Brand Name	Vraylar
Active Ingredient(s)	cariprazine
Strength	1.5 mg 3 mg 4.5 mg 6 mg
Dosage Form	capsule
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).
NDC	61874-115-30, 61874-115-90 61874-130-30, 61874-130-90 61874-145-30, 61874-145-90 61874-160-30, 61874-160-90
DIN	02526794 02526808 02526816 02526824
Canadian Distributor	AbbVie Corporation 8401 Trans-Canada Highway, Saint-Laurent, Quebec, Canada H4S 1Z1
NDA Number	NDA204370
US Distributor (NDA Holder)	Allergan USA, Inc. 5 Giralda Farms, Dodge Dr, Madison, NJ 07940 USA
Manufacturer (Final Packager)	Forest Laboratories Ireland Limited Dublin, Ireland
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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----------

Indications and Usage (1)	12/2022
Dosage and Administration (2.5)	12/2022
Warnings and Precautions (5.7, 5.12)	12/2022

----------INDICATIONS AND USAGE----------
VRAYLAR is an atypical antipsychotic indicated for:
- 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)
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) 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
Adjunctive therapy to antidepressants for MDD (2.5)	1.5 mg daily	1.5 mg or 3 mg daily

- Schizophrenia and Bipolar Mania: Maximum recommended daily dosage is 6 mg. 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: Maximum recommended daily dosage is 3 mg (2.4)
- Adjunctive therapy for treatment of MDD: Maximum recommended daily dosage is 3 mg (2.5)

----------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 and Syncope*: 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
- Adjunctive treatment of MDD: akathisia, restlessness, fatigue, constipation, nausea, insomnia, increased appetite, dizziness, 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 (2.6, 7.1)
- CYP3A4 inducers: Concomitant use is not recommended (2.6, 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: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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:

- 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)]*
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults *[see Clinical Studies (14.4)]*

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), Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage in Schizophrenia

The starting dosage of VRAYLAR is 1.5 mg once daily. The recommended dosage range is 1.5 mg to 6 mg once 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 Recommended Dosage in Manic or Mixed Episodes Associated with Bipolar I Disorder

The starting dosage of VRAYLAR is 1.5 mg once daily and should be increased to 3 mg once daily on Day 2. The recommended dosage range is 3 mg to 6 mg once daily. 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 Recommended Dosage in Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The starting dosage 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 Recommended Dosage for Adjunctive Therapy to Antidepressants in Treatment of Major Depressive Disorder

The starting dosage 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. In clinical trials, dosage titration at intervals of less than 14 days resulted in a higher incidence of adverse reactions *[see Adverse Reactions* (*6.1)*]. Maximum recommended dosage is 3 mg once daily.

2.6 Dosage Adjustments for CYP3A4 Inhibitors and Inducers

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)]*.

2.7 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 reactions 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 patients 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 reactions 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. There have been reports of hyperglycemia in patients treated with VRAYLAR. Although all 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%).

Adjunctive Treatment of Major Depressive Disorder

In two 6-week placebo-controlled trials of adult patients with major depressive disorder, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) was greatest in the VRAYLAR 3 mg per day + antidepressant therapy arm (3.2%) compared with those taking VRAYLAR 1.5 mg per day + antidepressant therapy (2%) or those placebo-treated (1.3%). The proportion of patients with shifts from normal to borderline (≥100 and <126 mg/dL) or from borderline to high were similar in patients treated with VRAYLAR and placebo. In a long-term, open-label adjunctive treatment of MDD study, 7% patients with normal hemoglobin A1c baseline values developed elevated levels (> 6%).

In one 8-week placebo-controlled trial of adult patients with major depressive disorder, the changes from baseline to end of the trial in fasting glucose were similar among the VRAYLAR and placebo + antidepressant therapy treatment groups. During the 8-week trial, serum insulin levels increased by 12 pmol/L in the VRAYLAR 1 mg to 2 mg per day group, 20 pmol/L in the VRAYLAR 2 mg to 4.5 mg per day group, and 8.5 pmol/L in the placebo group.

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.

