
| **Previous Depressive Episodes**, Mean (SD) | - | 7.0 (5.7) | 6.8 (8.9) | 7.3 (7.4) |
| **RGH-MD-56** | | | | |
| **Age**, years, M (SD) | 40 (11) | 41 (11) | 43 (11) | 44 (12) |
| **Sex**, n (%) | | | | |
| Male | 50 (36%) | 54 (37%) | 58 (40%) | 56 (39%) |
| Female | 91 (64%) | 92 (63%) | 88 (60%) | 89 (61%) |
| **Race Category**, n (%) | | | | |
| Black/African American | 26 (18%) | 30 (20%) | 26 (18%) | 30 (21%) |
| White | 111 (79%) | 109 (74%) | 113 (77%) | 110 (76%) |
| Other | 4 (3%) | 7 (6%) | 7 (5%) | 5 (3%) |
| **Ethnicity Category**, n (%) | | | | |
| Hispanic | 13 (9%) | 11 (8%) | 12 (8%) | 12 (8%) |
| Non-Hispanic | 128 (91%) | 135 (92%) | 134 (92%) | 133 (92%) |
| **Duration Current Episode,** Mean Months (SD) | 3.8 (2.6) | 3.7 (2.7) | 3.5 (2.4) | 3.3 (2.3) |
| **Previous Depressive Episodes**, Mean (SD) | 5.7 (5.2) | 7.2 (8.0) | 6.8 (7.0) | 6.2 (5.8) |

Efficacy results show that 1.5 mg was superior to placebo in all three submitted studies (Table 3 and Table 4). The 3 mg dose was superior to placebo in Study RGH-MD-54. In Study RGH-MD-53, the 3-mg dose separated from placebo, but the statistical significance did not survive corrections for multiple comparisons. The correction for multiple comparisons in these studies was meant to produce a family-wise error rate of 5% using a matched, parallel-gatekeeping procedure. In this procedure, four (Studies RGH-MD-53 and -54) to six (Study RGH-MD-56) null hypotheses were grouped into families. Hypothesis families for Studies RGH-MD-53 and -54 were:

- F1 = {$H_{11}$: 6-week CFB MARDS for 3 mg; $H_{12}$: 6-week CFB MARDS for 1.5 mg}
- F2 = {$H_{21}$: 6-week CFB CGI-S for 3 mg; $H_{22}$: 6-week CFB CGI-S for 1.5 mg}

F1 was the parallel gatekeeper for F2 (i.e., hypotheses in F2 were only tested if the corresponding hypothesis was rejected in F1). The Applicant used the Simes test to derive the local p-values for the intersection hypotheses and adjusted them using certain weights (see the Biometrics Review for more details and the table of weights used for hypotheses intersections).

Despite not reaching corrected statistical significance in Study RGH-MD-56, the magnitude of change in the 3-mg group was similar to that in the 1.5-mg group. A 0.75 mg dose was tested in the phase 2b study but did not separate from placebo; this dose was not advanced to the phase 3 studies.

**Table 3. Efficacy Results from Studies RGH-MD-53 and -54.**

| MADRS | Cariprazine | | Placebo |
|---|---|---|---|
| | 1.5 mg | 3 mg | |
| **RGH-MD-53** | | | |
| LS Mean | -14.8 | -14.1 | -12.2 |
| 95% CI | -16.3, -13.3 | -15.6, -12.6 | -13.9, -10.9 |
| LS Mean Difference (SE) | -2.4 (1.1) | -1.7 (1.1) | - |
| Raw p-value | 0.02 | 0.11 | - |
| Adjusted p-value | 0.05 | 0.11 | - |
| **RGH-MD-54** | | | |
| LS Mean | -15.1 | -15.6 | -12.6 |
| 95% CI | -16.6, -13.6 | -17.1, -14.1 | -14.1, -11.1 |
| LS Mean Difference (SE) | -2.5 (1.1) | -3.0 (1.1) | - |
| Raw p-value | 0.02 | 0.005 | - |
| Adjusted p-value | 0.04 | 0.01 | - |

**Table 4. Efficacy Results from Studies RGH-MD-56.**

| MADRS | Cariprazine | | | Placebo |
|---|---|---|---|---|
| | 0.75 mg | 1.5 mg | 3 mg | |
| LS Mean | -13.0 | -15.1 | -13.7 | -11.1 |
| 95% CI | -14.7, -11.3 | -16.7, -13.5 | -15.4, -12.0 | -12.8, -9.4 |
| LS Mean Difference (SE) | -1.9 (1.2) | -4.0 (1.2) | -2.6 (1.2) | - |
| Raw p-value | 0.13 | 0.0009 | 0.03 | - |
| Adjusted p-value | 0.13 | 0.003 | 0.1 | - |

There were no subgroup differences with respect to age, gender, and race.

The studies included sites in the United States, Bulgaria, Canada, Colombia, Croatia, Estonia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, and the Ukraine. In RGH-MD-56, both U.S. and non-U.S. patients showed similar efficacy. In RGH-MD-53, the non-U.S. patients

showed greater efficacy than U.S. patients. In RGH-MD-54, the U.S. patients showed greater efficacy than the non-U.S. patients. Therefore, there was no consistent pattern of efficacy in non-U.S. versus U.S. patients.

In conclusion, there is enough evidence to establish the effectiveness of cariprazine for the treatment of bipolar depression. The biometrics and clinical review teams recommend approval. Dr. Dickinson believed that the positive study with 3 mg, coupled with the corroborative evidence from Study RGH-MD-53, supported approval of the 3-mg dose along with the 1.5-mg dose. We agree.

# 8. Safety

The primary clinical reviewer was Nancy Dickinson; the secondary reviewer was Team Leader (and CDTL) Bernard Fischer.

There were no deaths in this development program. In the two 6-week trials, there were six serious adverse events (SAEs) in the cariprazine groups and seven in the placebo groups. In the 8-week study, there were two SAEs in the cariprazine 1.5-mg group, two in the 3-mg group, and five in the placebo group. There was no consistent pattern of SAEs in the cariprazine groups. The placebo group SAEs largely included worsening depression and suicidal ideation.

No ocular adverse events (AEs) of special interest were reported in the 6-week studies. In the 8-week study, the most common ocular AE was blurred vision, which was reported in 0.7% of patients in the placebo group and 1.4% of patients in the combined cariprazine group. Common AEs are presented in Table 5 and Table 6. Akathisia and restlessness AEs were more common in the 8-week study than the 6-week studies and showed a dose-dependent relationship. Most other AEs did not show dose-dependence.

**Table 5. Cariprazine Adverse Events ≥ 2% and Placebo in 6-Week Studies.**

| **Adverse Events** | **Placebo** (n=323) | **Cariprazine 1.5 mg/d** (n=324) | **Cariprazine 3.0 mg/d** (n=323) |
|---|---|---|---|
| Akathisia | 8 (2%) | 19 (6%) | 25 (8%) |
| Somnolence | 9 (3%) | 18 (6%) | 17 (5%) |
| Dizziness | 6 (2%) | 15 (5%) | 15 (5%) |
| Tremor | 4 (1%) | 5 (2%) | 4 (1%) |
| Extrapyramidal disorder | 3 (1%) | 0 | 5 (2%) |
| Restlessness | 11 (3%) | 7 (2%) | 28 (9%) |
| Drooling | 0 | 2 (1%) | 0 |
| Dyskinesia | 0 | 0 | 1 |
| Myoclonus | 0 | 1 | 0 |
| Musculoskeletal stiffness | 1 | 0 | 5 (2%) |

**Table 6. Cariprazine Adverse Events ≥ 2% and Placebo in 8-Week Study.**

| Adverse Events | Placebo (n=145) | Cariprazine 1.5 mg/d (n=146) | Cariprazine 3.0 mg/d (n=146) |
|---|---|---|---|
| Depression | 5 (3%) | 6 (4%) | 3 (2%) |
| Agitation | 2 (1%) | 4 (3%) | 7 (5%) |
| Insomnia[a] | 12 (8%) | 11 (8%) | 17 (12%) |
| Restlessness | 5 (3%) | 6 (4%) | 13 (9%) |
| Akathisia | 2 (1%) | 7 (5%) | 22 (15%) |
| Extrapyramidal disorder | 0 | 0 | 3 (2%) |
| Dizziness | 4 (3%) | 6 (4%) | 3 (2%) |
| Somnolence[b] | 9 (6%) | 14 (10%) | 12 (8%) |
| Nausea | 7 (5%) | 14 (10%) | 12 (8%) |
| Dry mouth | 3 (2%) | 5 (3%) | 2 (1%) |
| Constipation | 1 (1%) | 4 (3%) | 5 (3%) |
| Upper respiratory tract infection | 1 (1%) | 3 (2%) | 3 (2%) |
| Weight increased | 1 (1%) | 3 (2%) | 6 (4%) |
| Blood pressure increased | 1 (1%) | 1 (1%) | 3 (2%) |
| Increased appetite | 2 (1%) | 3 (2%) | 4 (2%) |
| Vision Blurred | 1 (1%) | 2 (1%) | 3 (2%) |

[a]Includes: Insomnia, initial insomnia, middle insomnia, terminal insomnia, and poor sleep quality.
[b]Includes: Somnolence, hypersomnnia, and sedation.

There were no clinically meaningful differences in laboratory values—including in the rates of elevated CPK—between the cariprazine treatment arms and placebo arms. Likewise, there were no meaningful cariprazine-placebo differences in vital signs or electrocardiograms. The mean weight change over the two phase 3 studies (the 6-week trials) was +0.5 kg for cariprazine 1.5 mg, +0.2 kg for cariprazine 3 mg, and -0.2 kg for placebo.

We identified no new safety signals with this supplement. We believe all risks can be mitigated by labeling. In summary, the safety profile of cariprazine for the treatment of bipolar depression is acceptable.

## 9. Advisory Committee Meeting

This section is not applicable to this application.

## 10. Pediatrics

A 6-week safety and efficacy study will enroll pediatric patients (10 to ≤ 18 years) diagnosed with bipolar I depression. Initiation of the efficacy trial is dependent upon results of an ongoing pharmacokinetic (PK) trial to evaluate an appropriate dose and titration schedule for pediatric patients (10 to ≤ 18 years) with bipolar I disorder or schizophrenia (13 to ≤ 18 years; PMR 2947-3).

## 11. Other Relevant Regulatory Issues

None.

## 12. Labeling

The Agency included proton pump inhibitor pharmacokinetic data in labeling.

Based on previously reviewed nonclinical data, the Division required language in highlights regarding a potential teratogenic risk. This was correcting an omission from previous approvals and not because the risk is different in bipolar depression.

The Agency also requested that the Applicant number their studies sequentially across indications and not re-start at 1 for each indication (this makes it easier to reference studies).

## 13. Postmarketing Requirements/Commitments

The Applicant will conduct the 6-week safety and efficacy study discussed in Section 10. *Pediatrics*.

In 2015, PMR 2947-10 was required for the study of bipolar I disorder maintenance. This trial is ongoing and will assess depressive episodes using the MADRS.

## 14. Recommended Comments to the Applicant

None.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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BERNARD A FISCHER
05/24/2019 03:05:35 PM

TIFFANY R FARCHIONE
05/24/2019 04:28:41 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

| | |
|---|---|
| **Application Type** | Supplemental Efficacy NDA |
| **Application Number(s)** | 204370/S-006 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | 7/24/18 |
| **Received Date(s)** | 7/24/18 |
| **PDUFA Goal Date** | 5/25/19 |
| **Division/Office** | ODE I/DPP |
| **Reviewer Name(s)** | Nancy Dickinson, PharmD. |
| **Review Completion Date** | 5/19/19 |
| **Established/Proper Name** | Cariprazine |
| **(Proposed) Trade Name** | Vraylar |
| **Applicant** | Allergan |
| **Dosage Form(s)** | Oral capsule |
| **Applicant Proposed Dosing Regimen(s)** | 1.5 or 3 mg once daily |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of depressive episodes associated with bipolar I disorder |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** | Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The clinical data submitted in support of supplemental NDA 204370/S-005 provides reasonable evidence of safety and effectiveness. I recommend approval of cariprazine 1.5 and 3 mg/day for the treatment of depressive episodes associated with bipolar I disorder in adults.

## 1.2 Risk-Benefit Assessment

Patients with bipolar I disorder (BP) cycle through episodes of mania and depression. The depressive episodes may last three times longer than the manic episodes. The risk of suicide in BP is twice that of unipolar depression. If untreated, BP may lead to substance abuse, violence, and suicide.

Medications for the treatment of bipolar I depression are already approved.
Three atypical antipsychotics are approved for the treatment of depressive episodes in bipolar I disorder in adults and pediatric patients: lurasidone, quetiapine, and olanzapine/fluoxetine. Atypical antipsychotics are increasingly becoming first-line treatment. Due to the risk of triggering a manic or mixed episode, antidepressants are not preferred, but may be used adjunctly if patients are acutely suicidal. Mood stabilizers treat the manic episodes but should be taken chronically. The addition of lithium, valproate, carbamazepine, or lamotrigine may be helpful for bipolar depression.

Cariprazine is already an approved drug for psychiatric conditions. The doses studied in NDA supplement 005 were lower than those approved for BP's manic and mixed states and for schizophrenia. Results of three adequately-designed safety and efficacy trials demonstrated reasonable safety and effectiveness for cariprazine 1.5 and 3 mg capsules. The 3 mg dose was only modestly effective and had more adverse events than the 1.5 mg or placebo, but I recommend approval because there was enough supporting evidence of its potential effectiveness and the dose is already approved for other indications and will be prescribed.

The safety profile of cariprazine 1.5 and 3 mg is better than the doses up to 6 mg approved for BP's manic and mixed states and schizophrenia. Based on studies up to 8-weeks in bipolar depression, the safety issues identified in the original application are diminished. Those safety issues were:

- Ocular events including cataracts based on nonclinical data
- Elevated blood pressure
- Elevated creatinine phosphokinase

- Severe akathisia (especially from the long-term safety trial)

The most common reported adverse events with cariprazine in this supplemental NDA are restlessness and akathisia, which can be distressing to patients. Compared to the already-approved atypical antipsychotics for depressive episodes, cariprazine's metabolic profile appears similar to lurasidone. Lurasidone may have a lower propensity to cause a metabolic syndrome than olanzapine/fluoxetine and quetiapine.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

### 1.4 Recommendations for Postmarketing Requirements and Commitments

A PREA-related, 6-week safety and efficacy trial will be required for the study of pediatric patients (10- to 17- years) diagnosed with bipolar I depression. The Applicant submitted an agreed-to pediatric plan dated July 6, 2016, for this 6-week trial. Initiation of the efficacy trial is dependent upon results of an ongoing pharmacokinetic (PK) trial to evaluate an appropriate dose and titration schedule for pediatric patients (10- to 17-years) with bipolar I disorder or schizophrenia (13- to 17- years). (PMR 2947-3)

In 2015, PMR 2947-10, was required for the study of maintenance treatment of bipolar I disorder. The protocol RGH-MD-25, entitled "A Double-Blind, Placebo-Controlled, Randomized Withdrawal Multicenter Clinical Trial Evaluating the Efficacy, Safety, and Tolerability of Cariprazine in a Dose-Reduction Paradigm in the Prevention of Relapse in Bipolar I Disorder Patients Whose Current or Most Recent Episode is Manic, with or without Mixed Features." This trial is ongoing and will be assessing depressive episodes in bipolar disorder using the same depression scale as the trials described in this sNDA review.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Vraylar (cariprazine) is an atypical antipsychotic, acting at the dopamine D3/D2 receptor. The drug was approved on September 17, 2015, for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adult patients. The dosage strengths of 1.5, 3, 4.5, and 6 mg capsules are approved for oral ingestion once daily with or without food.

One of the major active metabolites, didesmethylcariprazine (DDCAR), has a half-life of 3-weeks and is responsible for late-occurring adverse events (AEs), such as extrapyramidal symptoms (EPS), somnolence, and akathisia.

(b) (4)

The original NDA application was issued a Complete Response on November 19, 2013. The NDA resubmission provided clinical data for doses 1.5 to 6 mg per day, which had less AEs.

## 2.2 Table of Currently Available Treatments for Proposed Indication

**Table 1: FDA-approved drugs for depressive episodes in bipolar I disorder**

| Product (s) Name | Relevant Indication | Route and Frequency of Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|
| Latuda (lurasidone) | Bipolar I depression | Oral tablet 20 to 120mg/day Take with 350 calorie meal. | Adults Pediatrics | DDI with strong CYP3A4 inhibitors; low risk of metabolic syndrome |
| Symbyax (Olanzapine and fluoxetine) | Acute Bipolar depression with fluoxetine | capsules 3mg/25mg to 12mg/50mg | Adults Pediatrics (10 to 17) | High risk of Metabolic syndrome |
| Seroquel (quetiapine) | Acute bipolar depression | Oral tablet 300 mg | Adults Children adolescents | Moderate risk of metabolic syndrome |

(Source: Reviewer modified from Pharmacist's Letter)

## 2.3 Availability of Proposed Active Ingredient in the United States

Vraylar (cariprazine) is marketed in the United States.

## 2.4 Summary of Presubmission Regulatory Activity

The protocols for this NDA S-005 were reviewed under IND 77726. The development milestones are as follows:

- 10/19/2015- Type B End of Phase 2 Meeting held with Forest Research Institute to agree on Phase 3 trial design.
- 7/6/2016- Agreement letter issued for Agreed Initial Pediatric Study Plan.

- 1/2/2018- Change of Sponsorship from Forest to Allergan Sales.
- 5/10/2018- Type B Pre-sNDA Meeting held with Allergan; agreed that three studies (RGH-MD-53, -54, and -56) were acceptable to support a supplemental NDA submission for the treatment of bipolar depression. The meeting minutes noted that the efficacy results for the 3 mg/day dosage appeared less robust than those for the 1.5 mg/day dosage.

### 2.5 Other Relevant Background Information

None

# 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The Division of Psychiatry Products (DPP) filed Allergan's efficacy supplement on September 12, 2018. From a clinical perspective, the application was written in a straightforward manner and inclusive of the necessary information in the electronic Common Technical Document (eCTD) format. A Reviewer's Guide was provided. The submission included standard (SDTM) and analysis (ADaM) data.

### 3.2 Compliance with Good Clinical Practices

Studies RGH-MD-53, -54, and -56 were conducted in conformance with the ICH E8 Guidance on General Considerations for Clinical Trials, ICH E6 guideline for GCP, and the principles of the Declaration of Helsinki, and 21 CFR §312.120.

### 3.3 Financial Disclosures

Was a list of clinical investigators provided: Yes ☒ No ☐

Total number of investigators identified: RGH-MD-53 = 95 (49 U.S., 46 foreign); RGH-MD-54 = 80 (49 U.S., 31 foreign); RGH-MD-56 = 98 (43 U.S., 55 foreign)

Number of investigators who are Applicant employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3 (One investigator provided study design advice, but does not own stock, nor was compensated).

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _0__

Significant payments of other sorts: __2_

Proprietary interest in the product tested held by investigator: _0__

Significant equity interest held by investigator in sponsor of covered study: _0__

Is an attachment provided with details of the disclosable financial interests/ arrangements: Yes ☒ No ☐ N/A ☐

Is a description of the steps taken to minimize potential bias provided: Yes ☒ No ☐ N/A ☐

Number of investigators with certification of due diligence (FDA 3454, box 3) _RGH-MD-56 only- 8 subinvestigators___

Is an attachment provided with the reason: Yes ☒ No ☐ N/A ☐

# 4 Significant Issues from Other Review Disciplines

The Office of Scientific Investigations (OSI) and DPP chose four clinical sites for OSI to inspect for compliance. From RGH-MD-53, clinical sites #6 and #41 were inspected because they ranked high on the OSI's Site Selection Tool due to complaints and because they drove efficacy results. From RGH-MD-54, clinical site #1 had high enrollment (n=15) and #15 demonstrated good treatment effects.

The OSI report of the inspections, dated April 9, 2019, concluded that the two Phase 3 trials appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. During the sNDA cycle, clinical site #6, was determined to be out of business and the inspection was canceled.

## 4.1 Chemistry Manufacturing and Controls

No clinically relevant CMC issues were identified regarding approvability of the application.

## 4.2 Clinical Microbiology

No clinical microbiology studies were submitted.

## 4.3 Preclinical Pharmacology-Toxicology

No preclinical studies were submitted.

## 4.4 Clinical Pharmacology

No clinically relevant clinical pharmacology issues were identified regarding approvability of the application.

## 4.5 Controlled Substances

Not applicable.

## 4.6 Pediatric and Maternal Health

Not applicable.

# 5 Sources of Clinical Data

## 5.1 Table of Clinical Trials

**Table 2: Clinical Studies Supporting sNDA 204370/S-006**

| Study Number | Description | Population and Formulation | Dose (#N) | Duration |
|---|---|---|---|---|
| RGH-MD-52 | Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study | Male and female outpatients who are 18 to 65 years with bipolar I or II, current depressive episode | cariprazine 0.25-0.75 mg/day (N=75)<br><br>cariprazine 1.5-3 mg/day (N=75)<br><br>placebo (N=77) | 8-weeks |
| RGH-MD-53 | Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study | Male and female outpatients who were 18 to 65 years with bipolar I disorder without psychotic features with a current major depressive episode of at least 4 weeks and not exceeding 12 months | cariprazine 1.5 mg/day (N=167)<br><br>cariprazine 3 mg/day (N=158)<br><br>Placebo (N=165) | 6-weeks |
| RGH-MD-54 | Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study | Male and female outpatients who were 18 to 65 years with bipolar I disorder without psychotic features with a current major depressive episode of at least 4 weeks and not exceeding 12 months | cariprazine 1.5 mg/day (N=157)<br><br>cariprazine 3 mg/day (N=165)<br><br>Placebo (N=158) | 6-weeks |
| RGH-MD-56 | Phase 2b, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study | Male and female outpatients who were 18 to 65 years with bipolar I disorder without psychotic features with a current major depressive episode of at least 4 weeks and not exceeding 12 months | cariprazine 0.75 mg/day (N=141)<br><br>cariprazine 1.5 mg/day (N=146)<br><br>cariprazine 3 mg/day (N=146)<br><br>Placebo (N=145) | 8-weeks |

### 5.2 Review Strategy

Efficacy and safety of cariprazine for treatment of depressive episodes associated with BP was evaluated by reviewing three clinical trials: RGH-MD-53, -54, and -56.

Safety datasets and patient demographics were analyzed using the review tools JMP Clinical 7.0 and JMP 13.0. Initially, I analyzed the three trials by creating one safety dataset. However, the 2-week difference in duration between the 8-week study (RGH-MD-56) and the two 6-week studies (-53 and -54) had implications on the amount of accumulated active metabolite, DDCAR, which is responsible for late-occurring AEs. Thus, the safety datasets I analyzed for the Adverse Reaction section of the label were from Study -56 and from a combined dataset of Studies -53 and -54.

I combined MedDRA terms from the verbatim level in the categories of restlessness, akathisia, types of EPS, somnolence, and insomnia. For example, muscle tightness was included in EPS.

Study RGH-MD-52 was not reviewed for this supplemental efficacy application because it was an exploratory, flexible-dose, Phase 2 trial conducted in patients diagnosed with bipolar I or II disorder. The study design is unlike the fixed-dose studies and includes patients with a different diagnosis. Furthermore, minutes from the Pre-NDA meeting indicate that RGH-MD-52 would not be used to support the application.

# 6 Review of Efficacy

***Efficacy Summary***

Allergan submitted three fixed-dose, placebo-controlled, double-blind, safety and efficacy clinical trials for review in this sNDA, S-005, proposed for the treatment of bipolar depression. Study RGH-MD-56 was an 8-week Phase 2b trial. The two 6-week Phase 3 trials were RGH-MD-53 and RGH-MD-54. The three trials each contained about 50% U.S. patients.

Overall, the conclusion of efficacy is supported by the three studies. The cariprazine 1.5 mg dose consistently met statistical significance. For the cariprazine 3 mg dose, the statistical evidence was less consistent. Only one study (RGH-MD-54) showed evidence that cariprazine 3mg improved depressive symptoms compared to placebo.

### 6.1 Methods (RGH-MD-53 and RGH-MD-54)

Clinical trials RGH-MD-53 and RGH-MD-54 were both entitled, “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Fixed-Dose Clinical Trial Evaluating the Efficacy, Safety and Tolerability of Cariprazine in Patients with Bipolar I Depression.” The protocols had the same study design.

The primary study objective of these two Phase 3 studies was to evaluate the efficacy, safety, and tolerability of cariprazine 1.5 and 3 mg/day relative to placebo in subjects with bipolar I depression. Both studies were randomized, double-blind, placebo-controlled, fixed-dose, 6-week studies in adult subjects aged 18 to 65 years with bipolar I depression.

Eligible subjects were randomized 1:1:1 to cariprazine 1.5 mg/day, 3 mg/day, or placebo. All subjects randomized to cariprazine were to receive cariprazine 1.5 mg/day for 2 weeks (from Day 1 through Day 14). For subjects randomized to the cariprazine 3 mg/day group, the dose was increased to 3 mg/day on Day 15. Subjects visited the study center on Visit 1 (screening), Visit 2 (baseline), Visits 3 to 6 (6-week double-blind treatment period), and Visit 7 (safety follow-up period).

The primary efficacy endpoint was the change from Baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. The secondary efficacy endpoint was the change from Baseline to Week 6 in Clinical Global Impressions-Severity (CGI-S) Score. The CGI-S is a validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1- (normal, not at all ill) to 7-point (extremely ill) scale.

Major study eligibility criteria included subjects meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for bipolar I disorder without psychotic features confirmed by the administration of the Mini International Neuropsychiatric Interview (MINI), having a current major depressive episode of at least 4 weeks and not exceeding 12 months in duration, a minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HAMD-17), a minimum score of 2 on item 1 of the HAMD-17, and a minimum score of 4 on the CGI-S Scale (CGI-S) at screening. Patients were relatively medically-healthy and females were confirmed as not pregnant.

In addition to the above enrollment criteria, patients were excluded if they had:

1. Young Mania Rating Scale (YMRS) total score > 12
2. Four or more episodes of a mood disturbance (depression, mania, hypomania, or mixed state) within the 12 months before Visit 1
3. Any current "Axis I" psychiatric diagnosis other than bipolar disorder with the exception of specific phobias
4. DSM-5–based diagnosis of borderline or antisocial personality disorder or other "Axis II" disorder of sufficient severity to interfere with participation in this study
5. History of meeting DSM-5 criteria for substance-related disorders (excluding caffeine-related and tobacco-related disorders) within the 6 months before Visit 1
6. Risk of suicide

*Reviewer's Comment: The two Phase 3 trials were adequately designed to demonstrate efficacy.*

## 6.2 Subject Disposition

For Study RGH-MD-53, the Applicant enrolled 493 patients; 478 randomized patients were in the intent-to-treat population. The treatment arm distribution was: Placebo (n=163), cariprazine 1.5 mg (n=162), and cariprazine 3 mg (n=153).

There were 89 clinical sites: 43 in the United States, 6 in Bulgaria, 6 in Croatia, 5 in Romania, 11 in Serbia, 6 in Slovakia, and 12 in Ukraine. The patients who discontinued RGH-MD-35 prematurely are listed in Table 3.

**Table 3: RGH-MD-53: Number of Patients by Dropout Reason and Treatment Arm**

| | Dropout AE | Dropout LOE | Dropout Else | Completer | N |
|---|---|---|---|---|---|
| Placebo | 5 | 7 | 16 | 135 | 163 |
| Cariprazine 1.5 mg | 3 | 1 | 22 | 136 | 162 |
| Cariprazine 3 mg | 10 | 2 | 13 | 128 | 153 |
| N | 18 | 10 | 51 | 399 | 478 |

(Adapted from Biometrics review dated 4/26/19)

*Reviewer's Comment: Approximately 50% of the clinical sites were in the United States, thus the patient population can be generalized to U.S. patients. The foreign sites did not drive or diminish overall efficacy.*

*There were roughly equivalent dropout rates of 16% across all treatment arms. Unsurprisingly, the cariprazine 3 mg arm contained the most dropouts due to AEs and the placebo arm had the most dropouts due to lack of efficacy (LOE).*

For Study RGH-MD-54, the Applicant enrolled 488 subjects with 474 randomized: Placebo (n=156), cariprazine 1.5 mg (n=154), and cariprazine 3 mg (n=164) in the ITT population.

This study had 74 clinical sites: 43 in the United States, 16 in Bulgaria, 3 in Estonia, 4 in Lithuania, and 8 in Poland. The patients who discontinued the trial early are listed in Table 4.

**Table 4: RGH-MD-54: Number of Patients by Dropout Reason and Treatment Arm**

| | Dropout AE | Dropout LOE | Dropout Else | Completer | N |
|---|---|---|---|---|---|
| Placebo | 4 | 2 | 15 | 135 | 156 |
| Cariprazine 1.5 mg | 5 | 0 | 15 | 134 | 154 |
| Cariprazine 3 mg | 9 | 3 | 18 | 134 | 164 |
| N | 18 | 5 | 48 | 403 | 474 |

(Adapted from Biometrics review dated 4/26/19)

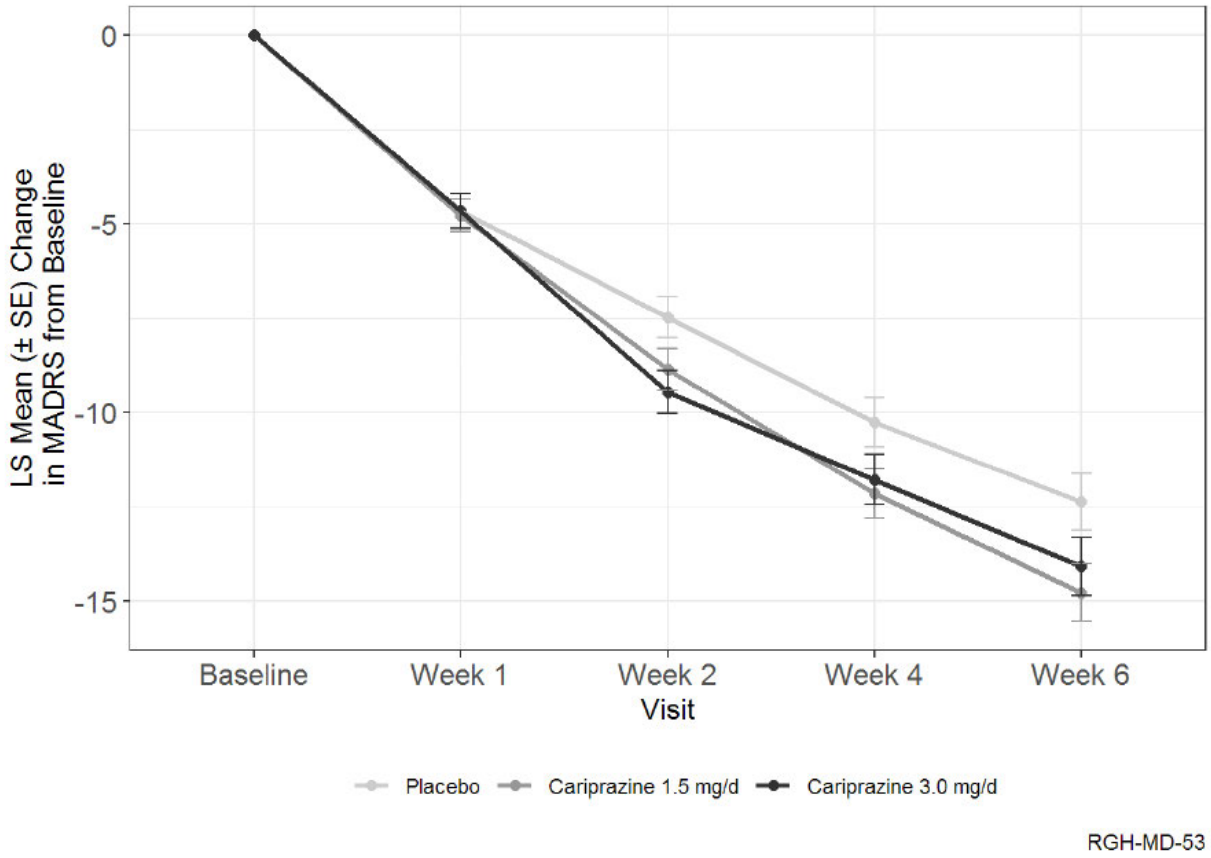
*Reviewer's Comment: Over 50% of the global clinical sites were in the United States. As in Study -53, the trial population can be generalized to U.S. bipolar I depression patients. Except for dropouts due to lack of efficacy (LOE), the reasons for discontinuation across treatment groups are consistent with the other Phase 3 trial. However, the cariprazine 3 mg group had the highest percent of dropouts at 27%. The higher dropout rate is counter-intuitive because Study -54 showed evidence that cariprazine 3mg improved depressive symptoms over placebo, as described in Section 6.3.*

## 6.3 Analysis of Primary and Secondary Endpoints (Study -53, -54)

*Reviewer Comment: In both Phase 3 trials, the cariprazine 1.5 mg dose demonstrated statistical significance over placebo. The team's Biostatisician recreated and concurs with the Applicant's results for the primary analysis in MD-53 and MD-54. (Refer to the Biometrics review for more detailed information on efficacy results.)*

*Results from RGH-MD-53 show cariprazine 1.5 mg and 3 mg were superior to placebo at the end of Week 6 on the MADRS total score. However, the 3 mg dose was not statistically significant compared to placebo. Figure 1 represents the change in MADRS from baseline to 6-weeks (the primary efficacy endpoint). For the secondary endpoint, CGI-S, only the 1.5 mg dose was tested because the 3 mg dose did not meet the primary endpoint. The CGI-S in the caripirazine 1.5 mg group was statistically significant over placebo.*

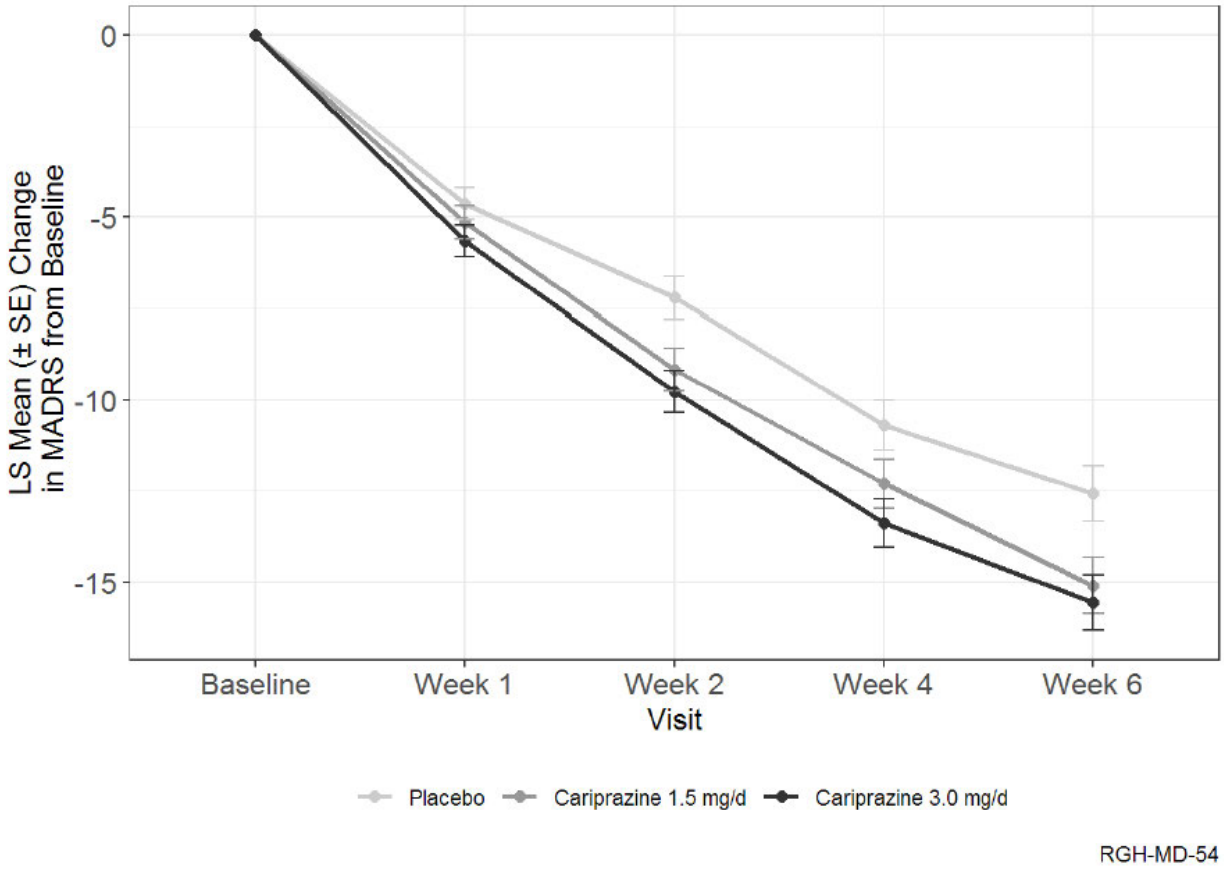
**Figure 1: Change in MADRS from Baseline to 6-weeks (Study -53)**




(Source: Biometrics review dated 4/26/19)

*The efficacy results of the second Phase 3 trial of cariprazine 1.5 mg/day and 3 mg/day compared to placebo demonstrated that the 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S. The efficacy results from RGH-MD-54 are displayed in Figure 2, where the change in MADRS scores in the cariprazine-treated patients from baseline to 6-weeks were statistically significant over the scores in the placebo group. In this trial, the 3 mg dose was superior to the placebo arm, indicating a dose-response in efficacy.*

**Figure 2: Change in MADRS from Baseline to 6-weeks (Study -54)**




(Source: Biometrics review dated 4/26/19)

*In Study -53, greater mean reductions from baseline in MADRS total score were observed in the cariprazine 1.5 and 3 mg treatment groups than in the placebo group at Week 6. The least squares mean difference versus placebo was –2.5 with cariprazine 1.5 mg, which was statistically significant (p = 0.0208), and –1.8 with cariprazine 3 mg, which was not statistically significant (p = 0.1051), as listed in Table 5.*

*In Study -54, as in the other 6-week trial, greater mean reductions from baseline in MADRS total score were observed in the cariprazine 1.5 and 3.0 mg treatment groups than in the placebo group at Week 6. The least squares mean difference versus placebo was –2.5 with cariprazine 1.5 mg (p = 0.0204) and –3.0 with cariprazine 3.0 mg (p = 0.0052), also listed in Table 5. This was the only trial where the 3 mg dose was superior to placebo.*

**Table 5: LS Mean Change from Baseline to 6-weeks in MADRS (Studies -53, -54)**

| Study Number | Treatment Group (# ITT patients) | Primary Efficacy Endpoint: MADRS Total | | |
|---|---|---|---|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
| **RGH-MD-54** | VRAYLAR (1.5 mg/day)* (n=154) | 30.7 (4.3) | -15.1 (0.8) | -2.5 (-4.6, -0.4) |
| | VRAYLAR (3 mg/day)* (n=164) | 31.0 (4.9) | -15.6 (0.8) | -3.0 (-5.1, -0.9) |
| | Placebo (n=156) | 30.2 (4.4) | -12.6 (0.8) | |
| **RGH-MD-53** | VRAYLAR (1.5 mg/day)* (n=162) | 31.5 (4.3) | -14.8 (0.8) | -2.5 (-4.6, -0.4) |
| | VRAYLAR (3 mg/day) (n=153) | 31.5 (4.8) | -14.1 (0.8) | -1.8 (-3.9, 0.4) |
| | Placebo (n=163) | 31.4 (4.5) | -12.4 (0.8) | |

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo
(Source: Adapted from draft label dated 5/18/19)

### 6.1.1 Methods (RGH-MD-56)

Clinical trial RGH-MD-56 was entitled, "A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients with Bipolar Depression." This trial included a fixed-dose treatment arm of 0.75 mg/day. This cariprazine arm is not discussed further due to lack of efficacy.

The primary study objective of this Phase 2b study was to evaluate the efficacy, safety, and tolerability of 1.5 or 3 mg cariprazine relative to placebo in subjects with bipolar I depression. The study was a randomized, double-blind, placebo-controlled, fixed-dose, 8-week study.

The primary efficacy endpoint was the change from baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. The 6-week endpoint was added as an amendment to the protocol; It was originally at Week 8. The secondary efficacy endpoint was the change from baseline to Week 8 in Clinical Global Impressions-

Severity (CGI-S) Score. The duration of the trial was up to 11 weeks. The treatment periods were:

- Screening to Baseline (2-weeks)
- 8-week double-blind treatment period (primary endpoint at 6-weeks)
- 1-week safety follow-up

Major eligibility criteria included male and female outpatients who were 18 to 65 years of age; met DSM-IV-TR criteria for bipolar I disorder with a current major depressive episode of at least 4 weeks and not exceeding 6 months in duration, and had a minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HAMD-17), a minimum score of 2 on item 1 of the HAMD-17, a minimum score of 4 on Clinical Global Impressions–Severity (CGI-S) scale, and a maximum score of 10 on the Young Mania Rating Scale (YMRS) at both Visit 1 (Screening) and Visit 2 (Baseline). Patients were relatively medically-healthy and females were confirmed as not pregnant.
In addition to the above enrollment criteria, patients were excluded if they had:

- Young Mania Rating Scale (YMRS) total score > 12
- Four or more episodes of a mood disturbance (depression, mania, hypomania, or mixed state) within the 12 months before Visit 1
- Any current “Axis 1” psychiatric diagnosis other than bipolar disorder with the exception of specific phobias
- Principal DSM-IV-TR–based diagnosis of an “Axis I” disorder other than bipolar disorder or any “Axis I” disorder other than bipolar disorder that was the primary focus of treatment within 6 months before Visit 1 (secondary diagnoses of comorbid generalized anxiety disorder, social anxiety disorder, or specific phobias are acceptable)
- History of meeting DSM-IV-TR criteria for substance-related disorders (excluding
- caffeine-related and tobacco-related disorders) within the 6 months before Visit 1
- Risk of suicide

*Reviewer’s Comment: The Phase 2b was adequately designed to demonstrate efficacy and add support to the Phase 3 trials discussed above.*

### 6.2.1 Subject Disposition

For Study RGH-MD-56, the Applicant enrolled 493 patients; 478 randomized patients were in the intent-to-treat population. The treatment arm distribution was: Placebo (n=163), cariprazine 1.5 mg (n=162), and cariprazine 3 mg (n=153).