Adjunctive Treatment of Major Depressive Disorder

In two 6-week placebo-controlled trials of adult patients with major depressive disorder, the proportion of patients with shifts in total cholesterol, fasting LDL, HDL, and fasting 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, 4, and 5 show the change in body weight occurring from baseline to endpoint in 6-week trials of schizophrenia, 3-week bipolar mania trials, 6-week and 8-week bipolar depression trials, and 6-week and 8-week trials of adjunctive treatment for major depressive disorder, 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%

Table 5. Change in Body Weight (kg) in two 6-Week and one 8-Week Adjunctive Treatment for Major Depressive Disorder Trials

		VRAYLAR	
6-week Trials	Placebo +ADT (N=503)	1.5 mg/day +ADT (N=502)	3 mg/day +ADT (N=503)
Mean Change at Endpoint	+0.2	+0.7	+0.7
Proportion of Patients with Weight Increase (≥7%)	1%	2%	2%
8-week Trial	Placebo + ADT (N=266)	1 to 2 mg/day + ADT (N=273)	2 to 4.5 mg/day + ADT (N=273)
Mean Change at Endpoint	0	+0.9	+0.9
Proportion of Patients with Weight Increase (≥7%)	2%	2%	3%

In the long-term, open-label adjunctive treatment of MDD trial, 2 patients (0.6%) discontinued due to weight increase. VRAYLAR was associated with mean change from baseline in weight of 1.7 kg at Week 26. In the long-term, open-label adjunctive treatment of MDD trial, 19% of patients demonstrated a ≥7% increase in body weight, and 5% demonstrated a ≥7% decrease in body weight.

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, may cause somnolence and 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. In two 6-week and one 8-week trials of depressive episodes of bipolar I disorder, VRAYLAR-treated patients reported 7% somnolence and 4% in the placebo-treated patients. In 6-week adjunctive treatment of major depressive disorder trials, somnolence was reported in 6% of VRAYLAR-treated patients compared to 4% of placebo-treated patients. In one 8-week adjunctive treatment of major depressive disorder trial, somnolence was reported in 11% of VRAYLAR-treated patients compared to 6% 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 6,722 adult patients exposed to one or more doses of VRAYLAR for the treatment of schizophrenia, manic or mixed episodes associated with bipolar I disorder, bipolar depression, and adjunctive treatment of major depressive disorder in placebo-controlled studies. This experience corresponds with a total experience of 1,182.8 patient-years. A total of 4,329 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 6.

Table 6. 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 to 3 mg/day (N=539) (%)	VRAYLAR* 4.5 to 6 mg/day (N=575) (%)	VRAYLAR* 9 to 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

Table 6. 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 to 3 mg/day (N=539) (%)	VRAYLAR* 4.5 to 6 mg/day (N=575) (%)	VRAYLAR* 9 to 12 mg/day (N=203) (%)
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
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 7.

Table 7. 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 to 6 mg/day (N=263) (%)	9 to 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

Table 7. 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 to 6 mg/day (N=263) (%)	VRAYLAR* 9 to 12 mg/day◦ (N=360) (%)
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 8.

Table 8. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in Two 6-Week and One 8-Week Bipolar Depression Trials

	Placebo (N=468) (%)	VRAYLAR 1.5 mg/day (N=470) (%)	VRAYLAR 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

Adjunctive Therapy in Major Depressive Disorder

The following findings are based on two placebo-controlled, fixed-dose 6-week trials with VRAYLAR doses of 1.5 and 3 mg once daily plus an antidepressant and one placebo-controlled, flexible-dose 8-week trial with VRAYLAR doses of (1 to 2 mg) and (2 to 4.5 mg) once daily plus an antidepressant for adjunctive therapy in MDD.

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, 6% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 3% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): Akathisia, nausea, and insomnia occurred in two 6-week, fixed-dose trials. Akathisia, restlessness, fatigue, constipation, nausea, increased appetite, dizziness, insomnia, and extrapyramidal symptoms occurred in one 8-week flexible-dose trial.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 9.

Table 9. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in Two Fixed-Dose 6-Week

Placebo-Controlled Trials of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	Placebo + ADT (N=503) (%)	VRAYLAR 1.5 mg/day + ADT (N=502) (%)	VRAYLAR 3 mg/day + ADT (N=503) (%)
Eye Disorders			
Vision Blurred	<1	<1	2
Gastrointestinal Disorders			
Nausea	3	7	6
Dry Mouth	2	3	3
Constipation	1	2	2
Vomiting	1	1	2
General Disorders			
Fatigue	2	3	3
Investigations			
Weight increased	1	2	2
Nervous System Disorders			
Akathisia[a]	2	7	10
Somnolence[b]	4	5	7
Extrapyramidal Symptoms[c]	4	5	6
Psychiatric Disorders			
Insomnia[d]	5	9	10
Restlessness	2	4	4
Anxiety	1	2	1
Skin and Subcutaneous Tissue Disorders			
Hyperhidrosis	1	1	2