There were 86 clinical sites:  41 in the United States, 3 in Canada, 11 in Bulgaria, 17 in Russia, 11 in Ukraine, and 3 in Colombia. The patients who discontinued RGH-MD-35 prematurely are listed in Table 6.

**Table 6: RGH-MD-56: Number of Patients by Dropout Reason and Treatment Arm**

| | Dropout AE | Dropout LOE | Dropout Else | Completer | N |
|---|---|---|---|---|---|
| Placebo | 15 | 5 | 16 | 105 | 141 |
| Cariprazine 1.5 mg/d | 11 | 2 | 15 | 117 | 145 |
| Cariprazine 3.0 mg/d | 17 | 4 | 30 | 94 | 145 |
| N | 43 | 11 | 61 | 316 | 431 |

(Source: Adapted from Biometrics review dated 4/26/19)

*Reviewer's Comment: By 6-weeks, 20% of subjects dropped out of the trial. The cariprazine 3-mg arm contained the most dropouts for any reason. The dropout rate was likely the impetus to plan the Phase 3 trials to include the primary endpoint at 6-weeks, instead of 8-weeks. As with the Phase 3 studies, about 50% of the population were U.S. patients.*

### 6.3.1 Analysis of Primary and Secondary Endpoints (Study -56)

*Reviewer's Comment: In this 8-week, placebo-controlled trial involving two fixed doses of cariprazine (1.5 and 3 mg/day), cariprazine 1.5 mg was superior to placebo at end of Week 8 on the MADRS total score and the CGI-S. In the primary efficacy endpoint, change in MADRS total score, the 1.5 mg dose arm showed evidence of efficacy with p = 0.0024, while the 3 mg dose arm (p = 0.984) showed evidence of efficacy compared to a threshold of 0.05. Like RGH-MD-53, only the 1.5 mg dose was statistically significant on the secondary endpoint, CGI-S. The least squared mean scores are in Table 7.*

**Table 7: LS Mean Score Changed in MADRS from Baseline to 8-weeks (Study -56)**

| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
|---|---|---|---|---|
| RGH-MD-56 | | | | |
| | VRAYLAR (1.5 mg/day)* (n=145) | 30.3 (4.4) | -15.1 (0.8) | -4.0 (-6.3, -1.6) |
| | VRAYLAR (3 mg/day) (n=145) | 30.6 (4.7) | -13.7 (0.9) | -2.5 (-4.9, -0.1) |
| | Placebo (n=141) | 30.4 (4.6) | -11.1 (0.9) | |

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo
(Source: Adapted from draft label dated 5/18/19)

### 6.6 Subpopulations

Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

### 6.7 Clinical Information Relevant to Dosing Recommendations

During review and resubmission of the original NDA for cariprazine, the approvable dose recommendations were to use lower doses (1.5 to 6 mg/day) (b) (4) (b) (4)

Study RGH-MD-56 (Phase 2b trial) included a cariprazine treatment arm of 0.75 mg/day. That dose lacked efficacy and was not studied in the two Phase 3 trials.

## 7 Review of Safety

### ***Safety Summary***

Cariprazine is reasonably safe in patients suffering from bipolar I depression based on data from three clinical trials.

Adverse events reported during the double-blind periods of three clinical trials demonstrate that cariprazine has dose-related AEs. In the two 6-week trials, AEs were reported at rates of 27% in the placebo arm, 34% in the cariprazine 1.5-mg arm, and 42% in cariprazine 3-mg treatment arm. Likewise, in the 8-week study, 25 AEs were

reported as “severe”; of these, 20% were in the placebo group, 8% in the cariprazine 1.5-mg group, and 56% in patients taking cariprazine 3 mg.

## 7.1 Methods

### 7.1.1 Studies Used to Evaluate Safety

The studies used to evaluate safety were RGH-MD-53, -54, and -56.

### 7.1.2 Categorization of Adverse Events

The Applicant categorized adverse events using MedDRA versions as follows:

- RGH-MD-53, version 20.1
- RGH-MD-54, version 20.0
- RGH-MD-56, version 16.1

I analyzed Adverse Events Analysis Datasets (ADAE) by body system, dictionary-derived term category (AEDECOD), and the reported terms for the AE (AETERM). I determined if the AETERMs were appropriately collected in the AEDECOD, combining similar terms together (e.g., restlessness, inner tension) for analysis.

### 7.1.3 Pooling of Data across Studies to Estimate and Compare Incidence

The two Phase 3 trials were pooled for analysis because they used the same trial design. Study RGH-MD-56 was analyzed separately because the duration was 2 weeks longer than the 6-week Phase 3 trials, thus allowing time for DDCAR to accumulate. Ultimately, in the label the three trials are represented as pooled data because, in the totality of the label with the other psychiatric indications’ data, there were less AEs from the trials in bipolar I depression than the other indications and the differences in akathisia between the trials would not be meaningful.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The entire cariprazine development program, thus far, has a total of 2568 cariprazine-treated patients with at least 6 weeks of exposure. In the bipolar I depression trials, the doses of 1.5 and 3 mg/day were adequate to avoid blood pressure elevation and increased CPK versus with higher doses of cariprazine (6 to 12 mg/day) in bipolar I mania trials. The 6-week or 8-week duration of exposure in studies RGH-MD-53, -54,

and -56 was adequate to observe late-occurring AEs related to the accumulation of DDCAR.

The demographic characteristics in the three trials were reasonably representative of U.S. patients with bipolar I disorder, except for an underrepresentation of patients with Hispanic ethnicity. Among the treatment groups, age, sex, and race were generally evenly distributed as displayed in Tables 8 and 9. The Applicant noted that there was a statistically significant difference in age (p = 0.0163) between treatment groups in study RGH-MD-56. That is not clinically meaningful in my assessment of the study.

**Table 8: Patient Demographics in Two 6-week Trials**

| | | RGH-MD-53 and RGH-MD-54 | | |
|---|---|---|---|---|
| | | Cariprazine 1.5 mg (n=324) | Cariprazine 3 mg (n=323) | Placebo (n=323) |
| Age, years | M (SD) | 42.5 (12) | 42.9 (12) | 44.2 (12) |
| | Range | 18 to 65 | 18 to 64 | 18 to 65 |
| Female Sex, % (n) | | 63.3 (205) | 61.0 (197) | 58.5 (189) |
| Race, % (n) | Asian | 0.3 (1) | 0.6 (2) | 0.9 (3) |
| | Black/African-American | 21.6 (70) | 23.5 (76) | 25.4 (82) |
| | White | 75.0 (243) | 75.2 (243) | 72.8 (235) |
| | Other | 1.9 (6) | 0.6 (2) | 0.9 (3) |
| Hispanic, % (n) | | 11.1 (36) | 9.0 (29) | 9.3 (30) |

(Reviewer created using JMP Clinical 7.0)

**Table 9: Patient Demographics in 8-week Trial**

| | | RGH-MD-56 | | |
|---|---|---|---|---|
| | | Cariprazine 1.5 mg (n=145) | Cariprazine 3 mg (n=145) | Placebo (n=141) |
| Age, years | M (SD) | 40.9 (11) | 42.8 (11) | 43.6 (12) |
| | Range | 18 to 65 | 19 to 65 | 19 to 65 |
| Female Sex, % (n) | | 63.0 (92) | 60.3 (88) | 61.4 (89) |
| Race, % (n) | Asian | 1.4 (2) | 0 | 0.7 (1) |
| | Black/African-American | 20.5 (30) | 17.8 (26) | 20.7 (30) |
| | White | 74.7 (109) | 77.4 (113) | 75.9 (110) |
| | Other | 2.7 (4) | 2.7 (4) | 1.4 (2) |
| Hispanic, % (n) | | 7.5 (11) | 8.2 (12) | 8.3 (12) |

(Reviewer created from Table 11.2.1-1, CSR RGH-MD-56)

### 7.2.2 Explorations for Dose Response

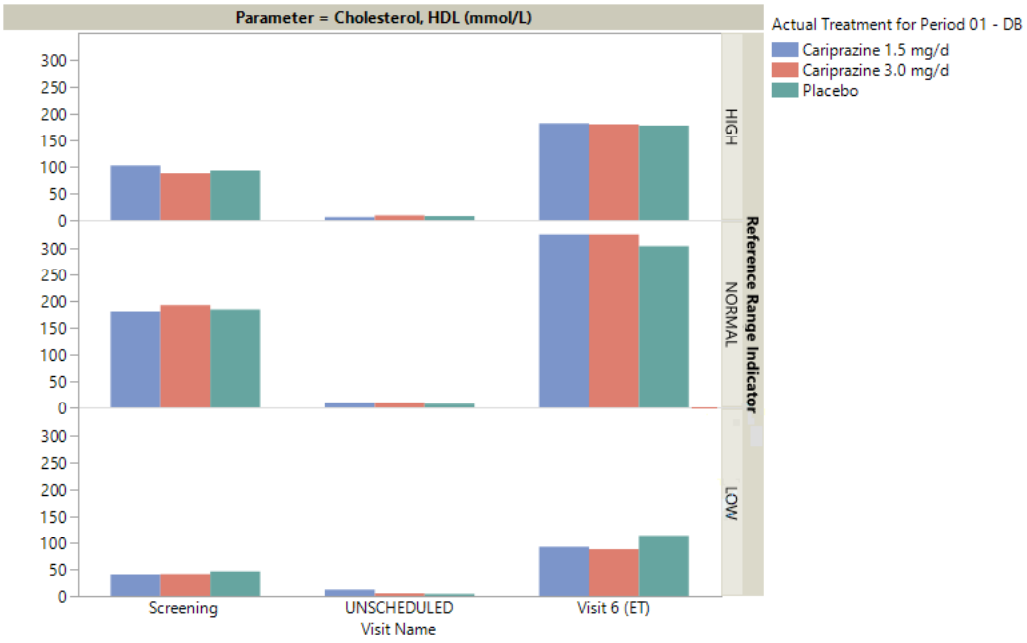
The Phase 2b study, RGH-MD-56, included a cariprazine 0.75 mg/day treatment arm. This dose lacked efficacy and is not included in this review. Based on the differential results of 1.5 versus 3 mg, there is currently no evidence for a dose-response in bipolar depression.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The atypical antipsychotics, olanzapine (with fluoxetine), lurasidone, quetiapine that are already approved for treatment of a depressive episode in bipolar I disorder, have numerous antipsychotic class warnings. Patients taking cariprazine were monitored for these adverse reactions also. My safety analysis focused on the metabolic syndrome warning because olanzapine and quetiapine both have fairly high risk of inducing metabolic changes in a short time.

I analyzed the two Phase 2 trials' safety data for changes in weight, cholesterol parameters (i.e., total, HDL, LDL, triglycerides), hemoglobin A1c, and fasting glucose. Overall, the risk for metabolic changes appears low, but is difficult to quantify in the clinical trial setting due to short duration and lack of information on patients' previous bipolar medications. Total cholesterol and HDL had a noticeable increase from screening to Week 6 of 50 mmol/L; there was no difference in treatment group, including placebo. Figure 3 illustrates the increase in HDL cholesterol after 6-weeks. The other aforementioned metabolic parameters, except weight, did not change.

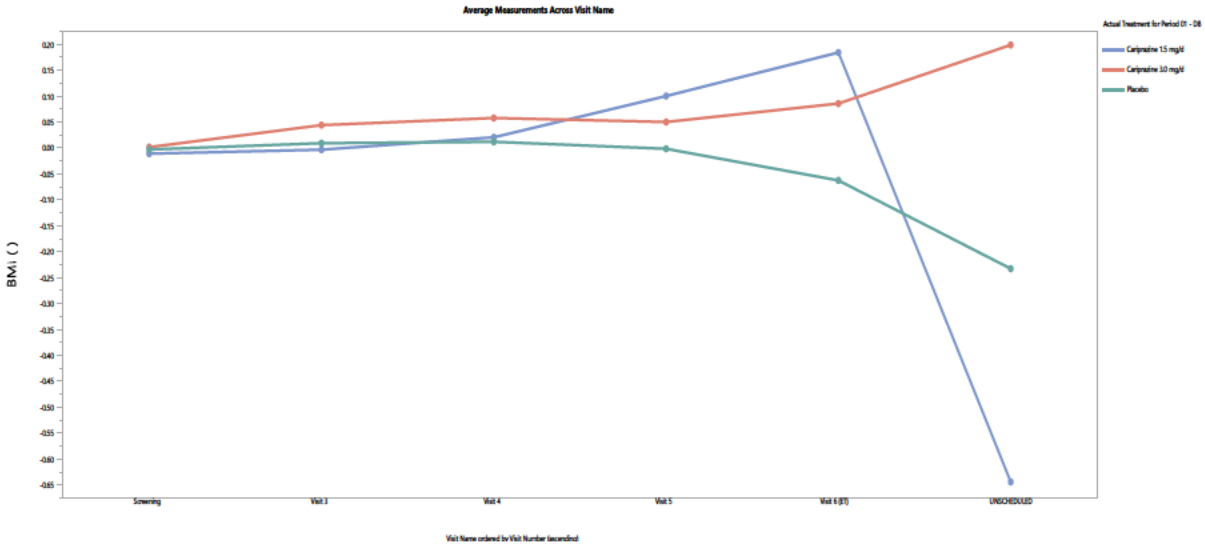
**Figure 3: HDL Cholesterol Change from Screening to Week 6 (Studies -53, -54)**




(Reviewer created using JMP Clinical 7.0)

Change in weight was assessed by body mass index (BMI). In Figure 4, from screening to Week 6, the end of the Phase 3 trials, patients' average BMI increased by 0.10 kg/m$^2$ in the cariprazine 3 mg group and by 0.2 kg/m$^2$ in the cariprazine 1.5 mg group. Patients in the placebo group had a 0.05 kg/m$^2$ average loss in BMI. The mean weight change over 6-weeks was +0.5 kg (cariprazine 1.5 mg), +0.2 kg (3 mg), and -0.2 kg (placebo) Long-term weight gain with cariprazine should be monitored.

**Figure 4: Change in BMI from screening to Week 6 (Studies -53, -54)**




(Reviewer created using JMP Clinical 7.0)

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths reported in the double-blind periods of RGH-MD-53, -54, and -56.

### 7.3.2 Nonfatal Serious Adverse Events

In the two 6-week trials, there were no differences in serious adverse events (SAEs) in the cariprazine (n=6) and placebo (n=7) groups. In the 8-week study, the number of SAEs were 2, 2, and 5 in the cariprazine 1.5-mg, 3-mg, and placebo treatment groups, respectively. No pattern was identified in the patients receiving cariprazine. Many of the placebo-related SAEs were worsening of depression, mania, and suicidal ideation.

### 7.3.3 Dropouts and Discontinuations

There were cariprazine dose-related dropouts in the Phase 3 trials, depicted in Tables 10 and 11. Nine patients in the Phase 3 trials had cariprazine 1.5 or 3 mg withdrawn and all patients recovered. The reasons for drug discontinuation were akathisia (n=4), nausea (n=2), agitation (n=1), insomnia (n=1), or dizziness (n=1). The reasons are consistent with the AE data tables in Section 7.4.1. This data differs from how the

Applicant submitted discontinuation information about AEs in the clinical study reports for Studies -53 and -54.

**Table 10: Percent of Patients Discontinuing RGH-MD-53 and -54**

| | Cariprazine 1.5 mg (n=324) | Cariprazine 3 mg (n=323) | Placebo (n=323) |
|---|---|---|---|
| AE leading to D/C | 3.7% (12) | 6.2% (20) | 2.8% (9) |

(Reviewer created)

In the 8-week trial, adverse event-related reasons for discontinuation were not statistically different between the cariprazine and placebo treatment arms.

**Table 11: Percent of Patients Discontinuing RGH-MD-56 due to AE**

| | Cariprazine 1.5 mg (n=146) | Cariprazine 3 mg (n=146) | Placebo (n=145) |
|---|---|---|---|
| AE leading to D/C | 8.2% (12) | 11.6% (17) | 10.3% (15) |

(Reviewer created from CSR of RGH-MD-56)

### 7.3.4 Significant Adverse Events

Early in the cariprazine development program, ocular events, such as cataracts, were documented in nonclinical studies. The Applicant continues to monitor for ocular adverse events at the direction of FDA. In the three bipolar I depression trials, the ocular events of special interest were:

- cataract, lens, or lenticular abnormality or change, opacity, opacification or opalescence
- blindness, night blindness, visual acuity or vision decrease, abnormality or change,
- visual acuity test abnormality or change
- retinal, macular, or optic nerve degeneration, abnormality or change; retinal pigment epithelium detachment, abnormality or change
- color vision decrease, abnormality or change

Although we do not require extensive ocular examinations for short-term (i.e., < 6-months) trials of cariprazine, I assessed the eye disorders reported in the three trials in bipolar I depression. No ocular events of special interest were reported in RGH-MD-53. In RGH-MD-54, no treatment emergent ocular event during the double-blind period was reported. In RGH-MD-56, the most common ocular AE was blurred vision, which was reported in 0.7% of patients in the placebo group, and 1.4% of patients in the cariprazine 1.5- and 3-mg treatment groups. This trial data on blurred vision may indicate that cariprazine has late-occurring anticholinergic-related AEs.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Studies RGH-MD-53 and RGH-MD-54

The AEs reported over 5% in the cariprazine treatment arms were akathisia, somnolence, dizziness, and restlessness. Table 12 lists the AEs which occurred over 2% in the cariprazine-treated patients, compared to those in the placebo-treated patients.

**Table 12: AEs >2% and Greater than Placebo in two 6-week Trials (Studies -53, -54)**

| Adverse Events | Placebo (N=323) | % | Cariprazine 1.5 mg/d (N=324) | % | Cariprazine 3.0 mg/d (N=323) | % |
|---|---|---|---|---|---|---|
| Akathisia | 8 | 2% | 19 | 6% | 25 | 8% |
| Somnolence | 9 | 3% | 18 | 6% | 17 | 5% |
| Dizziness | 6 | 2% | 15 | 5% | 15 | 5% |
| Tremor | 4 | 1% | 5 | 2% | 4 | 1% |
| Extrapyramidal disorder | 3 | 1% | 0 | 0% | 5 | 2% |
| Restlessness | 11 | 3% | 7 | 2% | 28 | 9% |
| Drooling | 0 | 0% | 2 | 1% | 0 | 0% |
| Dyskinesia | 0 | 0% | 0 | 0% | 1 | 0% |
| Myoclonus | 0 | 0% | 1 | 0% | 0 | 0% |
| Musculoskeletal stiffness | 1 | 0% | 0 | 0% | 5 | 2% |

(Reviewer created from safety datasets from RGH-MD-53 and -54 using JMP)

Study RGH-MD-56

The AEs reported over 5% in the treatment groups were agitation (potentially related to akathisia), insomnia, somnolence, nausea, restlessness, and akathisia. Tables 13 and 14 list the AEs reported by the cariprazine-treated patients compared to the placebo-treated ones. Patients in the 8-week trial reported more akathisia than in the 6-week trials—likely because the metabolite, DDCAR, had 2 more weeks to accumulate, hence leading to late-occurring AEs.

**Table 13: AEs >2% and Greater than Placebo in 8-week Trial (Study RGH-MD-56)**

| Adverse events (Count, percent) | placebo (N=145) | | Cariprazine 1.5mg (N=146) | | Cariprazine 3mg (N=146) | |
|---|---|---|---|---|---|---|
| Depression | 5 | 3% | 6 | 4% | 3 | 2% |
| Agitation | 2 | 1% | 4 | 3% | 7 | 5% |
| Insomnia[a] | 12 | 8% | 11 | 8% | 17 | 12% |
| restlessness | 5 | 3% | 6 | 4% | 13 | 9% |
| Akathisia | 2 | 1% | 7 | 5% | 22 | 15% |
| Extrapyramidal disorder | 0 | 0% | 0 | 0% | 3 | 2% |
| Dizziness | 4 | 3% | 6 | 4% | 3 | 2% |
| Somnolence[b] | 9 | 6% | 14 | 10% | 12 | 8% |
| Nausea | 7 | 5% | 14 | 10% | 12 | 8% |
| Dry mouth | 3 | 2% | 5 | 3% | 2 | 1% |
| Constipation | 1 | 0.7% | 4 | 2.7% | 5 | 3.4% |
| Upper respiratory tract infection | 1 | 0.7% | 3 | 2.1% | 3 | 2.1% |
| Weight increased | 1 | 0.7% | 3 | 2.1% | 6 | 4.1% |
| Blood pressure increased | 1 | 0.7% | 1 | 0.7% | 3 | 2.1% |
| Increased appetite | 2 | 1.4% | 3 | 2.1% | 4 | 2.7% |
| Vision blurred | 1 | 0.7% | 2 | 1.4% | 3 | 2.1% |

[a]insomnia terms: initial insomnia, insomnia, middle insomnia, terminal insomnia, poor sleep quality, sleep disorder

[b]somnolence terms: somnolence, hypersomnnia, sedation

(Reviewer created from safety dataset RGH-MD-56 using JMP)

**Table 14: EPS events in 8-week trial (Study -56)**

| EPS events (Count, percent) | placebo (N=145) | | Cariprazine 1.5mg (N=146) | | Cariprazine 3mg (N=146) | |
|---|---|---|---|---|---|---|
| Dyskinesia | 0 | 0% | 0 | 0% | 1 | 1% |
| Tremor | 2 | 1% | 2 | 1% | 1 | 1% |
| Extrapyramidal disorder | 0 | 0% | 0 | 0% | 3 | 2% |
| Akathisia | 2 | 1% | 7 | 5% | 22 | 15% |

(Reviewer created from safety dataset RGH-MD-56 using JMP)

### 7.4.2 Laboratory Findings

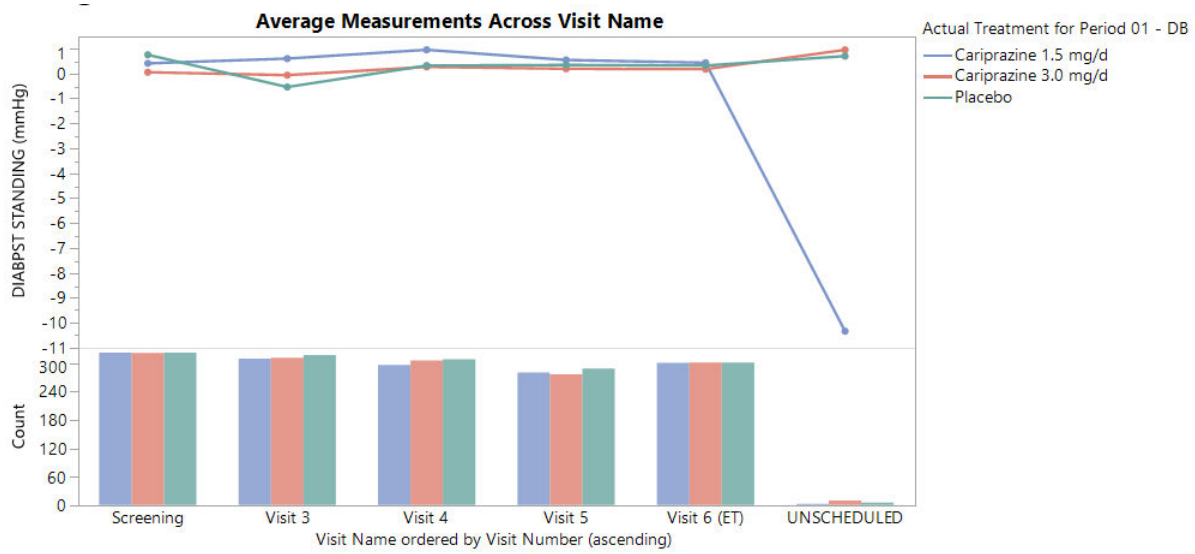
Refer to Section 7.2.6.

Due to elevated CPK levels during the development programs for earlier indications and with cariprazine doses >6 mg/day the Applicant was monitoring during the bipolar I depression trials. There was no difference in the rate of elevated CPK between the cariprazine treatment arms and placebo arms.

### 7.4.3 Vital Signs

I analyzed supine and standing diastolic and systolic blood pressure over time using JMP Clinical. There were no clinically meaningful changes in any parameter of blood pressure in any treatment group (i.e., cariprazine 1.5 mg (n=324), 3 mg (n=323), or placebo (n=323)) during the Phase 3 clinical trials. In Figure 5, I have included the analysis for standing diastolic blood pressure change from Screening to Visit 6, Week 6 as a representative for my analysis. The figures for the additional parameters (e.g., supine systolic blood pressure) were similar.

**Figure 5: Mean Change in Diastolic BP (mmHg) Standing (Studies -53, -54)**




(Reviewer created using JMP for safety datasets RGH-MD-53, -54)

### 7.4.4 Electrocardiograms (EKGs)

Although changes in ECG parameters occurred in the three trials, the changes were similar among treatment groups and no associated AEs were reported.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose and Time Dependency for Adverse Events

Cariprazine has both dose- and time-dependent AEs. Patients in the 8-week trial (Study -56) reported more AEs (e.g., akathisia) than in the 6-week trials (-53 and -54), especially patients taking the higher dose of 3 mg, compared to 1.5 mg/day. The major active metabolite, DDCAR, takes 1- to 3-weeks to accumulate at steady-state and is associated with late-occurring AEs after cariprazine initiation or a dose increase. Because of this, the Applicant is required to conduct protocol RGH-MD-25, entitled "A Double-Blind, Placebo-Controlled, Randomized Withdrawal Multicenter Clinical Trial Evaluating the Efficacy, Safety, and Tolerability of Cariprazine in a Dose-Reduction Paradigm in the Prevention of Relapse in Bipolar I Disorder Patients Whose Current or Most Recent Episode is Manic, with or without Mixed Features." This PMR was required in 2015, at the time of original approval.

## 8 Postmarketing Experience

The Office of Surveillance and Epidemiology/ Division of Pharmacovigilance (OSE/DPV) provided a postmarketing safety report dated April 2, 2019, for cariprazine. The post-market review did not identify new safety signals to add to the label. The postmarketing safety summary reviewed specific events of interest, such as ocular events. DPV reviewed all cases coded with preferred terms included in the Standardised MedDRA Queries Lens Disorders (narrow) (n=23). The FAERS cases mostly reported mild cases of cataract, with insufficient information to assess causality with cariprazine. There is insufficient evidence for additional labeling recommendations. They will continue to monitor.

## 9 Appendices

### 9.1 Literature Review/References

The Applicant submitted 36 articles of published biomedical literature about the endpoint measures and about treatment of bipolar disorder. These were reviewed as necessary to make the determination on approvability for cariprazine in the treatment a depressive episode of bipolar I disorder.

### 9.2 Labeling Recommendations

The Applicant's proposed label followed other atypical antipsychotics that have the bipolar depression indication. The Applicant presented data in the Adverse Reaction

section (6.1) from the Integrated Summary of Safety which contained four studies of different design. I recommended separating the 8-week trial safety data from the two 6-week trials (Studies -53 and -54). Data from Study RGH-MD-52 was not included in the label.

## 9.3 Advisory Committee Meeting

No questions for an Advisory Committee arose during the review of this sNDA application.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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NANCY C DICKINSON
05/23/2019 01:33:10 PM

BERNARD A FISCHER
05/23/2019 07:44:08 PM
Lead Medical Officer

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA #:** | NDA 204-370 |
| **Supplement #:** | 6 |
| **Drug Name:** | VRAYLAR (Cariprazine): 1.5 mg, 3 mg |
| **Indication(s):** | Treatment of depressive episodes in bipolar I depression |
| **Applicant:** | Allergan Sales, Inc |
| **Date(s):** | Submission date: 7/24/2018, PDUFA date: 5/24/2019 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Division of Biometrics I |
| **Statistical Reviewer:** | Andrew N. Potter, PhD |
| **Concurring Reviewers:** | Peiling Yang, PhD |
| | H.M. James Hung, PhD |
| **Medical Division:** | Division of Psychiatry Products |
| **Clinical Team:** | Nancy Dickinson, PharmD |
| **Project Manager:** | Danbi Lee, PharmD |

**Keywords:** mixed models**,** sensitivity analyses, data imputation (except LOCF), multiple comparisons

## Table of Contents

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# 1 EXECUTIVE SUMMARY

Allergan Sales, Inc., submitted three studies (RGH-MD-53, -54, and -56) in support of an efficacy supplement for NDA 204370 to add an indication of VRAYLAR (cariprazine) for the treatment of bipolar depression. These studies investigated changes in depressive symptoms, measured by MADRS total score, at six weeks for three doses (0.75 mg, 1.5 mg, and 3 mg per day) of cariprazine. In all three studies, 1.5 mg cariprazine dose showed efficacy to improve depressive symptoms in bipolar depression. For the 3 mg cariprazine dose, the statistical evidence was less consistent. Only one study (MD-54) showed evidence that 3 mg cariprazine improved depressive symptoms. In Study MD-56, there appeared to be some evidence for 3 mg cariprazine's efficacy; however, it was not demonstrated after adjusting for multiple comparisons. The lowest dose (0.75 mg) cariprazine did not show any effect of improving depressive symptoms in MD-56 and was not studied further. In summary, the statistical evidence supports approval of 1.5 mg cariprazine. Regarding the 3 mg cariprazine, the collective evidence to support approval is weaker, and we defer to Division of Psychiatry Products.

# 2 INTRODUCTION

## 2.1 Overview

This original NDA contains three phase 2/3, multi-center, double-blind, placebo-controlled, fixed dose, parallel-group studies designed to evaluate the efficacy and safety of cariprazine in adults 18+ with bipolar depression (BPD). Cariprazine was studied in doses 0.75 mg, 1.5 mg, and 3 mg daily.

Cariprazine is currently approved for the treatment of schizophrenia (1.5 mg to 6 mg per day) and bipolar mania (3 mg to 6 mg per day).

The original protocols were reviewed under IND 77,726.

**Table 1: List of all studies included in analysis**

| | Phase and Design* | Treatment Period | # of Subjects per Arm | Study Population |
|---|---|---|---|---|
| *RGH-MD-53* | *Phase 3 - MC, R, DB, PG, PC trial* | *6 weeks* | *Cariprazine 1.5 mg / Cariprazine 3 mg / Placebo /* | *Adults ages 18-65 with BPD* |
| *RGH-MD-54* | *Phase 3 - MC, R, DB, PG, PC trial* | *6 weeks* | *Cariprazine 1.5 mg / Cariprazine 3 mg / Placebo /* | *Adults ages 18-65 with BPD* |
| *RGH-MD-56* | *Phase 2 - MC, RW, DB, PG, PC trial* | *8 weeks with primary analysis at 6 weeks* | *Cariprazine 0.75 mg / Cariprazine 1.5 mg / Cariprazine 3 mg / Placebo /* | *Adults ages 18-65 with BPD* |

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled

## 2.2 Data Sources

The following data sources were considered in this review:
Study RGH-MD-53: adsl, adeff
Study RGH-MD-54: adsl, adeff
Study RGH-MD-56: adsl, adeff

All studies are referred to by MD-5X.

The electronic location of the submission is: \\cdsesub1\evsprod\NDA204370\0134.

# 3 STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

The Applicant submitted all necessary analysis datasets and SAS programs. This reviewer found the datasets acceptable.

## 3.2 Evaluation of Efficacy

### 3.2.1 Statistical Review Issues

- Is the statistical evidence for the 3 mg cariprazine dose sufficient and robust enough for approval?

### 3.2.2 Acute Efficacy Studies

Studies MD-53 and MD-54 are identical, six-week, randomized, double-blind, phase 3 studies comparing 1.5 mg and 3 mg cariprazine to placebo. Study MD-56 is an eight week, randomized, double-blind, phase 2 study comparing 0.75 mg, 1.5 mg, and 3 mg cariprazine to placebo with the primary analysis planned at 6 weeks. For all studies:

- Primary efficacy endpoint is change from baseline (CFB) to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Study MD-56 includes a secondary endpoint of change from baseline to week 8 in MADRS total score. MADRS total score is measured at baseline and weeks 1, 2, 4, 6, and 8 (MD-56 only).

- Secondary efficacy endpoint for potential inclusion in labeling is change from baseline to week 6 in Clinician Global Impressions-Severity Scale (CGI-S). Study MD-56 includes a supportive secondary endpoint of change from baseline to week 8 in CGI-S; however, it was no intended for inclusion in labeling. CGI-S is measured at baseline and weeks 2, 4, 6, and 8 (MD-56 only).

- In MD-53 and MD-54, the Applicant planned to enroll 160 patients per arm to provide approximately 82% power to show a statistically significant effect in each cariprazine dose controlling alpha at a family-wise error rate of 5% using a matched parallel gatekeeping produce. The cariprazine treatment effect was assumed to be 0.36 (treatment difference relative to standard deviation) with 22% of patients dropping out by week 6. The within patient correlation between visits and endpoints is assumed to be 0.6. Patients are randomized at 1:1:1.

- Both CFB MADRS total score and CFB CGI-S are analyzed using a mixed model for repeated measures (MMRM) with fixed effects of treatment group, pooled study center, visit, baseline value, treatment by visit interaction terms, and baseline value by visit interaction terms with an unstructured covariance matrix. Treatment effects and standards errors are estimated with least square means (LS mean).

- The Applicant adjusts p-values for multiple comparisons using a matched parallel gatekeeping procedure. For MD-53 and MD-54, four null hypotheses are grouped in families: $F_1$ = {$H_{11}$: 6-week CFB MARDS for 3 mg, $H_{12}$: 6-week CFB MARDS for 1.5 mg} and $F_2$ = {$H_{21}$: 6-week CFB CGI-S for 3 mg, $H_{22}$: 6-week CFB CGI-S for 1.5 mg}. $F_1$ is a parallel gatekeeper for $F_2$. The Applicant uses the Simes test to derive the local p-values for the intersection hypotheses and adjusts them using the weights in Table 2. All

adjusted p-values are compared to 0.05 threshold. Hypotheses in $F_2$ are only tested if the corresponding hypothesis is rejected in $F_1$.

***Reviewer's Note:*** *For the Simes test to control type 1 error, all pairwise correlation coefficients between hypotheses must be positive. This Reviewer estimated the pairwise correlation coefficients for the $F_1$ and $F_2$ hypotheses in each study. These coefficients are positive. Therefore, it is unlikely that the condition for the Simes test to control type I error is violated. However, the correlation between the primary and secondary families were not estimated.*

- In MD-56, the Applicant controls multiplicity across 6 null hypotheses consisting of both CFB MADRS and CFB CGI-S at weeks 6 for three doses (0.75 mg, 1.5 mg, and 3 mg) using a matched parallel gatekeeping procedure.

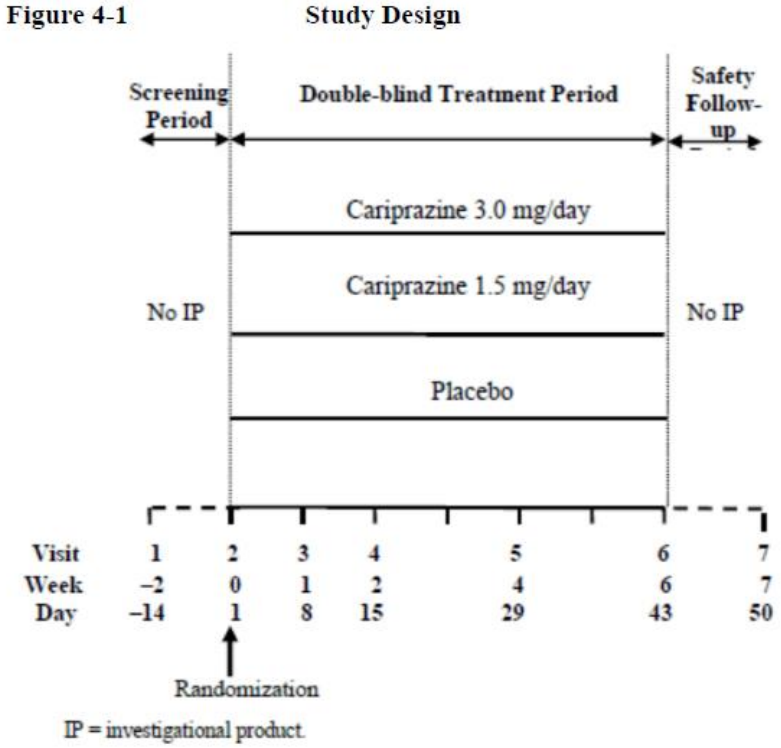
- To explore potential effects of violations of the MAR assumption, the Applicant planned a non-future dependent pattern mixture model (NFD PMM) sensitivity analysis. Departures from MAR are modeled as shifts in the mean for all the dropouts. Positive shift values indicate less decline in the dropout's distribution mean compared to completers. After imputation, datasets are analyzed with ANCOVA and combined using Rubin's Rules.

**Table 2: Weights for Intersection Tests in the Matched Parallel Gatekeeping Procedure**

| *Intersection hypothesis* | *Weights* | | | |
|---|---|---|---|---|
| | $H_{11}$ | $H_{12}$ | $H_{21}$ | $H_{22}$ |
| $H_{11} \cap H_{12} \cap H_{21} \cap H_{22}$ | 0.5 | 0.5 | 0 | 0 |
| $H_{11} \cap H_{12} \cap H_{21}$ | 0.5 | 0.5 | 0 | 0 |
| $H_{11} \cap H_{12} \cap H_{22}$ | 0.5 | 0.5 | 0 | 0 |
| $H_{11} \cap H_{12}$ | 0.5 | 0.5 | 0 | 0 |
| $H_{11} \cap H_{21} \cap H_{22}$ | 0.5 | 0 | 0 | 0.5 |
| $H_{11} \cap H_{21}$ | 1 | 0 | 0 | 0 |
| $H_{11} \cap H_{22}$ | 0.5 | 0 | 0 | 0.5 |
| $H_{11}$ | 1 | 0 | 0 | 0 |
| $H_{12} \cap H_{21} \cap H_{22}$ | 0 | 0.5 | 0.5 | 0 |
| $H_{12} \cap H_{21}$ | 0 | 0.5 | 0.5 | 0 |
| $H_{12} \cap H_{22}$ | 0 | 1 | 0 | 0 |
| $H_{12}$ | 0 | 1 | 0 | 0 |
| $H_{21} \cap H_{22}$ | 0 | 0 | 0.5 | 0.5 |
| $H_{21}$ | 0 | 0 | 1 | 0 |
| $H_{22}$ | 0 | 0 | 0 | 1 |

Source: Applicant's SAP for RGH-MD-53.

**Figure 1: Study Schematic for RGH-MD-53 and RGH-MD-54**




Source: Applicant's Statistical Analysis Plan for RGH-MD-53.

### 3.2.3 Studies RGH-MD-53 and RGH-MD-54

#### 3.2.3.1 Protocol Amendments

No amendments affected the statistical plans.

#### 3.2.3.2 Patient Disposition, Demographic and Baseline Characteristics

In MD-53, 478 randomized subjects in the intent-to-treat (ITT) population were randomized with 163 subjects in placebo, 162 subjects in 1.5 mg cariprazine, and 153 subjects in 3 mg cariprazine. In MD-54, 474 randomized subjects in the intent-to-treat (ITT) population were randomized with 156 subjects in placebo, 154 subjects in 1.5 mg cariprazine, and 164 subjects in 3 mg cariprazine. In MD-53, sixteen percent of subjects dropped out of the double-blind (DB) phase with roughly equivalent dropout rates across doses. In MD-54, fourteen percent of subjects dropped out of the double-blind (DB) phase with the 3 mg dose having the highest dropout rate = 27%. Additional details of patient disposition are presented in Table 3.

**Table 3: Patient Disposition (MD-53)**

*RGH-MD-53: Number of Patients per Study Visit*

| | Baseline | Week 1 | Week 2 | Week 4 | Week 6 |
|---|---|---|---|---|---|
| Placebo | 163 | 161 | 157 | 147 | 138 |
| Cariprazine 1.5 mg/d | 162 | 162 | 151 | 144 | 137 |
| Cariprazine 3.0 mg/d | 153 | 151 | 146 | 140 | 128 |
| N | 478 | 474 | 454 | 431 | 403 |

*RGH-MD-53: Number of Patients by Dropout Reason*

| | Number of Patients | Percent of Patients |
|---|---|---|
| Dropout AE | 18 | 3.77 |
| Dropout LOE | 10 | 2.09 |
| Dropout Else | 51 | 10.67 |
| Completer | 399 | 83.47 |
| N | 478 | 100.00 |

*RGH-MD-53: Number of Patients by Dropout Reason and Treatment Arm*

| | Dropout AE | Dropout LOE | Dropout Else | Completer | N |
|---|---|---|---|---|---|
| Placebo | 5 | 7 | 16 | 135 | 163 |
| Cariprazine 1.5 mg/d | 3 | 1 | 22 | 136 | 162 |
| Cariprazine 3.0 mg/d | 10 | 2 | 13 | 128 | 153 |
| N | 18 | 10 | 51 | 399 | 478 |

**Table 4: Patient Disposition (MD-54)**

*RGH-MD-54: Number of Patients per Study Visit*

| | Baseline | Week 1 | Week 2 | Week 4 | Week 6 |
|---|---|---|---|---|---|
| Placebo | 156 | 155 | 153 | 146 | 137 |
| Cariprazine 1.5 mg/d | 154 | 152 | 147 | 141 | 135 |
| Cariprazine 3.0 mg/d | 164 | 164 | 159 | 151 | 136 |
| N | 474 | 471 | 459 | 438 | 408 |

*RGH-MD-54: Number of Patient by Dropout Reason.*

| | Number of Patients | Percent of Patients |
|---|---|---|
| Dropout AE | 18 | 3.80 |
| Dropout LOE | 5 | 1.05 |
| Dropout Else | 48 | 10.13 |
| Completer | 403 | 85.02 |
| N | 474 | 100.00 |

*RGH-MD-54: Number of Patients by Dropout Reason and Treatment Arm*

| | Dropout AE | Dropout LOE | Dropout Else | Completer | N |
|---|---|---|---|---|---|
| Placebo | 4 | 2 | 15 | 135 | 156 |
| Cariprazine 1.5 mg/d | 5 | 0 | 15 | 134 | 154 |
| Cariprazine 3.0 mg/d | 9 | 3 | 18 | 134 | 164 |
| N | 18 | 5 | 48 | 403 | 474 |

At baseline, no treatment arm showed any imbalance in MADRS total score, see Table 6 and Table 6. These studies had similar baseline disease severity measured on the MADRS total score.