Note: Figures rounded to the nearest integer

[a] **Akathisia terms:** akathisia**,** psychomotor hyperactivity, feeling jittery, nervousness, tension

[b] **Somnolence terms**: hypersomnia, sedation, lethargy, somnolence

[c] **Extrapyramidal symptoms terms**: drooling, dyskinesia, extrapyramidal disorder, hypotonia, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, oromandibular

dystonia, parkinsonism, resting tremor, restless legs syndrome, stiff leg syndrome, salivary hypersecretion, stiff tongue, tardive dyskinesia, tremor, trismus

[d]**Insomnia terms**: initial insomnia, insomnia, middle insomnia, poor sleep quality, sleep disorder, terminal insomnia

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1 mg to 2 mg per day or 2 mg to 4.5 mg per day doses are shown in Table 10.

Table 10. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in a Flexible-dose 8-Week Placebo-Controlled Trial of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	Placebo + ADT (N=266) (%)	VRAYLAR 1 to 2 mg/day + ADT (N=273) (%)	VRAYLAR 2 to 4.5 mg/day + ADT (N=273) (%)
Cardiac disorders			
Palpitations	1	2	<1
Eye disorders			
Vision blurred	1	1	4
Gastrointestinal disorders			
Nausea	5	7	13
Constipation	2	2	5
Dry mouth	3	5	4
Vomiting	<1	1	3
General disorders			
Fatigue	4	7	10
Edema	<1	2	1
Infections			
Nasopharyngitis	2	4	1
Investigations			
Increased appetite	2	2	5
Weight increased	1	2	3
Musculoskeletal and Connective Tissue disorders			
Back pain	1	2	3
Myalgia	0	1	2
Nervous System disorders			
Akathisia[a]	3	8	23
Extrapyramidal symptoms[b]	5	12	18
Somnolence[c]	6	10	11
Dizziness	2	4	5
Psychiatric disorders			
Insomnia[d]	8	14	16
Restlessness	3	8	8
Agitation	<1	<1	3
Anxiety	<1	1	3

[a] **Akathisia terms:** akathisia, feeling jittery, nervousness, tension

[b] **Extrapyramidal symptoms terms**: cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypertonia, jaw stiffness, muscle contractions involuntary, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, nuchal rigidity, parkinsonism, psychomotor retardation, reduced facial expression, resting tremor, restless legs syndrome, sensation of heaviness, salivary hypersecretion, tremor

[c] **Somnolence terms**: hypersomnia, sedation, lethargy, somnolence

[d] **Insomnia terms**: initial insomnia, insomnia, middle insomnia, terminal insomnia, sleep disorder, poor sleep quality

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, bipolar depression and adjunctive treatment of major depressive disorder 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 adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness was 17% for VRAYLAR-treated patients versus 8% for placebo-treated patients. These reactions 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 reactions led to discontinuation in 0.5% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients.

In 3-week bipolar mania trials, the incidence of reported adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for VRAYLAR-treated patients versus 12% for placebo-treated patients. These reactions 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 reactions led to discontinuation in 2% of VRAYLAR-treated patients versus 0% of placebo-treated patients.

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

In the two 6-week adjunctive treatment of major depressive disorder trials, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 6% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 0.3% of VRAYLAR-treated patients versus 0.6% of placebo-treated patients. The combined incidence of akathisia and restlessness was 12% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 2% of VRAYLAR-treated patients versus 0.4% of placebo-treated patients.

In one 8-week adjunctive treatment of major depressive disorder trial, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 12% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These reactions led to discontinuation in 1% of VRAYLAR-treated patients versus 0.4% of placebo-treated patients. The incidence of akathisia and restlessness was 22% for VRAYLAR-treated patients versus 6% for placebo-treated patients. These reactions led to discontinuation in 3% of VRAYLAR-treated patients versus 0.0% of placebo-treated patients.

Cataracts

The development of cataracts was observed in nonclinical studies *[see Nonclinical Toxicology (13.2)]*. Cataracts were reported during the premarketing clinical trials of cariprazine; however, the duration of trials was too short to assess any association to cariprazine usage.

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. VRAYLAR-treated patients' supine blood pressure increased by 0.1 to 0.3 mmHg; placebo-treated patients' supine blood pressure increased by 0.2 mmHg.