**Table 5: MADRS Total Score at Baseline (MD-53: ITT)**

| | | | Cariprazine | |
|---|---|---|---|---|
| Scale | Statistics | Placebo (N=163) | 1.5 mg (N=162) | 3 mg (N=153) |
| MADRS | Mean | 31.39 | 31.54 | 31.51 |
| | SD | 4.45 | 4.27 | 4.87 |
| | Median | 32 | 31 | 31 |
| | Min, Max | 17, 44 | 21, 42 | 21, 43 |
| CGI-S | Mean | 4.53 | 4.53 | 4.51 |
| | SD | 0.53 | 0.61 | 0.56 |
| | Median | 5 | 4 | 4 |
| | Min, Max | 4, 6 | 4, 6 | 4, 6 |

Source: Reviewer.

**Table 6: MADRS Total Score at Baseline (MD-54: ITT)**

| | | | Cariprazine | |
|---|---|---|---|---|
| Scale | Statistics | Placebo (N=156) | 1.5 mg (N=154) | 3 mg (N=162) |
| MADRS | Mean | 30.24 | 30.66 | 31.11 |
| | SD | 4.53 | 4.24 | 4.82 |
| | Median | 30 | 30 | 31 |
| | Min, Max | 19, 43 | 20, 43 | 21, 44 |
| CGI-S | Mean | 4.51 | 4.51 | 4.46 |
| | SD | 0.51 | 0.53 | 0.52 |
| | Median | 5 | 5 | 4 |
| | Min, Max | 4, 6 | 4, 6 | 4, 6 |

### 3.2.3.3 Results and Conclusions

**Applicant's Results**

**MD-53:** In the primary efficacy endpoint family (change from baseline to week 6 (CFB6) in MADRS total score), 1.5 mg dose arm showed evidence of efficacy with p = 0.0464, and 3 mg dose arm did not have evidence of efficacy with p = 0.1088. In the secondary endpoint family (CFB6 in CGI-S), only the 1.5 mg dose was tested because the 3 mg dose did not reject the primary test for CFB6 MADRS. The 1.5 mg dose had a greater placebo subtracted treatment difference (ΔΔMADRS) of -2.43 points compared to the 3 mg dose's ΔΔMADRS = -1.73. Detailed results are found in Table 7. Adjusted p-values were compared to threshold of 0.05. Throughout this Section, negative change indicates improvement.

**MD-54:** In the primary efficacy endpoint family (change from baseline to week 6 (CFB6) in MADRS total score), both the 1.5 mg dose arm (p = 0.0376) and 3 mg dose arm (p = 0.0102) showed evidence of efficacy. In the secondary endpoint family (CFB6 in CGI-S), neither dose

had sufficient statistical evidence compared to 0.05. The 1.5 mg dose had a ΔΔMADRS = -2.53 points compared to the 3 mg dose's ΔΔMADRS = -3.01. Detailed results are found in Table 8.

Studies MD-53 and MD-54 provide consistent evidence that 1.5 mg cariprazine is efficacious for treating BPD. However, these studies provide contradictory evidence about the efficacy of 3 mg cariprazine. See the results of MD-56 for additional information on the 3 mg dose.

**Table 7: MADRS Total Score at Four Weeks (MD-53: ITT)**

| Endpoint | Dose | Placebo | | Cariprazine | | LS Mean Difference (SE) | Raw p-value | Adjusted p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | LS Mean (95% CI) | N | LS Mean (95% CI) | | | |
| MADRS | 1.5 mg | 163 | -12.15 (-13.88, -10.88) | 162 | -14.78 (-16.28, -13.29) | -2.43 (1.07) | 0.0232 | 0.0464 |
| | 3 mg | | | 153 | -14.09 (-15.62, -12.56) | -1.73 (1.08) | 0.1088 | 0.1088 |
| CGI-S | 1.5 mg | 163 | -1.20 (-1.37, -1.02 | 162 | -1.50 (-16.8, -1.33 | -0.30 (0.13) | 0.0170 | 0.0340 |
| | 3 mg | | | 153 | -1.39 (-1.58, -1.21) | -0.19 (0.13) | 0.1304 | 0.2608 |

Source: Reviewer.

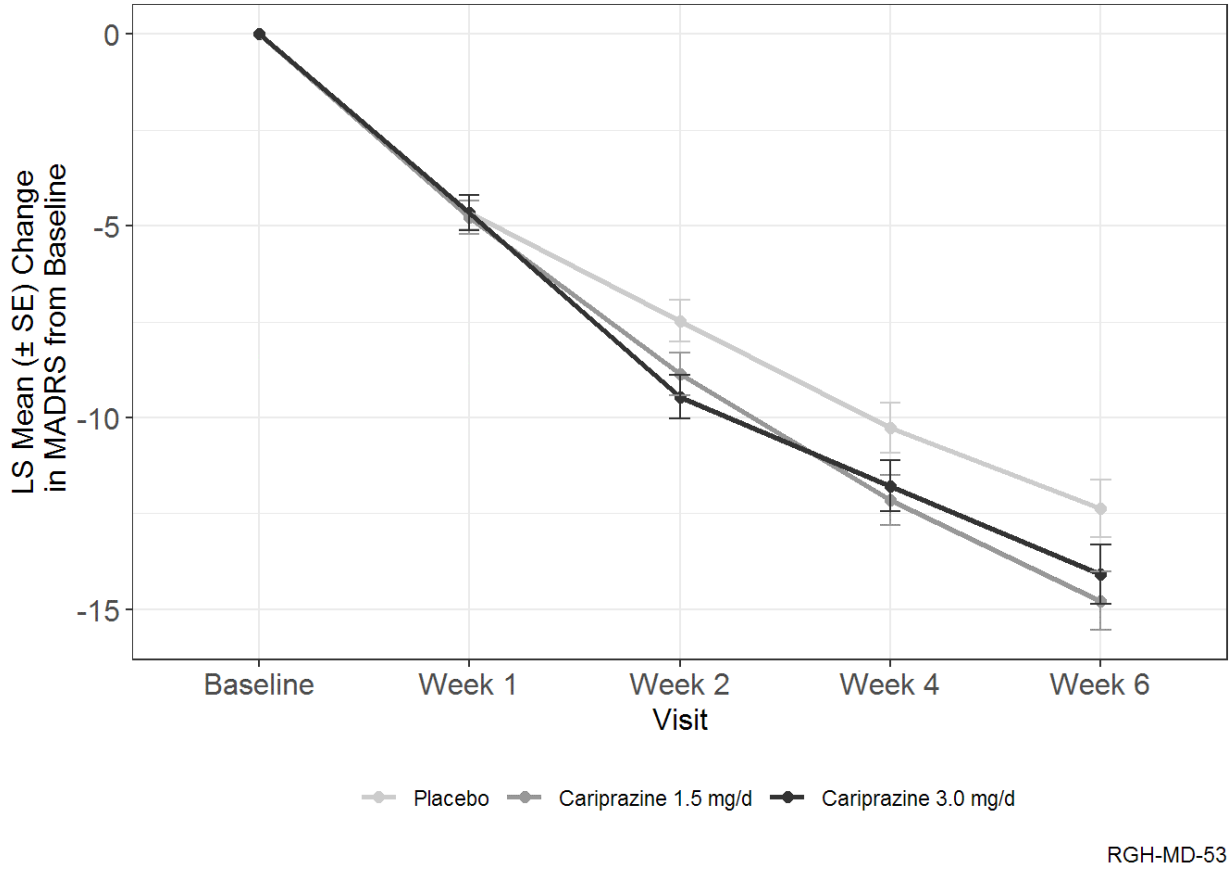
**Table 8: MADRS Total Score at Four Weeks (MD-54: ITT)**

| Endpoint | Dose | Placebo | | Cariprazine | | LS Mean Difference (SE) | Raw p-value | Adjusted p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | LS Mean (95% CI) | N | LS Mean (95% CI) | | | |
| MADRS | 1.5 mg | 156 | -12.56 (-14.05, -11.06) | 154 | -15.10 (-16.61, -13.59) | -2.53 (1.08) | 0.0188 | 0.0376 |
| | 3 mg | | | 162 | -15.57 (-17.05, -14.08) | -3.01 (1.07) | 0.0051 | 0.0102 |
| CGI-S | 1.5 mg | 156 | -1.35 (-1.53, -1.16) | 154 | -1.59 (-1.77, -1.40) | -0.24 (0.13) | 0.0711 | 0.0711 |
| | 3 mg | | | 162 | -1.62 (-1.81, -1.44) | -0.28 (0.13) | 0.0367 | 0.0734 |

Source: Reviewer.

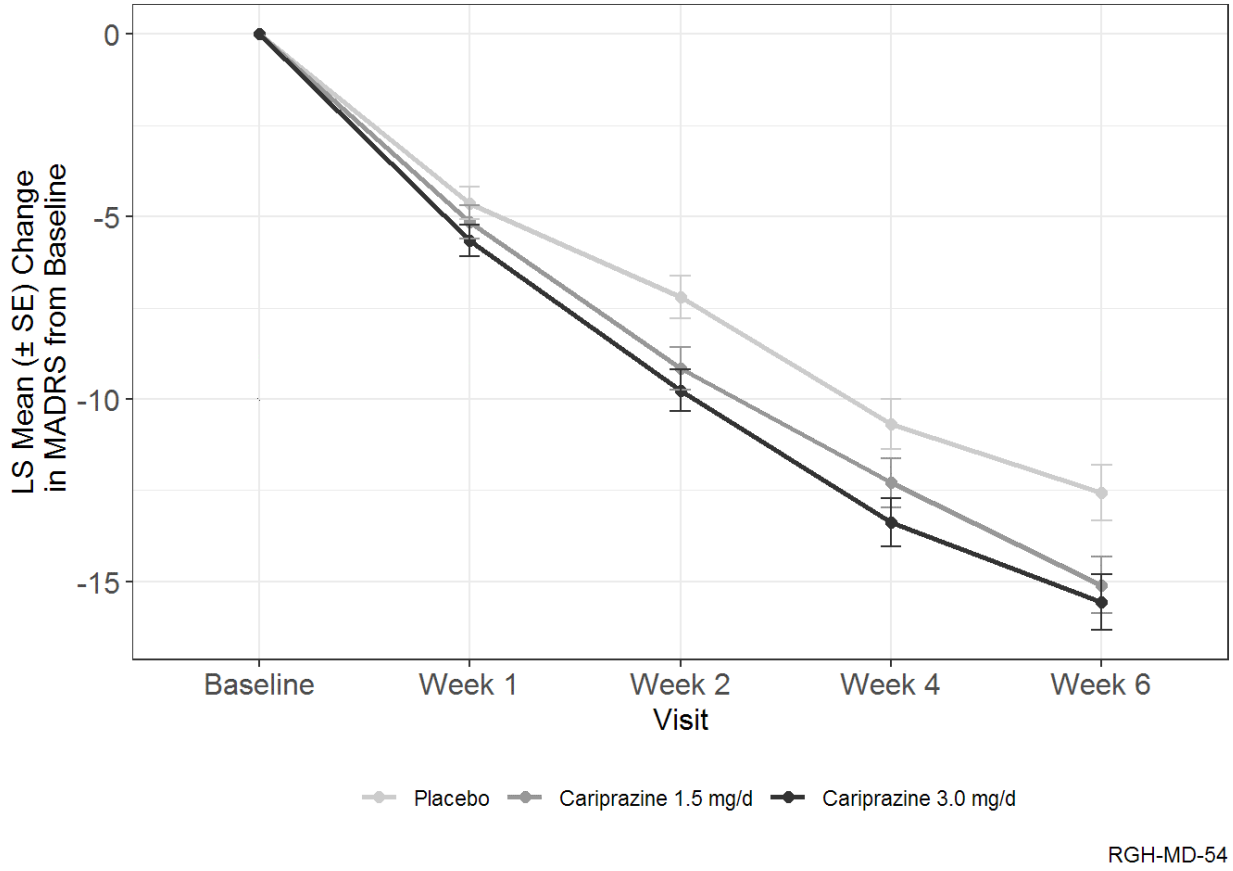
Over the six-week study period, the mean MADRS total score declined in all dose arms in both MD-53 and MD-54, see Figure 2 and Figure 3. Both cariprazine doses separate from placebo by week 2 and continue to decline through week 6. In MD-53, 1.5 mg dose arm appears to have a greater decrease in MADRS total score at week 6. However, 3 mg dose arm appears to have a greater decline at week 6 compared to 1.5 mg dose arm. The differences in 1.5 mg dose and 3 mg dose appear small at each week.

**Figure 2: MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (MD-53: ITT)**




Source: Reviewer

**Figure 3: MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (MD-54: ITT)**




Source: Reviewer

The Applicant's NFD PMM explored departures MAR under a mean shift model for the departures from MAR. Shifts values from 0 to 6 were investigated, see Appendix figures. In MD-53 and MD-54, the conclusions about cariprazine's efficacy appeared to be insensitive to departures from MAR despite changes in estimated treatment effect.

**Reviewer's Results**

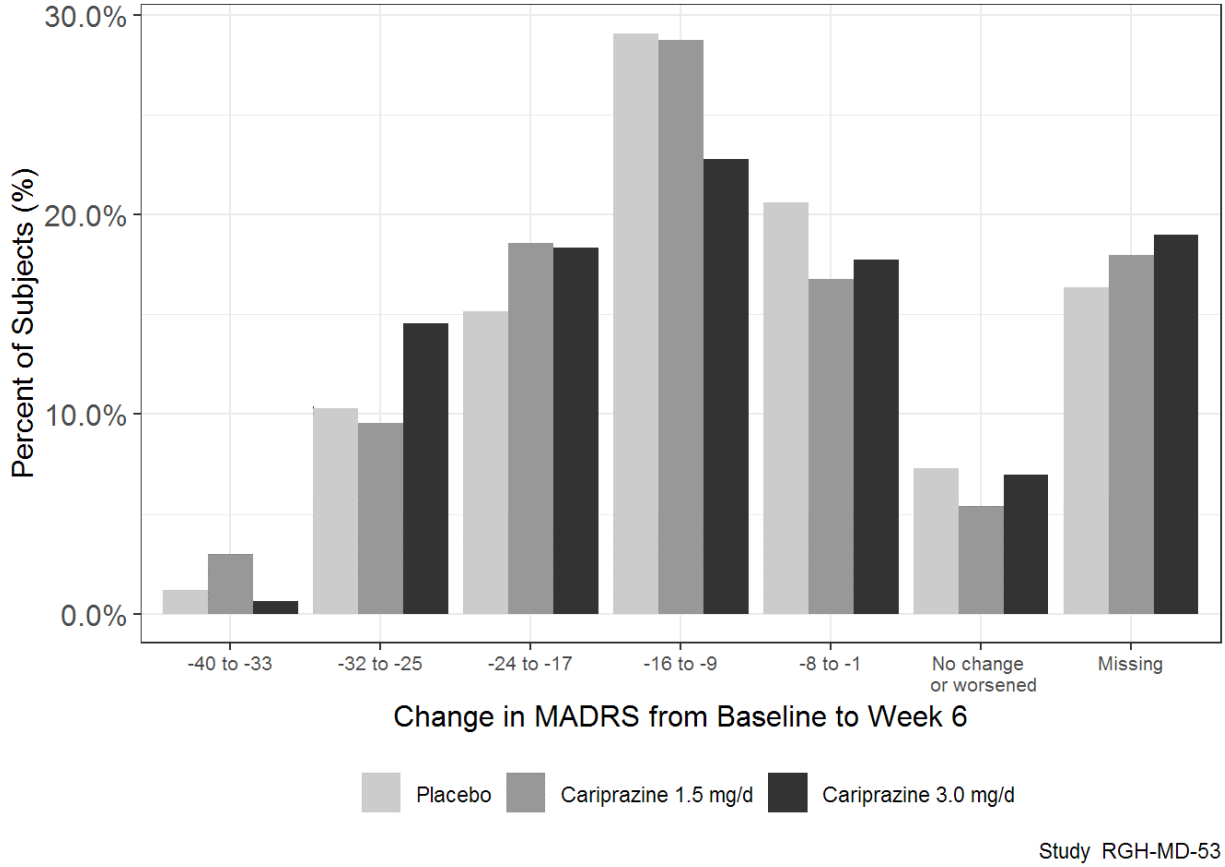
This Reviewer recreated and concurs with the results for the primary analysis in MD-53 and MD-54.

**Missing Data and Response Distributions**

In MD-53, 84% of patients completed the double-blind phase. In MD-54, 86% of patients completed the double-blind phase. Using Figure 4 and Figure 5, this Reviewer analyzed the usefulness of cariprazine in treating BPD. The histogram includes categories for patients who showed no improvement or worsening BPD. In addition, patients who dropped out before the sixth week are included in the "Missing" category. In the range of improvement (-40 to -17-point change from baseline in MADRS total score), both doses cariprazine show a greater

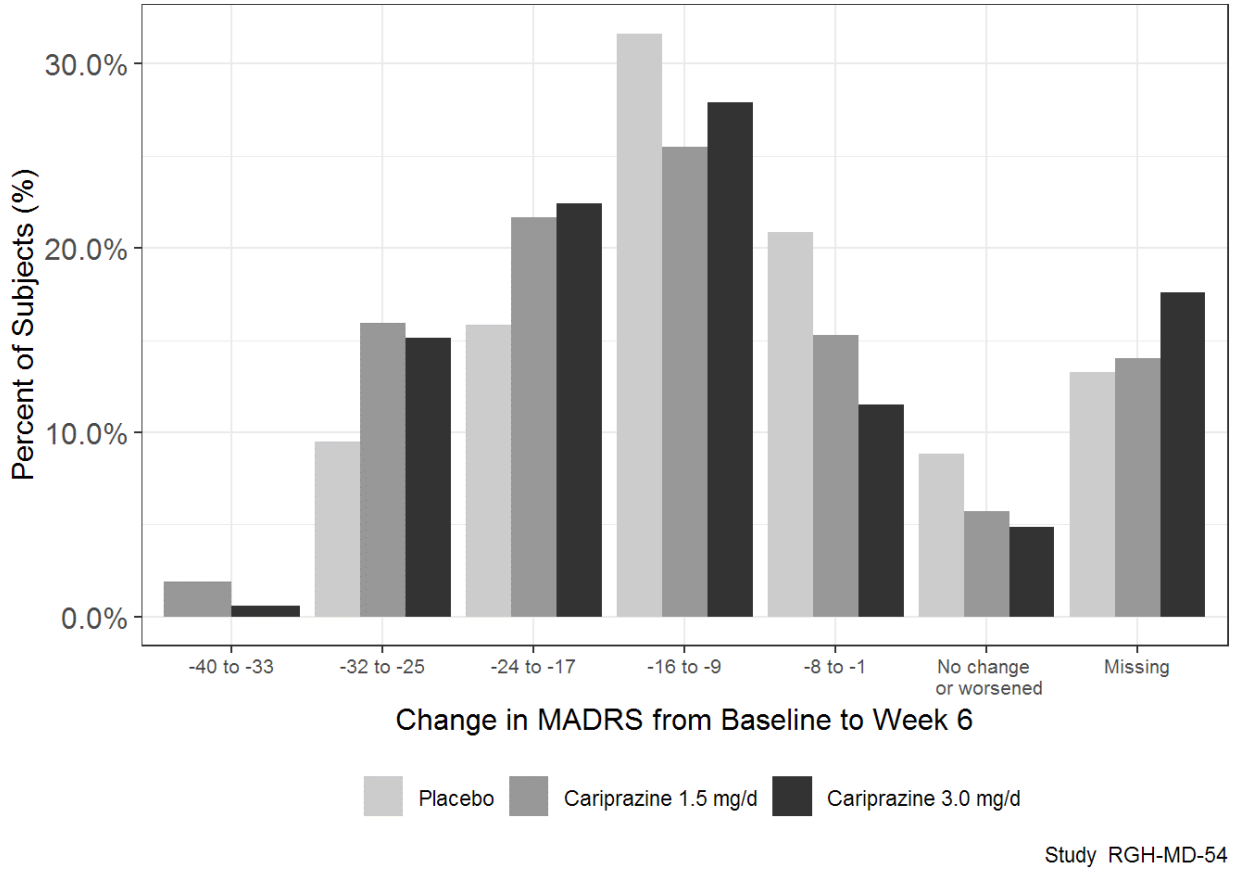
percentage of patients than placebo. Dropout rates are similar across all doses. Therefore, cariprazine may be slightly more useful than placebo in treating BPD.

**Figure 4: Percentage of Subjects with Specified Change in MADRS Total Score (MD-53: ITT)**




Source: Reviewer

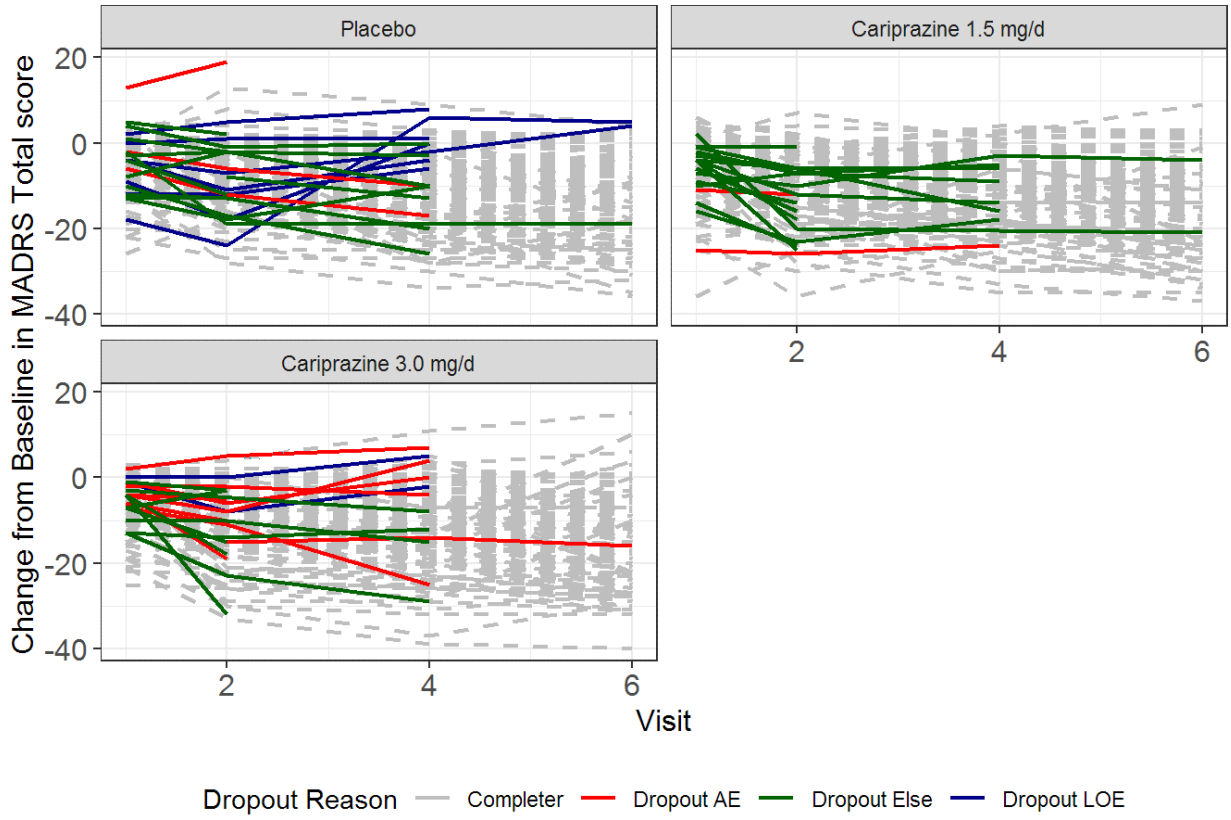
**Figure 5: Percentage of Subjects with Specified Change in MADRS Total Score (MD-54: ITT)**




Source: Reviewer

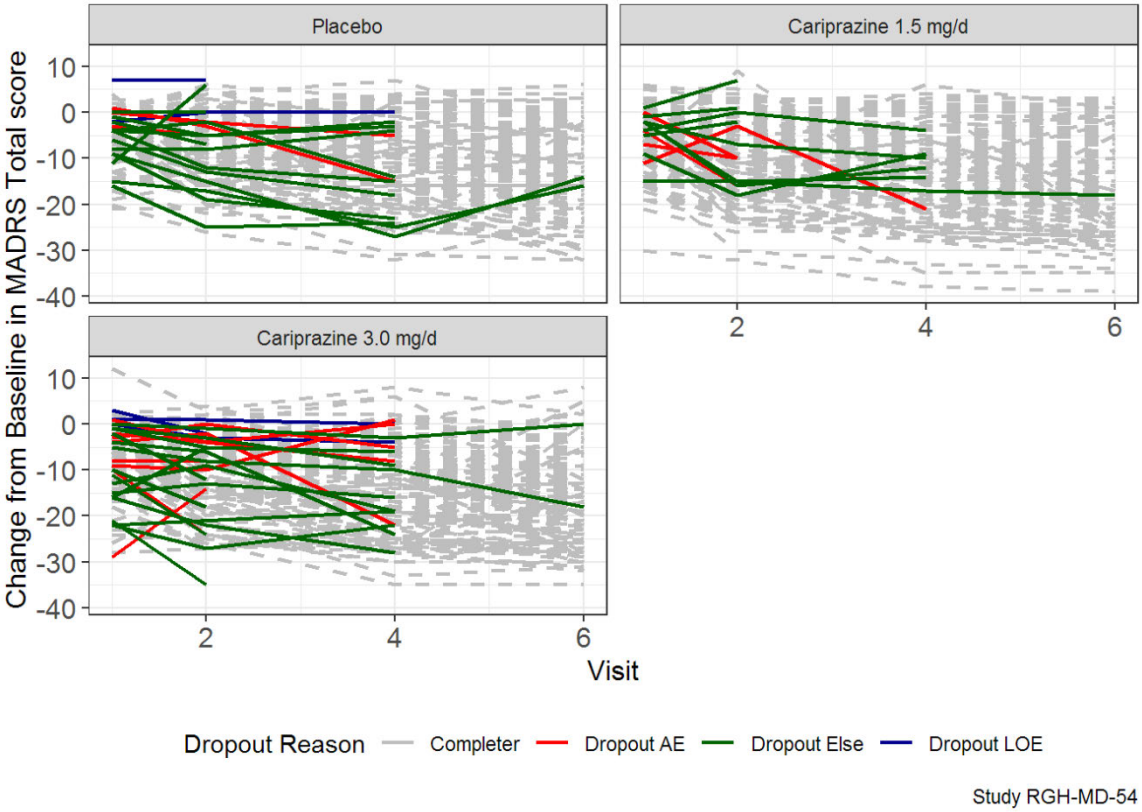
Patients MADRS trajectories are plotted by study visit in Figure 6 and Figure 7. Dropouts due to an adverse event are red, lack of efficacy dropouts are blue, other reason dropouts are green, and completers are dashed grey. In both studies, some patients experiencing adverse events have MADRS trajectories show an increase in MADRS before dropout. This pattern seems to suggest that an MAR missing data mechanism is insufficient.

**Figure 6: Patient Level MADRS Change Score Trajectories (MD-53: ITT).**




Source: Reviewer

**Figure 7: Patient Level MADRS Change Score Trajectories (MD-54: ITT).**




Source: Reviewer

### 3.2.4 Study RGH-MD-56

#### 3.2.4.1 Protocol Amendments

To address FDA's concerns about the week 8 CFB endpoints, the applicant removed the week 8 CFB MADRS and CGI-S hypothesis tests from the multiple comparison procedure in protocol amendment 3.

#### 3.2.4.2 Patient Disposition, Demographic and Baseline Characteristics

In MD-56, 571 randomized subjects in the intent-to-treat (ITT) population were randomized with 141 subjects in placebo, 140 subjects in 0.75 mg cariprazine, 145 subjects in 1.5 mg cariprazine, and 145 subjects in 3 mg cariprazine. By six weeks, twenty percent of subjects dropped out of the double-blind (DB) phase with the lowest dropout rate (15%) in the 1.5 mg dose arm. Additional details of patient disposition are presented in Table 9. Baseline MADRS total and CGI-S is similar across all doses, Table 10.

**Table 9: Patient Disposition (MD-56)**

*RGH-MD-56: Number of Patients per Study Visit*

| | Baseline | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 |
|---|---|---|---|---|---|---|
| Placebo | 141 | 138 | 132 | 119 | 113 | 106 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cariprazine 0.75 mg/d | 140 | 137 | 135 | 126 | 113 | 103 |
| Cariprazine 1.5 mg/d | 145 | 144 | 142 | 134 | 123 | 118 |
| Cariprazine 3.0 mg/d | 145 | 143 | 139 | 126 | 113 | 96 |
| N | 571 | 562 | 548 | 505 | 462 | 423 |

*RGH-MD-56: Number of Patient by Dropout Reason.*

| | Number of Patients | Percent of Patients |
|---|---|---|
| Dropout AE | 55 | 9.63 |
| Dropout LOE | 16 | 2.80 |
| Dropout Else | 81 | 14.19 |
| Completer | 419 | 73.38 |
| N | 571 | 100.00 |

*RGH-MD-56: Number of Patients by Dropout Reason and Treatment Arm*

| | Dropout AE | Dropout LOE | Dropout Else | Completer | N |
|---|---|---|---|---|---|
| Placebo | 15 | 5 | 16 | 105 | 141 |
| Cariprazine 0.75 mg/d | 12 | 5 | 20 | 103 | 140 |
| Cariprazine 1.5 mg/d | 11 | 2 | 15 | 117 | 145 |
| Cariprazine 3.0 mg/d | 17 | 4 | 30 | 94 | 145 |
| N | 55 | 16 | 81 | 419 | 571 |

**Table 10: MADRS Total Score at Baseline (MD-56: ITT)**

| | | | Cariprazine | | |
|---|---|---|---|---|---|
| **Scale** | **Statistics** | **Placebo (N=141)** | **0.75 mg (N=140)** | **1.5 mg (N=145)** | **3 mg (N=145)** |
| MADRS | Mean | 30.37 | 31.08 | 30.36 | 30.66 |
| | SD | 4.56 | 4.66 | 4.37 | 4.68 |
| | Median | 30 | 32 | 30 | 31 |
| | Min, Max | 17, 42 | 18, 41 | 19, 41 | 18, 42 |
| CGI-S | Mean | 4.37 | 4.44 | 4.43 | 4.41 |
| | SD | 0.51 | 0.54 | 0.52 | 0.55 |
| | Median | 4 | 4 | 4 | 4 |
| | Min, Max | 4, 6 | 4, 6 | 4, 6 | 4, 6 |

Source: Reviewer.

### 3.2.4.3 Results and Conclusions

**Applicant's Results at Six Weeks**

In the primary efficacy endpoint family (change from baseline to week 6 (CFB6) in MADRS total score), 1.5 mg dose arm showed evidence of efficacy with p = 0.0024, while neither 0.75 mg dose arm (p = 0.1292) nor 3 mg dose arm (p = 0.984) showed evidence of efficacy compared to a threshold of 0.05. In the secondary endpoint family (CFB6 in CGI-S), only the 1.5 mg dose was tested. The 1.5 mg dose had a ΔΔMADRS = -4.01 points compared to both the 3 mg dose's ΔΔMADRS = -2.60 and the 0.75 mg dose's ΔΔMADRS = -1.86. Detailed results are found in Table 11.

**Table 11: MADRS Total Score at Six Weeks (MD-56: ITT)**

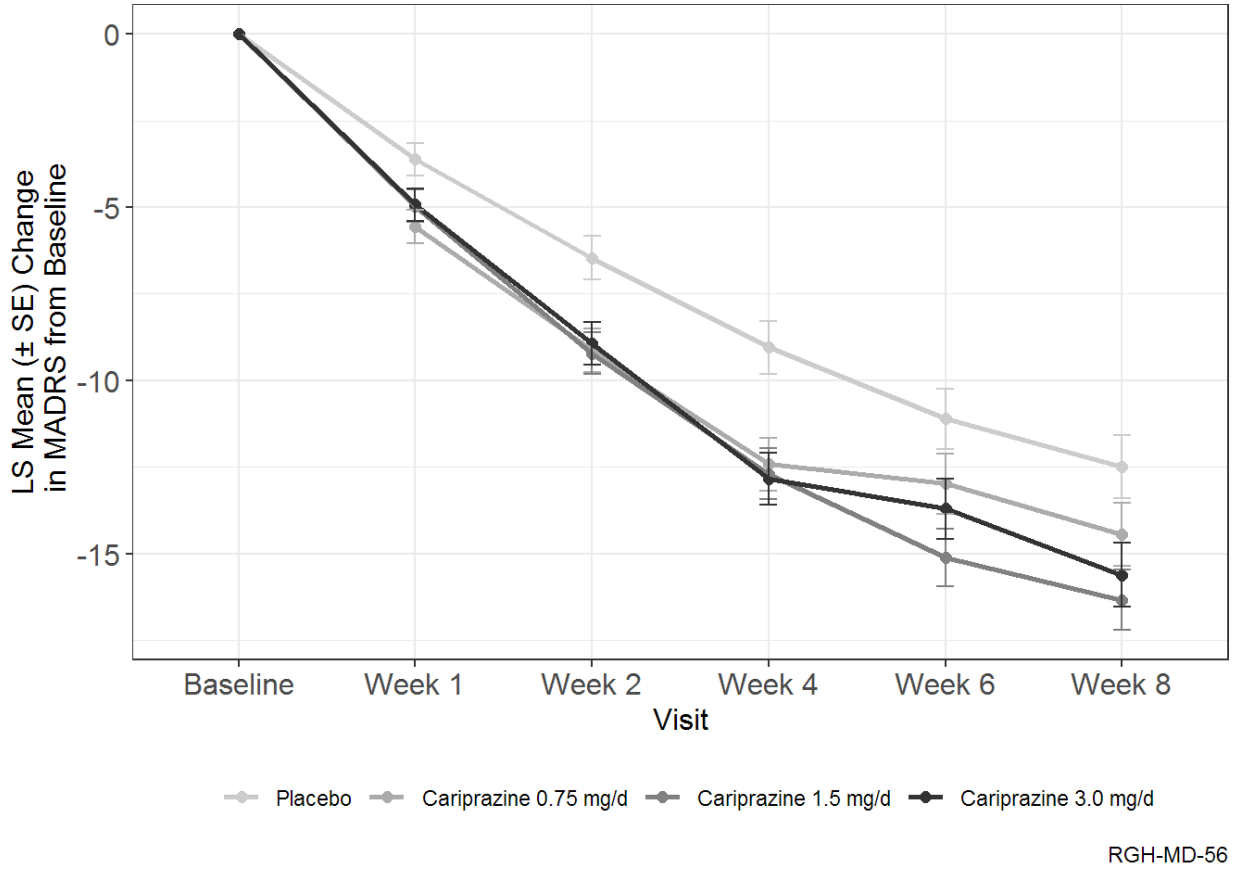
| Endpoint | Dose | Placebo | | Cariprazine | | LS Mean Difference (SE) | Raw p-value | Adjusted p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | LS Mean (95% CI) | N | LS Mean (95% CI) | | | |
| MADRS | 0.75 mg | 141 | -11.11 (-12.81, -9.41) | 140 | -12.98 (-14.68, -11.28) | -1.86 (1.22) | 0.1279 | 0.1292 |
| | 1.5 mg | | | 145 | -15.12 (-16.76, -13.48) | -4.01 (1.20) | 0.0009 | 0.0027 |
| | 3 mg | | | 145 | -13.71 (-15.40, -12.03) | -2.60 (1.22) | 0.0328 | 0.0984 |
| CGI-S | 0.75 mg | 141 | -0.98 (-1.17, -0.79) | 140 | -1.12 (-1.31, -0.93) | -0.14 (0.13) | 0.3125 | 0.3125 |
| | 1.5 mg | | | 145 | -1.36 (-1.54, -1.18) | -0.38 (0.13) | 0.0043 | 0.0102 |
| | 3 mg | | | 145 | -1.25 (-1.44, -1.06) | -0.27 (0.13) | 0.0445 | 0.1021 |

Source: Reviewer.

Over the eight-week study period, the mean MADRS total score declined in all dose arms in both MD-56, see Figure 8. All cariprazine doses separate from placebo by week 1 and generally decline through week 8. At weeks 6 and 8, the 1.5 mg dose arm suggests greater decline in MADRS total score compared to both 0.75 mg dose and 3 mg. This pattern is consistent with the MADRS trajectories in MD-53. However, more patients dropped out in MD-56 (27% dropout) compared to MD-53(4) (17% dropout). This attrition may affect interpretation of the MMRM analysis.

The Applicant's NFD PMM explored departures MAR under a mean shift model for the departures from MAR. Shifts values from 0 to 6 were investigated, see Appendix figures. For shifts at least 3, the unadjusted p-value for the 3 mg arm became greater than 0.05.

**Figure 8: MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (TRD3001: FAS Population)**




Source: Reviewer

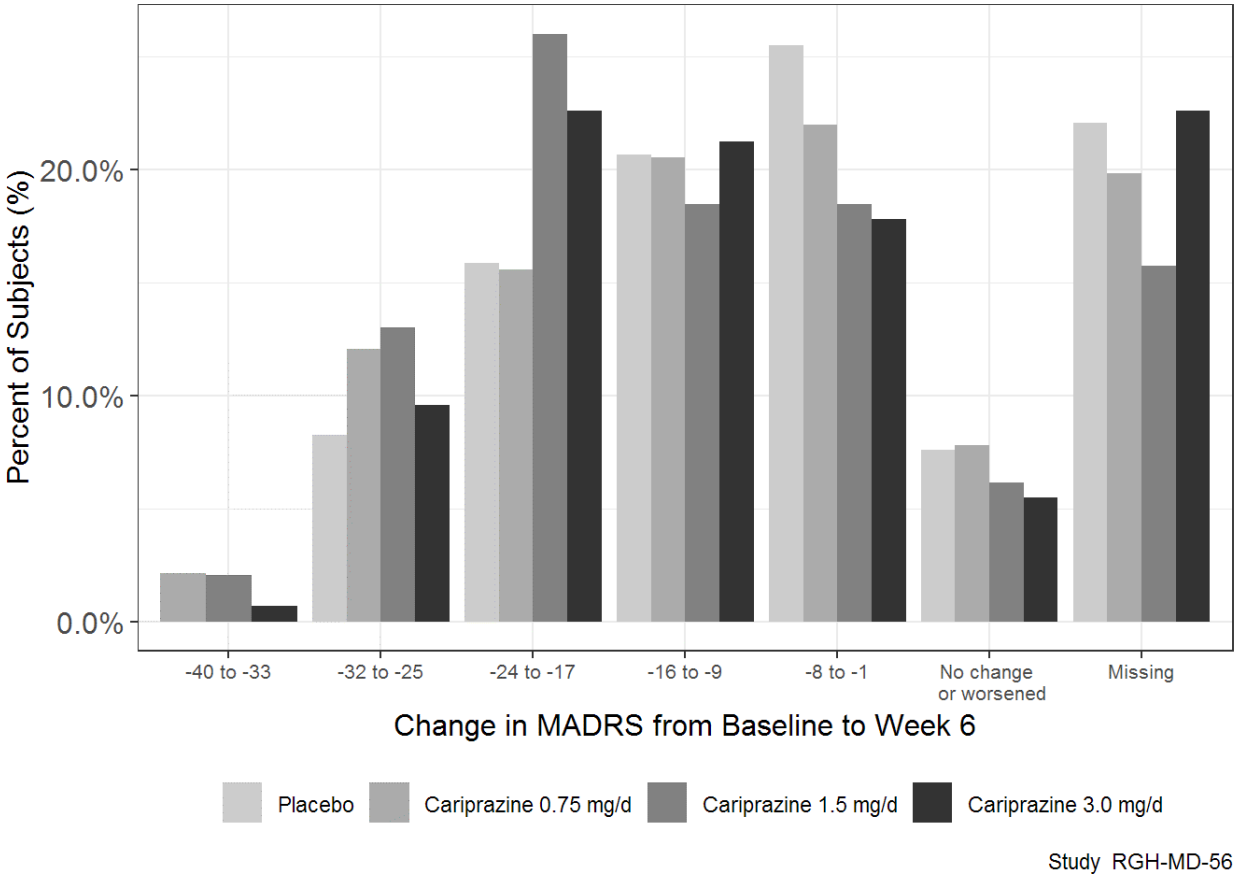
**Reviewer's Results**

This Reviewer recreated the results for the primary analysis in MD-56.

**Missing Data and Response Distributions**

In MD-56, 81% of patients completed the double-blind phase. In Figure 10, both 1.5 mg dose and 3 mg dose show a greater proportion of patients who improve at 17 points from baseline in MADRS total score. However, this pattern is not observed in 0.75 mg dose arm. In addition, note that 1.5 mg cariprazine had the lowest dropout rate and the 3 mg arm had the highest dropout rate. Therefore, cariprazine may be more useful than placebo in treating BPD.