In two 6-week and one 8-week adjunctive treatment of major depressive disorder 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. At the end of the 6-week trials, VRAYLAR-treated patients' supine systolic blood pressure decreased by 0.1 to 0.7 mmHg; placebo-treated patients' supine systolic blood pressure decreased by 0.1 mmHg. VRAYLAR-treated patients' supine diastolic blood pressure increased by 0.1 mmHg and placebo-treated patients' supine diastolic blood pressure increased by 0.2 mmHg.

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 transaminase elevations of ≥3 times the upper limits of the normal reference range in two 6-week adjunctive treatment of major depressive disorder trials ranged between 0% and 1% for VRAYLAR-treated patients depending on dose group administered and 0% 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. The proportions of patients with elevations of CPK greater than 1000 U/L in two 6-week

adjunctive treatment of major depressive disorder trials ranged between 0.6% and 0.8% for VRAYLAR-treated patients versus 0% 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 5,763 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 1/1,000 patients (rare).

Gastrointestinal Disorders: ***Infrequent****: gastroesophageal reflux disease, gastritis*
Hepatobiliary Disorders: ***Rare:*** *hepatitis*
Metabolism and Nutrition Disorders: ***Frequent****: decreased appetite;* ***Rare****: hyponatremia*
Musculoskeletal and Connective Tissue Disorders: ***Rare****: rhabdomyolysis*
Nervous System Disorders: ***Rare****: ischemic stroke*
Psychiatric Disorders: ***Infrequent:*** *suicide ideation;* ***Rare****: completed suicide, suicide attempts*
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 13. 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 (2.6)]*.
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, 2.6)]*.

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 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.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. 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.

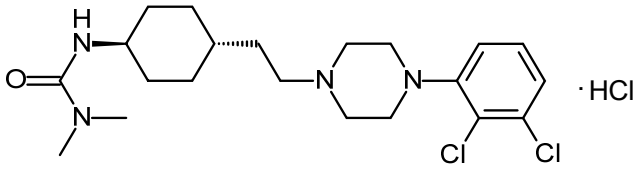
10 OVERDOSAGE

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, an atypical antipsychotic, in hydrochloride salt form. 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 $C_{21}H_{32}Cl_2N_4O$•HCl 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 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, desmethylcariprazine (DCAR) and didesmethylcariprazine (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 α_{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

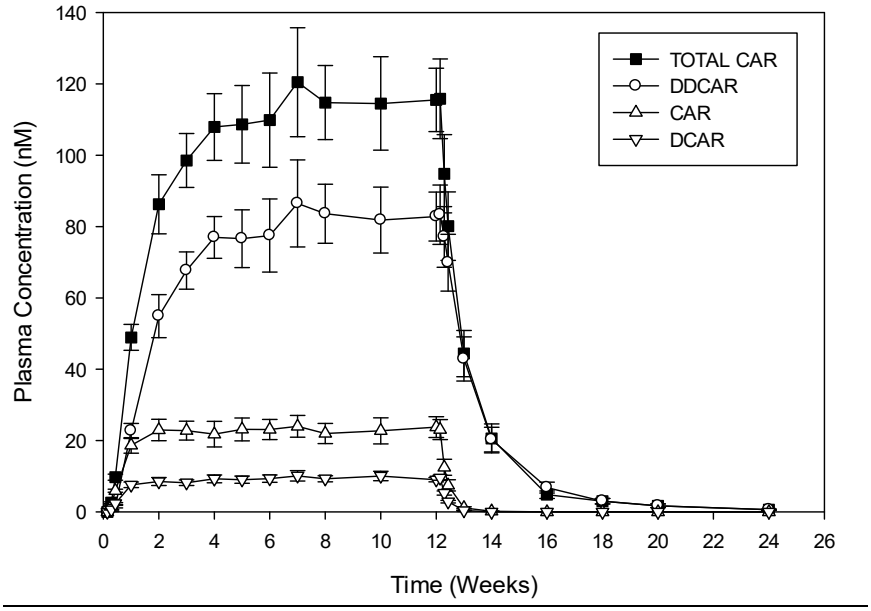
VRAYLAR activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

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 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

CYP3A4 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 (mean age of 37 years, aged 18 to 60 years; 31% were female; and 45% were Caucasian) who met Diagnostic and Statistical Manual of Mental Disorders 4th 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 14. 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.