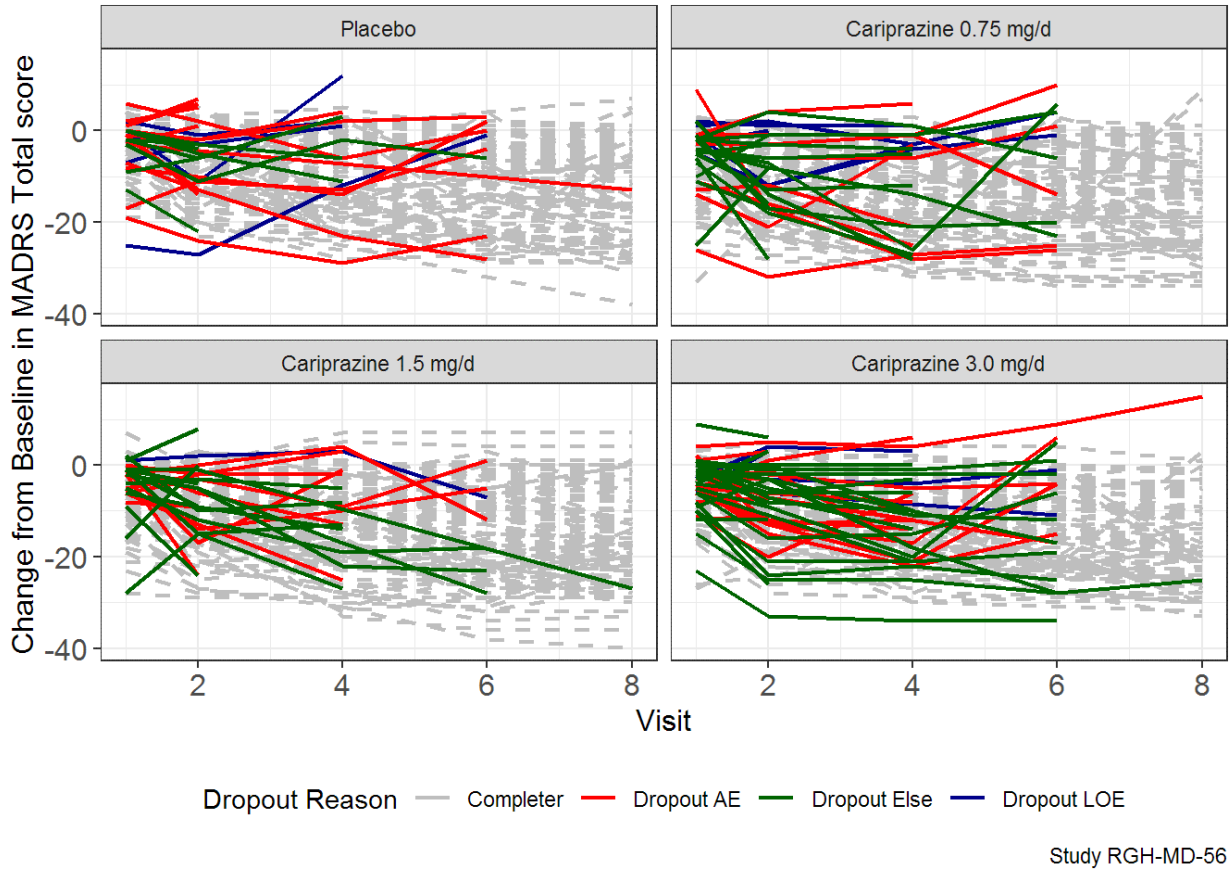
**Figure 9: Percentage of Subjects with Specified Change in MADRS Total Score (MD-53: FAS)**




Source: Reviewer

Patients MADRS trajectories are plotted by study visit in Figure 10. Dropouts due to an adverse event are red, lack of efficacy dropouts are blue, other reason dropouts are green, and completers are dashed grey. Many of the patients dropping out in the adverse event category have an increase in MADRS score at the last visit before dropout. This pattern may indicate informative dropout.

**Figure 10: Patient Level MADRS Change Score Trajectories (MD-56: FAS).**




Source: Reviewer

### 3.3 Evaluation of Safety

This review does not evaluate safety. Please refer to the clinical review for an evaluation of safety.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section contains the results of the Applicant's subgroup analyses. The Reviewer verified these analyses. All subgroup analyses are post hoc, exploratory analyses and should be interpreted with care.

**Table 12: Subgroup Analyses**

| Subgroup | RGH-MD-56[a] Placebo (N=141) | RGH-MD-56[a] Cariprazine 0.75 mg (N=140) | RGH-MD-56[a] Cariprazine 1.5 mg (N=145) | RGH-MD-56[a] Cariprazine 3.0 mg (N=145) | RGH-MD-53 Placebo (N=163) | RGH-MD-53 Cariprazine 1.5 mg (N=162) | RGH-MD-53 Cariprazine 3.0 mg (N=153) | RGH-MD-54 Placebo (N=156) | RGH-MD-54 Cariprazine 1.5 mg (N=154) | RGH-MD-54 Cariprazine 3.0 mg (N=164) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | | | | |
| < 55 yrs | | | | | | | | | | |
| n | 104 | 127 | 127 | 125 | 126 | 134 | 117 | 114 | 123 | 137 |
| Mean (SD) | -10.6 (9.8) | -12.4 (10.1) | -13.7 (10.1) | -12.8 (9.9) | -12.0 (9.0) | -14.5 (9.5) | -14.1 (10.9) | -11.9 (9.5) | -14.9 (9.7) | -14.9 (9.7) |
| Treatment difference (SE) | - | -1.7 (1.32) | -3.1 (1.31) | -2.1 (1.31) | - | -2.4 (1.15) | -2.0 (1.28) | - | -3.0 (1.25) | -3.0 (1.21) |
| ≥ 55 yrs | | | | | | | | | | |
| n | 37 | 13 | 18 | 20 | 37 | 28 | 36 | 42 | 31 | 27 |
| Mean (SD) | -7.6 (8.7) | -13.4 (12.0) | -15.6 (10.3) | -12.1 (7.6) | -11.0 (11.0) | -12.2 (7.2) | -11.6 (8.1) | -11.9 (8.2) | -11.0 (9.1) | -16.0 (7.7) |
| Treatment difference (SE) | - | -5.7 (3.62) | -8.0 (2.80) | -4.4 (2.21) | - | -1.2 (2.27) | -0.6 (2.26) | - | 0.9 (2.06) | -4.2 (1.94) |
| **Sex** | | | | | | | | | | |
| Female | | | | | | | | | | |
| n | 87 | 90 | 92 | 88 | 95 | 106 | 98 | 90 | 96 | 93 |
| Mean (SD) | -9.7 (9.9) | -11.9 (10.3) | -13.4 (10.6) | -12.1 (9.8) | -11.7 (8.9) | -14.4 (9.2) | -14.3 (10.4) | -11.1 (10.0) | -14.7 (10.4) | -15.2 (8.9) |
| Treatment difference (SE) | - | -2.2 (1.52) | -3.7 (1.53) | -2.4 (1.49) | - | -2.6 (1.28) | -2.5 (1.39) | - | -3.6 (1.50) | -4.1 (1.40) |
| Male | | | | | | | | | | |
| n | 54 | 50 | 53 | 57 | 68 | 56 | 55 | 66 | 58 | 71 |
| Mean (SD) | -10.1 (9.1) | -13.5 (10.2) | -15.0 (9.1) | -13.5 (9.3) | -11.9 (10.) | -13.5 (9.2) | -12.1 (10.1) | -13.0 (7.7) | -13.2 (8.3) | -14.9 (10.0) |
| Treatment difference (SE) | - | -3.4 (1.90) | -4.9 (1.76) | -3.3 (1.75) | - | -1.6 (1.74) | -0.2 (1.84) | - | -0.1 (1.44) | -1.9 (1.52) |

| Subgroup | RGH-MD-56[a] Placebo (N=141) | RGH-MD-56[a] Cariprazine 0.75 mg (N=140) | RGH-MD-56[a] Cariprazine 1.5 mg (N=145) | RGH-MD-56[a] Cariprazine 3.0 mg (N=145) | RGH-MD-53 Placebo (N=163) | RGH-MD-53 Cariprazine 1.5 mg (N=162) | RGH-MD-53 Cariprazine 3.0 mg (N=153) | RGH-MD-54 Placebo (N=156) | RGH-MD-54 Cariprazine 1.5 mg (N=154) | RGH-MD-54 Cariprazine 3.0 mg (N=164) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Race** | | | | | | | | | | |
| White | | | | | | | | | | |
| n | 109 | 110 | 108 | 112 | 119 | 116 | 114 | 114 | 122 | 125 |
| Mean (SD) | -9.7 (9.6) | -12.5 (10.0) | -13.4 (10.4) | -13.0 (9.1) | -11.2 (9.5) | -13.8 (9.0) | -13.4 (10.3) | -12.5 (8.8) | -14.0 (9.7) | -14.5 (9.0) |
| Treatment difference (SE) | - | -2.8 (1.33) | -3.7 (1.36) | -3.3 (1.26) | - | -2.6 (1.21) | -2.2 (1.30) | - | -1.6 (1.21) | -2.0 (1.15) |
| Non-White | | | | | | | | | | |
| n | 32 | 30 | 37 | 33 | 44 | 46 | 39 | 42 | 32 | 39 |
| Mean (SD) | -10.4 (9.6) | -12.4 (11.3) | -15.5 (9.2) | -11.4 (11.1) | -13.3 (9.1) | -14.7 (9.9) | -13.7 (10.6) | -10.3 (10.0) | -14.5 (9.6) | -16.9 (10.3) |
| Treatment difference (SE) | - | -1.9 (2.68) | -5.0 (2.27) | -0.9 (2.58) | - | -1.4 (2.00) | -0.4 (2.18) | - | -4.1 (2.30) | -6.6 (2.26) |
| **Region** | | | | | | | | | | |
| US | | | | | | | | | | |
| n | 77 | 82 | 88 | 83 | 104 | 102 | 94 | 90 | 89 | 98 |
| Mean (SD) | -10.4 (9.9) | -12.9 (10.5) | -14.5 (10.3) | -12.3 (9.7) | -12.2 (9.5) | -13.8 (10.0) | -13.5 (10.8) | -10.8 (9.4) | -14.2 (10.0) | -16.2 (10.1) |
| Treatment difference (SE) | - | -2.5 (1.62) | -4.1 (1.57) | -1.9 (1.55) | - | -1.6 (1.36) | -1.3 (1.46) | - | -3.4 (1.45) | -5.4 (1.42) |
| Non-US | | | | | | | | | | |
| n | 64 | 58 | 57 | 62 | 59 | 60 | 59 | 66 | 65 | 66 |
| Mean (SD) | -9.2 (9.3) | -11.9 (10.0) | -13.1 (9.8) | -13.2 (9.6) | -11.1 (9.3) | -14.5 (7.7) | -13.5 (9.5) | -13.4 (8.6) | -14.0 (9.4) | -13.4 (8.0) |
| Treatment difference (SE) | - | -2.7 (1.75) | -3.9 (1.74) | -3.9 (1.68) | - | -3.4 (1.56) | -2.4 (1.73) | - | -0.7 (1.57) | -0.1 (1.44) |

[a] Treatment difference is calculated as the mean change of cariprazine group minus the mean change of placebo group.

Source: Applicant's Integrated Summary of Efficacy.

## 4.1 Gender, Race, Age, and Geographic Region

The Applicant split age into two groups using 55 years old as a cutoff; however, this cutoff is arbitrary. Regardless, there is no evidence for any subgroup differences with respect to age, gender, and race.

***Geographic Region:*** In MD-56, both US and non-US regions show similar efficacy. In MD-53, the non-US patients suggest greater efficacy than US patients. This trend is reversed in MD-54 with the US patients having greater efficacy than the non-US.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

The main statistical issue in this efficacy supplement is the inconsistent statistical evidence from three studies for 3 mg per day of cariprazine for the treatment of bipolar depression. In all three studies, the ΔΔMADRS at 6 weeks ranged from -1.5 to -3.0 points. The multiplicity adjusted p-value ranged from 0.0102 to 0.1088 with only MD-54 ($p = 0.0102$) less than 0.05.

## 5.2 Collective Evidence

All three studies support the efficacy of 1.5 mg/day cariprazine for the treatment of bipolar depression; however, only one study (MD-54) provides strong evidence (adjusted $p = 0.0102$) for the efficacy of 3 mg/day cariprazine. An additional study (MD-56) provides additional supportive findings of 3 mg/day cariprazine's efficacy (adjusted $p = 0.10$; unadjusted $p=0.03$). The Applicant does not present any evidence for the efficacy of 0.75 mg/day.

## 5.3 Conclusions and Recommendations

The Applicant presented sufficient and replicated evidence that 1.5 mg/day cariprazine is effective in treating bipolar depression. The effect of 3 mg/day dose for treating bipolar depression was demonstrated in only one of the three studies. We recommend approval of 1.5 mg/day and defer to the Division of Psychiatry Products to determine if replication of statistical strength of evidence is required at the 3 mg/day dose.

# APPENDIX



**Table 11–2. Change from Baseline to Week 6 in MADRS Total Score: Sensitivity Analysis Using Pattern Mixture Model for Missing Data Imputation (ANCOVA) (Intent-to-Treat Population)**

| *Shift Parameter Statistics* | *Placebo (N = 163)* | *Cariprazine 1.5 mg (N = 162)* | *Cariprazine 3 mg (N = 153)* |
|---|---|---|---|
| Baseline, mean ± SD | 31.3 ± 4.1 | 31.5 ± 4.3 | 31.4 ± 4.7 |
| **Pattern mixture model** | | | |
| Shift parameter = 0 | | | |
| LS Mean (SE) | -12.5 (0.74) | -14.9 (0.77) | -14.2 (0.76) |
| LSMD vs placebo (95% CI) | | -2.4 (-4.4, -0.4) | -1.7 (-3.7, 0.4) |
| P-value vs placebo | | 0.0216 | 0.1141 |
| Shift parameter = 1 | | | |
| LS Mean (SE) | -12.3 (0.75) | -14.8 (0.76) | -14.0 (0.78) |
| LSMD vs placebo (95% CI) | | -2.5 (-4.6, -0.4) | -1.7 (-3.9, 0.4) |
| P-value vs placebo | | 0.0184 | 0.1133 |
| Shift parameter = 2 | | | |
| LS Mean (SE) | -12.2 (0.75) | -14.5 (0.77) | -13.9 (0.80) |
| LSMD vs placebo (95% CI) | | -2.4 (-4.5, -0.3) | -1.7 (-3.9, 0.4) |
| P-value vs placebo | | 0.0238 | 0.1148 |
| Shift parameter = 3 | | | |
| LS Mean (SE) | -12.1 (0.78) | -14.4 (0.78) | -13.7 (0.82) |
| LSMD vs placebo (95% CI) | | -2.3 (-4.5, -0.2) | -1.6 (-3.8, 0.6) |
| P-value vs placebo | | 0.0303 | 0.1540 |
| Shift parameter = 4 | | | |
| LS Mean (SE) | -12.0 (0.78) | -14.3 (0.78) | -13.7 (0.78) |
| LSMD vs placebo (95% CI) | | -2.3 (-4.4, -0.2) | -1.7 (-3.8, 0.5) |
| P-value vs placebo | | 0.0350 | 0.1234 |
| Shift parameter = 5 | | | |
| LS Mean (SE) | -11.8 (0.77) | -14.2 (0.76) | -13.4 (0.81) |
| LSMD vs placebo (95%CI) | | -2.3 (-4.5, -0.2) | -1.5 (-3.7, 0.6) |
| P-value vs placebo | | 0.0300 | 0.1684 |
| Shift parameter = 6 | | | |
| LS Mean (SE) | -11.7 (0.79) | -14.0 (0.77) | -13.2 (0.81) |
| LSMD vs placebo (95% CI) | | -2.3 (-4.5, -0.2) | -1.5 (-3.7, 0.8) |
| P-value vs placebo | | 0.0334 | 0.1953 |

**Table 11-2. Change from Baseline to Week 6 in MADRS Total Score: Sensitivity Analysis Using Pattern Mixture Model for Missing Data Imputation (ANCOVA) (Intent-to-Treat Population)**

| *Shift Parameter Statistics* | *Placebo (N = 156)* | *Cariprazine 1.5 mg (N = 154)* | *Cariprazine 3.0 mg (N = 164)* |
|---|---|---|---|
| Baseline, mean ± SD | 30.2 ± 4.4 | 30.7 ± 4.3 | 31.0 ± 4.9 |
| **Pattern mixture model** | | | |
| Shift parameter = 0 | | | |
| LS Mean (SE) | -12.5 (0.74) | -15.1 (0.76) | -15.6 (0.71) |
| LSMD vs placebo (95% CI) | | -2.6 (-4.7, -0.5) | -3.1 (-5.1, -1.1) |
| P-value vs placebo | | 0.0140 | 0.0024 |
| Shift parameter = 1 | | | |
| LS Mean (SE) | -12.3 (0.75) | -15.0 (0.76) | -15.5 (0.76) |
| LSMD vs placebo (95% CI) | | -2.7 (-4.7, -0.7) | -3.2 (-5.3, -1.1) |
| P-value vs placebo | | 0.0090 | 0.0028 |
| Shift parameter = 2 | | | |
| LS Mean (SE) | -12.2 (0.74) | -14.9 (0.75) | -15.3 (0.75) |
| LSMD vs placebo (95% CI) | | -2.7 (-4.7, -0.6) | -3.1 (-5.2, -1.1) |
| P-value vs placebo | | 0.0106 | 0.0031 |
| Shift parameter = 3 | | | |
| LS Mean (SE) | -12.1 (0.75) | -14.7 (0.75) | -15.2 (0.74) |
| LSMD vs placebo (95% CI) | | -2.6 (-4.6, -0.5) | -3.0 (-5.0, -1.0) |
| P-value vs placebo | | 0.0151 | 0.0032 |
| Shift parameter = 4 | | | |
| LS Mean (SE) | -11.9 (0.75) | -14.7 (0.77) | -15.0 (0.73) |
| LSMD vs placebo (95% CI) | | -2.8 (-4.8, -0.7) | -3.1 (-5.1, -1.1) |
| P-value vs placebo | | 0.0089 | 0.0027 |
| Shift parameter = 5 | | | |
| LS Mean (SE) | -11.9 (0.75) | -14.6 (0.80) | -14.9 (0.74) |
| LSMD vs placebo (95% CI) | | -2.6 (-4.7, -0.5) | -3.0 (-5.0, -0.9) |
| P-value vs placebo | | 0.0144 | 0.0049 |
| Shift parameter = 6 | | | |
| LS Mean (SE) | -11.7 (0.79) | -14.5 (0.77) | -14.7 (0.75) |
| LSMD vs placebo (95% CI) | | -2.8 (-4.9, -0.6) | -3.0 (-5.2, -0.9) |
| P-value vs placebo | | 0.0113 | 0.0057 |

P-value and 95% CI for the difference using contrast t-test

For each shift parameter value, missing values were imputed multiple times using a pattern-mixture model assuming non-future dependence. For each imputed dataset, ANCOVA was performed. The estimates and p-values were obtained from combining all the results from each individual analysis of the same shift parameter value.

**Table 11.4.1.1–2. Sensitivity Analyses of the Primary Efficacy Parameter: Change From Baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale Total Score (PMM and ANCOVA)—Intent-to-Treat Population**

| | *Placebo (N = 141)* | *Cariprazine 0.75 mg (N = 140)* | *Cariprazine 1.5 mg (N = 145)* | *Cariprazine 3 mg (N = 145)* |
|---|---|---|---|---|
| Baseline, mean ± SD | 30.4 ± 4.6 | 31.1 ± 4.7 | 30.3 ± 4.4 | 30.6 ± 4.7 |
| **ANCOVA (LOCF)[a]** | | | | |
| Change at Week 6, LS mean (SE) | –10.1 (0.8) | –12.4 (0.8) | –14.2 (0.8) | –12.8 (0.8) |
| LSMD vs placebo (95% CI) | — | –2.3 (–4.6, –0.1) | –4.1 (–6.3, –1.9) | –2.7 (–4.9, –0.5) |
| P-value vs placebo[a] | — | 0.0411 | 0.0003 | 0.0173 |
| **Pattern-mixture model[b]** | | | | |
| Shift parameter = 0 | | | | |
| LSMD vs placebo (95% CI) | — | –1.7 (–4.0, 0.7) | –3.7 (–6.0, –1.4) | –2.5 (–4.8, –0.1) |
| P-value vs placebo | — | 0.1646 | 0.0016 | 0.0372 |
| Shift parameter = 1 | | | | |
| LSMD vs placebo (95% CI) | — | –1.8 (–4.1, 0.6) | –3.8 (–6.1, –1.5) | –2.5 (–4.8, –0.1) |
| P-value vs placebo | — | 0.1436 | 0.0013 | 0.0390 |
| Shift parameter = 2 | | | | |
| LSMD vs placebo (95% CI) | — | –1.8 (–4.2, 0.6) | –3.9 (–6.2, –1.5) | –2.5 (–4.9, –0.1) |
| P-value vs placebo | — | 0.1480 | 0.0013 | 0.0387 |

**Table 11.4.1.1–2. Sensitivity Analyses of the Primary Efficacy Parameter: Change From Baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale Total Score (PMM and ANCOVA)—Intent-to-Treat Population**

| | *Placebo (N = 141)* | *Cariprazine 0.75 mg (N = 140)* | *Cariprazine 1.5 mg (N = 145)* | *Cariprazine 3 mg (N = 145)* |
|---|---|---|---|---|
| Shift parameter = 3 | | | | |
| LSMD vs placebo (95% CI) | — | –1.7 (–4.1, 0.7) | –3.8 (–6.2, –1.5) | –2.3 (–4.8, 0.1) |
| P-value vs placebo | — | 0.1649 | 0.0015 | 0.0566 |
| Shift parameter = 4 | | | | |
| LSMD vs placebo (95% CI) | — | –1.7 (–4.2, 0.7) | –3.9 (–6.3, –1.4) | –2.3 (–4.7, 0.2) |
| P-value vs placebo | — | 0.1668 | 0.0017 | 0.0674 |
| Shift parameter = 5 | | | | |
| LSMD vs placebo (95% CI) | — | –1.7 (–4.2, 0.7) | –3.9 (–6.4, –1.5) | –2.3 (–4.8, 0.2) |
| P-value vs placebo | — | 0.1717 | 0.0014 | 0.0729 |
| Shift parameter = 6 | | | | |
| LSMD vs placebo (95% CI) | — | –1.8 (–4.3, 0.7) | –4.0 (–6.5, –1.6) | –2.3 (–4.8, 0.2) |
| P-value vs placebo | — | 0.1596 | 0.0013 | 0.0711 |

a P-values were obtained from an ANCOVA model with treatment group and pooled study center as factors and the baseline value as a covariate. LOCF was used for imputation of missing values.

b For each shift parameter value, missing values were imputed multiple times using a pattern-mixture model assuming non-future dependent missing value restrictions. For each imputed dataset, an ANCOVA was performed. The estimates and p-values were obtained from combining all results for each shift parameter value.