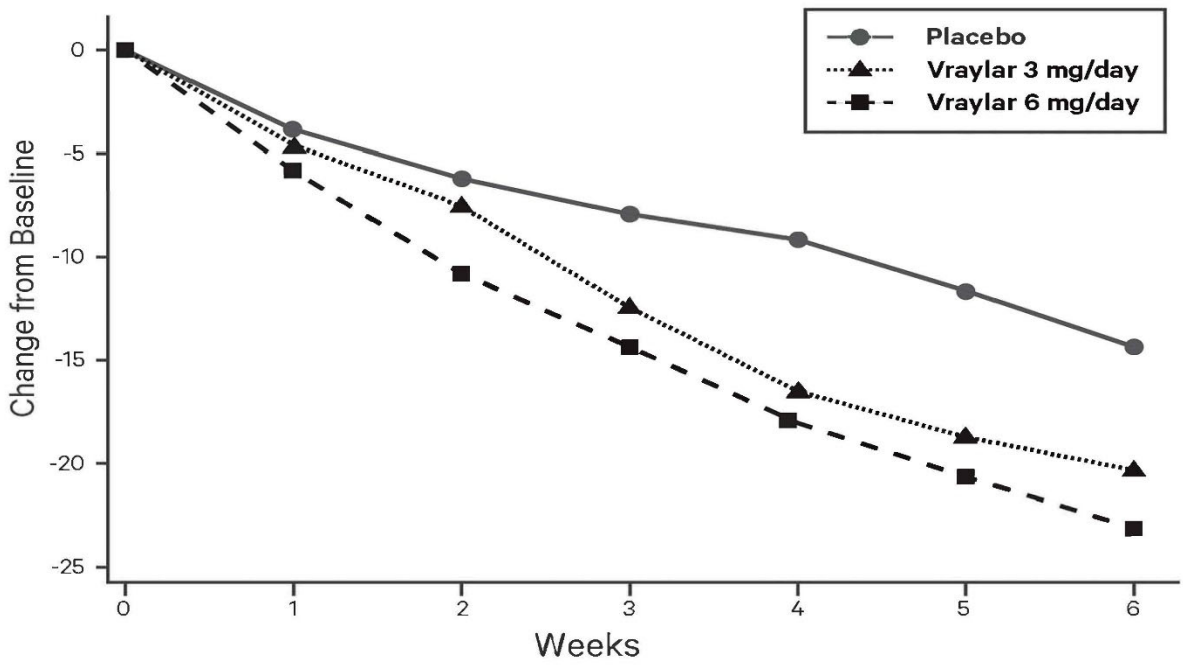
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 14. 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)