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference.

Source: Table 14.4.1.1.

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HSIEN MING J HUNG
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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Office of Clinical Pharmacology Memo

| | | |
|---|---|---|
| **NDA/eCTD#:** 204,370/0134 | **EDR Link:** \\CDSESUB1\evsprod\NDA204370\0134 | |
| **Relevant IND:** 71,958 | **Sponsor:** Allergan | **Submission Date:** 7/24/2018 |
| **Formulation:** Immediate-Release Capsules | | **Brand Name:** VRAYLAR |
| **Indications:** Schizophrenia, Bipolar Disorder | | **Generic Name:** Cariprazine |
| **Submission Type:** Efficacy Supplement (S006) | | **Strength (mg):** 0.5, 3, 4.5, 6 |
| **OCP Review Team:** Huixia Zhang; Luning (Ada) Zhuang | | |

VRAYLAR (cariprazine, NDA 204,370) was approved for the treatment of schizophrenia and bipolar mania in adults in 2015. In this efficacy supplement (S-006), a labeling change based on the results from a drug interaction study (RGH-PK-19) is proposed by the Sponsor.

The report for Study RGH-PK-19, entitled "Evaluation of the Effect of Pantoprazole, a Proton Pump Inhibitor, on Cariprazine Exposure in Patients with Schizophrenia", was submitted by the Sponsor on 3/28/2018, to fulfill PMR #2947-7 as outlined in the approval letter for VRAYLAR.

**PMR 2947-7** An in vivo drug-drug interaction study to assess cariprazine exposure when cariprazine is coadministered with a proton pump inhibitor.

The study showed, and the Agency agreed that coadministration of pantoprazole with VRAYLAR did not significantly affect the $C_{max}$ or AUC of cariprazine, or its two active metabolites: desmethylcariprazine and didesmethylcariprazine. Dosage adjustment of VRAYLAR is not deemed necessary when it is coadministered with a proton pump inhibitor (e.g., pantoprazole). OCP review of the study report can be found in DARRTS (signed off date 2/8/2019).

The Agency agree with the concept of the proposed labeling change based on the results from study RGH-PK-19. Pending satisfactory negotiation of the labeling language, the efficacy supplement is approvable from a clinical pharmacology perspective.

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204370Orig1s006

# OTHER REVIEW(S)

**REGULATORY PROJECT MANAGER**
**LABELING REVIEW**

Date: *{See appended electronic signature page}*
DRUG/NDA: Vraylar (cariprazine) Capsules 1.5 mg, 3 mg, 4.5 mg and 6 mg
NDA 204370/S-006
Sponsor: Allergan Sales, LLC
Indication: Treatment of depressive episodes in Bipolar I Disorder

Supplements under review:

| NDA | Supplement | Dated | Provides for | Status |
|---|---|---|---|---|
| 204370 | S-005 | 4/17/18 | PAS – proposes revisions to Pregnancy section 8.1 concerning the potential fetal risks of cariprazine after treatment discontinuation. | AP letter dated 11/28/18 |
| 204370 | S-006 | 7/24/18 | PAS – efficacy supplement proposing a new indication of treatment of depressive episodes associated with bipolar I disorder (bipolar depression). | Pending |

**NOTES**

- The last approved labeling, for comparison purposes, was the labeling attached to the 11/28/18 approval letter for supplemental application NDA 204370/S-005.
- In the original NDA approval letter dated 9/17/15, the following postmarketing requirement (PMR) was imposed and submission proposed labeling change based on the results from a drug interaction study (RGH-PK-19):

  PMR 2947-7 An in vivo drug-drug interaction study to assess cariprazine exposure when cariprazine is coadministered with a proton pump inhibitor.

- This review will encompass efficacy supplement S-006 as there are no other supplements pending under this NDA.

**REVIEW**

**204370/S-006**
**CBE: No**
**Reviewed by: Sharon Mills - DMPP (5/10/19), Nancy Dickinson -Clinical (5/23/19), Statistics – Andrew Potter (4/26/19), Loretta Holmes – DMEPA (3/18/19), Domenic Dalessandro - OPDP (4/15/19), Jenn Sellers – OSI (4/9/19), Huixia Zhang – OCP (3/11/19), Bernie Fischer - CDTL Memo (5/24/19)**

1. The review team included the following disciplines: clinical, clinical pharmacology, biostatistics, DMEPA, OPDP, DMPP, and OSI. All disciplines reviewed the proposed labeling changes and determined that 1.5 mg and 3.0 mg of Vraylar was effective in treating depressive episodes associated with bipolar I disorder.
2. As a result of adding this indication, Boxed Warning was updated to include suicide warning and accompanying Medication Guide (MG) was added. Associate Director of Labeling directed Applicant to reference Latuda MG for consistency.
3. The results from the final report for PMR 2947-7 was also included in Section 12.3 Pharmacokinetics to reflect dosage adjustment of Vraylar is not necessary when coadministered with a proton pump inhibitor.
4. Minor updates throughout the PI to use language that are consistent with most current depression indication PI.

**CONCLUSIONS**

1. A side by side review found no changes other than those specified above when compared to the last approved labeling dated 11/28/18.
2. The Applicant has agreed to the revisions proposed by the Agency and submitted verbatim labeling changes in submissions dated 5/22/19 (for MG) and 5/23/19 (for PI).
3. I recommend that an approval letter be issued for this pending supplemental application.

*{See appended electronic signature page}*
Danbi Lee, Pharm.D., Regulatory Project Manager

*{See appended electronic signature page}*
Paul David, R.Ph., CPMS

Enclosure:
Annotated labeling changes and MG

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DANBI LEE
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PAUL A DAVID
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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | May 10, 2019 |
| To: | Tiffany Farchione, MD<br>Acting Director<br>**Division of Psychiatry Products (DPP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Sharon R. Mills, BSN, RN, CCRP<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Aline Moukhtara, RN, MPH<br>Team Leader<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) |
| Drug Name (established name): | VRAYLAR (cariprazine) |
| Dosage Form and Route: | capsules, for oral use |
| Application Type/Number: | NDA 204370 |
| Supplement Number: | S-006 |
| Applicant: | Allergan Sales, LLC |

## 1 INTRODUCTION

On July 24, 2018, Allergan Sales, LLC submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved New Drug Application (NDA) 204370/S-006 for VRAYLAR (cariprazine) capsules.With the supplement, the Applicant proposes the following new indication for VRAYLAR (cariprazine) capsules: for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on April 26, 2019 and July 30, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU)] for VRAYLAR (cariprazine).

## 2 MATERIAL REVIEWED

- Draft VRAYLAR (cariprazine) capsules MG received on April 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 30, 2019.
- Draft VRAYLAR (cariprazine) capsules Prescribing Information (PI) received on July 24, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on April 26, 2019, further revised by the Review Division and accessed from SharePoint by DMPP on May 2, 2019.
- Draft VRAYLAR (cariprazine) capsules Prescribing Information (PI) received on July 24, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on April 5, 2019.
- Approved LATUDA (lurasidone hydrochloride) tablets comparator labeling dated March 5, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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ALINE M MOUKHTARA
05/10/2019 12:16:42 PM

LASHAWN M GRIFFITHS
05/10/2019 12:19:18 PM

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** April 15, 2019

**To:** Nancy C. Dickinson, PharmD
Division of Psychiatry Products (DPP)

Danbi Lee, PharmD, Regulatory Project Manager, (DPP)

Kimberly Updegraff, PharmD, Associate Director for Labeling, (DPP)

**From:** Domenic D'Alessandro, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, RN, MPH, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for VRAYLAR® (cariprazine) capsules, for oral use

**NDA**: 204370 / Supplement 006

---

In response to DPP consult request dated July 30, 2018, OPDP has reviewed the proposed product labeling (PI). This supplement (S-006) proposes to add a new indication for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Danbi Lee) on April 5, 2019, and are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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# Clinical Inspection Summary

| | |
|---|---|
| **Date** | April 9, 2019 |
| **From** | Jenn Sellers, M.D., Ph.D., Medical Officer<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations (OSI) |
| **To** | Danbi Lee, Pharm.D.<br>Regulatory Project Manager<br>Nancy Dickinson, Pharm.D., Clinical Reviewer<br>Bernard Fischer, M.D., Clinical Review Team Leader |
| **NDA #** | 204370-S006 |
| **Applicant** | Allergan Sales, LLC |
| **Drug** | Vraylar (Cariprazine Hydrochloride) |
| **NME** | No |
| **Therapeutic Classification** | Antipsychotics |
| **Proposed Indication** | Bipolar I Depression |
| **Consultation Request Date** | September 10, 2018 |
| **Summary Goal Date** | April 15, 2019 |
| **Action Goal Date** | May 24, 2019 |
| **PDUFA Date** | May 24, 2019 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The clinical sites of Drs. Ball, Kakar, and McGill were inspected in support of NDA 204370-S006, which included two double-blind efficacy and safety studies (RGH-MD-53 and RGH-MD-54) in patients with Bipolar I Depression. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of Drs. Ball, Kakar, and McGill was No Action Indicated (NAI).

## II. BACKGROUND

Cariprazine is a dopamine $D_3$-preferring $D_3/D_2$ receptor partial agonist. Cariprazine (Vraylar) is currently approved for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults, with the doses from 3 mg/day to 6 mg/day. The sponsor submitted this supplemental NDA to seek FDA's approval for the use of cariprazine in the treatment of depressive episodes associated with bipolar I disorder (bipolar depression), with recommended doses of 1.5 mg/day and 3 mg/day. Inspections were requested for the following protocols in support of the application:

**Protocols RGH-MD-53** and **RGH-MD-54**, "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Fixed-Dose Clinical Trial Evaluating the Efficacy, Safety and Tolerability of Cariprazine in Patients with Bipolar I Depression"

Both Protocols had the same study title and study design.

For Study **RGH-MD-53**, 493 subjects were enrolled. Eighty-nine (89) study centers screened subjects for this study: 43 in the United States, 6 in Bulgaria, 6 in Croatia, 5 in Romania, 11 in

Serbia, 6 in Slovakia and 12 in Ukraine. Study initiation and completion dates were 31 March 2016 and 18 January 2018.

For Study **RGH-MD-54**, 488 subjects were enrolled. Seventy-four (74) study centers screened subjects for this study: 43 in the United States, 16 in Bulgaria, 3 in Estonia, 4 in Lithuania, and 8 in Poland. Study initiation and completion dates were 17 March 2016 and 19 July 2017.

The primary study objective of these two Phase 3 studies was to evaluate the efficacy, safety, and tolerability of cariprazine 1.5 mg/day and 3 mg/day relative to placebo in subjects with bipolar I depression.

Both studies were randomized, double-blind, placebo-controlled, fixed-dose, 6-week studies in adult subjects aged 18 to 65 years with bipolar I depression. Major study eligibility criteria included subjects meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for bipolar I disorder without psychotic features confirmed by the administration of the Mini International Neuropsychiatric Interview (MINI), having a current major depressive episode of at least 4 weeks and not exceeding 12 months in duration, a minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HAMD-17), a minimum score of 2 on item 1 of the HAMD-17, and a minimum score of 4 on the CGI-S Scale (CGI-S) at screening.

Eligible subjects were randomized 1:1:1 to cariprazine 1.5 mg/day, 3 mg/day, or placebo. All subjects randomized to cariprazine were to receive cariprazine 1.5 mg/day for 2 weeks (from Day 1 through Day 14). For subjects randomized to the cariprazine 3 mg/day group, the dose was increased to 3 mg/day on Day 15. Subjects visited the study center on Visit 1 (screening), Visit 2 (baseline), Visits 3-6 (6- week double-blind treatment period), and Visit 7 (safety follow-up period).

The *primary efficacy endpoint* was the change from baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

The *secondary efficacy endpoint* was the change from baseline to Week 6 in Clinical Global Impressions-Severity (CGI-S) Score.

**Rationale for Clinical Investigator Site Selection**

- Dr. Ball’s site was selected because of high enrollment. He was inspected in 2005 (NAI).
- Dr. Kakar’s site was selected due to good treatment effect and no prior inspection history.
- Dr. McGill’s site was selected due to good treatment effect. She was inspected in 2009 (NAI).
- Dr. Benzar’s site was selected because of good treatment effect. He was inspected in 2012 (NAI).

## III. RESULTS (by site):

| Site #<br>Name of CI<br>Address | Protocol #/<br># of Enrolled Subjects | Inspection Dates | Classification |
|---|---|---|---|
| Site #1<br>**Roberta R. Ball, D.O.**<br>175 Cross Keys Road<br>Berlin, NJ 08009 | RGH-MD-54<br>Subjects: 15 | 24-26 Oct,<br>29 Oct -1 Nov 2018 | NAI |
| Site #41<br>**Rishi Kakar, M.D.**<br>7481 W. Oakland Park Blvd,<br>Lauderhill, FL 33319 | RGH-MD-53<br>Subjects: 10 | 10-11 Dec 2018 | NAI |
| Site #15<br>**Lora J. McGill, M.D.**<br>6401 Poplar Avenue, Ste 420<br>Memphis, TN 00003-8119 | RGH-MD-54<br>Subjects: 10 | 19-21 Feb 2019 | NAI |
| Site #6<br>**Zinoviy T. Benzar, M.D.**<br>2072 Bath Ave<br>Brooklyn, NY 11214 | RGH-MD-53<br>Subjects: 6 | 26 Nov 2018 | Not applicable (inspection cancelled) |

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable

### 1. Roberta R. Ball, D.O.

At this site for Protocol RGH-MD-54, 27 subjects were screened, 15 enrolled, and 14 subjects completed the study. One subject (# (b) (6) in cariprazine 1.5 mg/day treatment group) was discontinued due to falling under 80% drug compliance with the protocol.

The study and subject specific records reviewed during this inspection included, but were not limited to, informed consent forms, reconsenting of subjects, inclusion/exclusion criteria, documentation of screen failures, doctors' progress notes, the following of proper washout procedures, the primary efficacy endpoint data, adverse event (AE) reports, laboratory results, original ECGs, case report forms, delegation of authority logs, FDA Form 1572, financial disclosures, test article accountability logs, the site training records, monitoring visits reports conducted by the sponsor Allergan, and the audit trail of the data input onto electronic data capture (EDC).

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

Of note, the inspection revealed that Subject # (b) (6) in cariprazine 3.0 mg/day treatment group has missed two doses of cariprazine 1.5 mg/day in the week from Day 8 to Day 14, which made the subject 71% (5/7) drug compliant. The subject should therefore have been discontinued per

protocol due to poor drug compliance (< 80% measured by pill counts). Instead, this subject completed the study.

*Reviewer's comment: This protocol deviation was not reported to the FDA. Since this subject was in the cariprazine 3.0 mg/day treatment group, the subject had the dose increased to 3.0 mg/day from Day 15 and was compliant throughout the rest of the treatment phase. Missing two low doses of 1.5 mg/day before the dose was titrated to 3mg/day would unlikely affect the efficacy results of the study.*

**2. Rishi Kakar, M.D.**

At this site for Protocol RGH-MD-53, 14 subjects were screened, 10 were enrolled, and 4 subjects completed the study. Six were discontinued, two withdrew consent, and two were lost to follow-up. Subject # (b) (6) was requested by the sponsor to discontinue the study at Visit 1 due to screening lab showing leukopenia and neutropenia. Subject # (b) (6) had a positive lab result for tetrahydrocannabinol (THC) and therefore was discontinued.

The study and subject specific records reviewed during this inspection included, but were not limited to, Form FDA 1572s, financial disclosures, delegation list, the firm's training program, the clinical trial protocol and amendments, Institution Review Board (IRB) submissions and approvals, test article control and accountability, informed consent forms (for all 14 screened subjects), inclusion/exclusion criteria, the primary efficacy data, adverse event (AE) reports, monitoring, as well as the concomitant medications for the 4 subjects who completed the study.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

**3. Lora J. McGill, M.D.**

At this site for Protocol RGH-MD-54, 14 subjects were screened, 10 were enrolled, and 4 subjects completed the study. Six were discontinued, three withdrew consent, and two were lost to follow-up. Subject # (b) (6) in the cariprazine 1.5 mg/day group was discontinued due to the AE of tachycardia.

The inspection reviewed all enrolled subjects' informed consent forms, physical exams, follow up visits, efficacy data, AEs, concomitant medication logs, and protocol deviation reports as well as the regulatory binders that included FDA Form 1572s, financial disclosures, sponsor/monitor/IRB correspondence, test article accountability logs, and equipment records.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

**4. Zinoviy T. Benzar, M.D.**

It was determined by the Office of Regulatory Affairs that the firm was out of business and the clinical investigator could not be located. OSI and DPP agreed to cancel this inspection (rather than asking the sponsor to find the study records or selecting an alternate CI site) due to small enrollment at the site (6 subjects) and difficulty to locate the clinical investigator. In addition, the data from this site did not impact the overall efficacy results. The request to convert this assigned inspection to an Op 13 was granted.

*{See appended electronic signature page}*

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**cc:**
Central Doc. Rm. NDA #204370-S006
DPP/Clinical Reviewer/Nancy Dickinson
DPP/Clinical Team Leader/Bernard Fischer
DPP /Project Manager/Danbi Lee
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OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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/s/
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JENN W SELLERS
04/09/2019 03:14:42 PM

PHILLIP D KRONSTEIN
04/09/2019 03:33:46 PM

KASSA AYALEW
04/09/2019 03:40:03 PM

# MEMORANDUM

REVIEW OF LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | March 18, 2019 |
| Requesting Office or Division: | Division of Psychiatry Products (DPP) |
| Application Type and Number: | NDA 204370 |
| Product Name and Strength: | Vraylar (cariprazine) capsules<br>1.5 mg, 3 mg, 4.5 mg, and 6 mg |
| Applicant/Sponsor Name: | Allergan Sales, LLC |
| FDA Received Date: | July 24, 2018 and December 21, 2018 |
| OSE RCM #: | 2018-1628 |
| DMEPA Safety Evaluator: | Loretta Holmes, BSN, PharmD |
| DMEPA Team Leader: | Sevan Kolejian, PharmD, MBA |

## 1 PURPOSE OF MEMORANDUM

Allergan submitted efficacy supplement NDA 204370/S-006 on July 24, 2018. This supplement proposes a new indication of treatment of depressive episodes associated with bipolar I disorder (bipolar depression).

The Division of Psychiatry Products (DPP) requested that we review the proposed changes to the Prescribing Information (see Appendix A), to determine if they are acceptable from a medication error perspective.

## 2 ASSESSMENT

We reviewed the proposed Prescribing Information (PI) submitted on December 21, 2018 and focused on the proposed changes to the Dosage and Administration sections of the labeling. We did not identify any areas that are prone to medication errors. We also considered whether the revisions made to provide for S-006 require subsequent updates to the Vraylar container labels and other packaging components to ensure consistency and minimize the risk of confusion. We did not identify any areas where updates (e.g., proprietary name, dosage form, route of administration, or usual dosage statement) are needed. As such, we have no comments regarding the proposed PI, the container labels or other packaging components.

## 3 CONCLUSION

We find the proposed Prescribing Information acceptable from a medication error perspective. Thus, we have no recommendations at this time.

APPENDIX A. PRESCRIBING INFORMATION SUBMITTED ON DECEMBER 21, 2018

The proposed prescribing information can be accessed via the Electronic Document Room (EDR) via this link: \\cdsesub1\evsprod\nda204370\0149\m1\us\draft-labeling-text-annotated.pdf

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/s/

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LORETTA HOLMES
03/18/2019 04:46:26 PM

SEVAN H KOLEJIAN
03/18/2019 10:31:22 PM