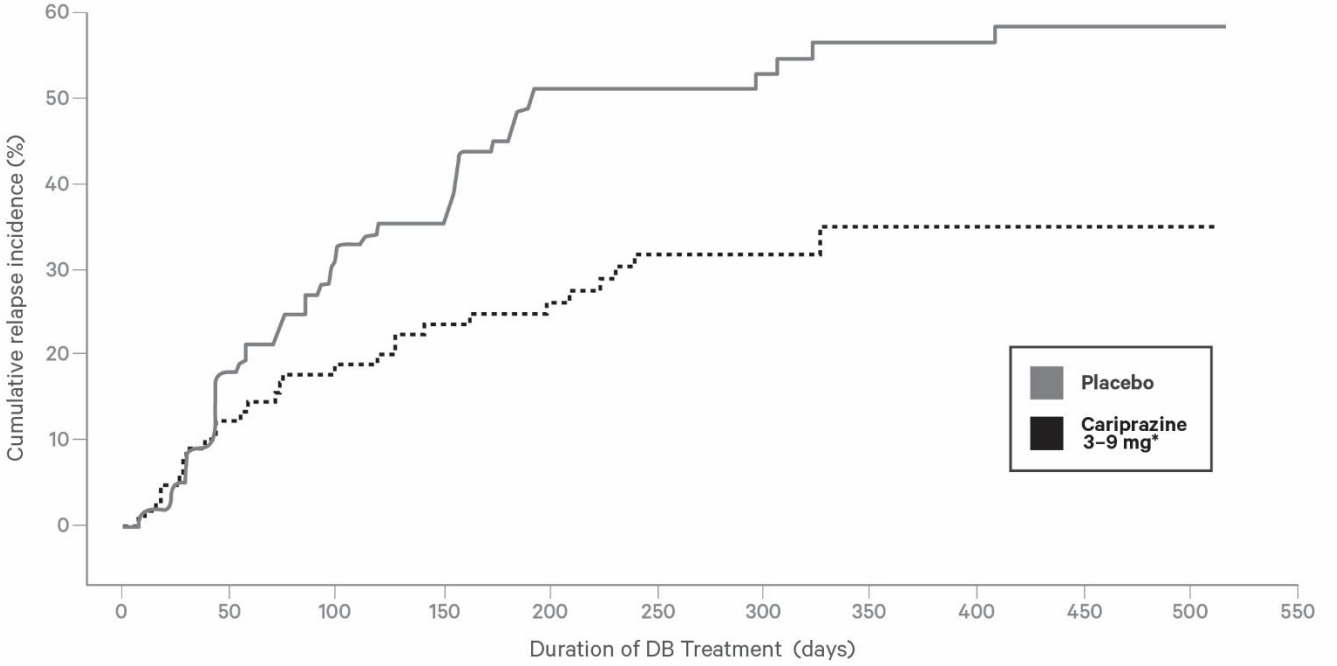


The safety and efficacy of VRAYLAR as maintenance treatment in adults with schizophrenia were demonstrated in a randomized withdrawal trial that included 200 patients meeting DSM-IV criteria for schizophrenia who were clinically stable following 20 weeks of open-label cariprazine at doses of 3 to 9 mg/day. 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; 40% were female; and 48% were Caucasian) 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 15. 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 15), and there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

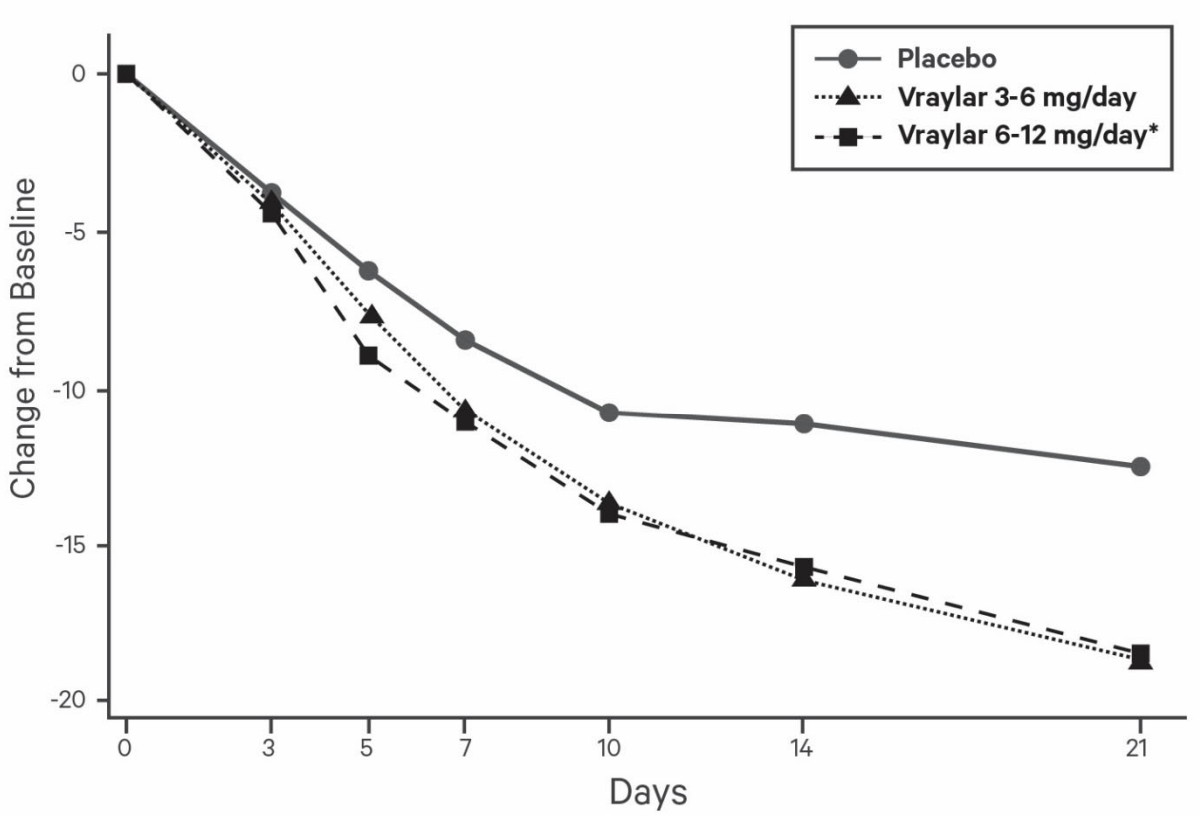
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 15. 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 43 years, range 18 to 65 years; 61% were female; and 75% were Caucasian) 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 16. 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.

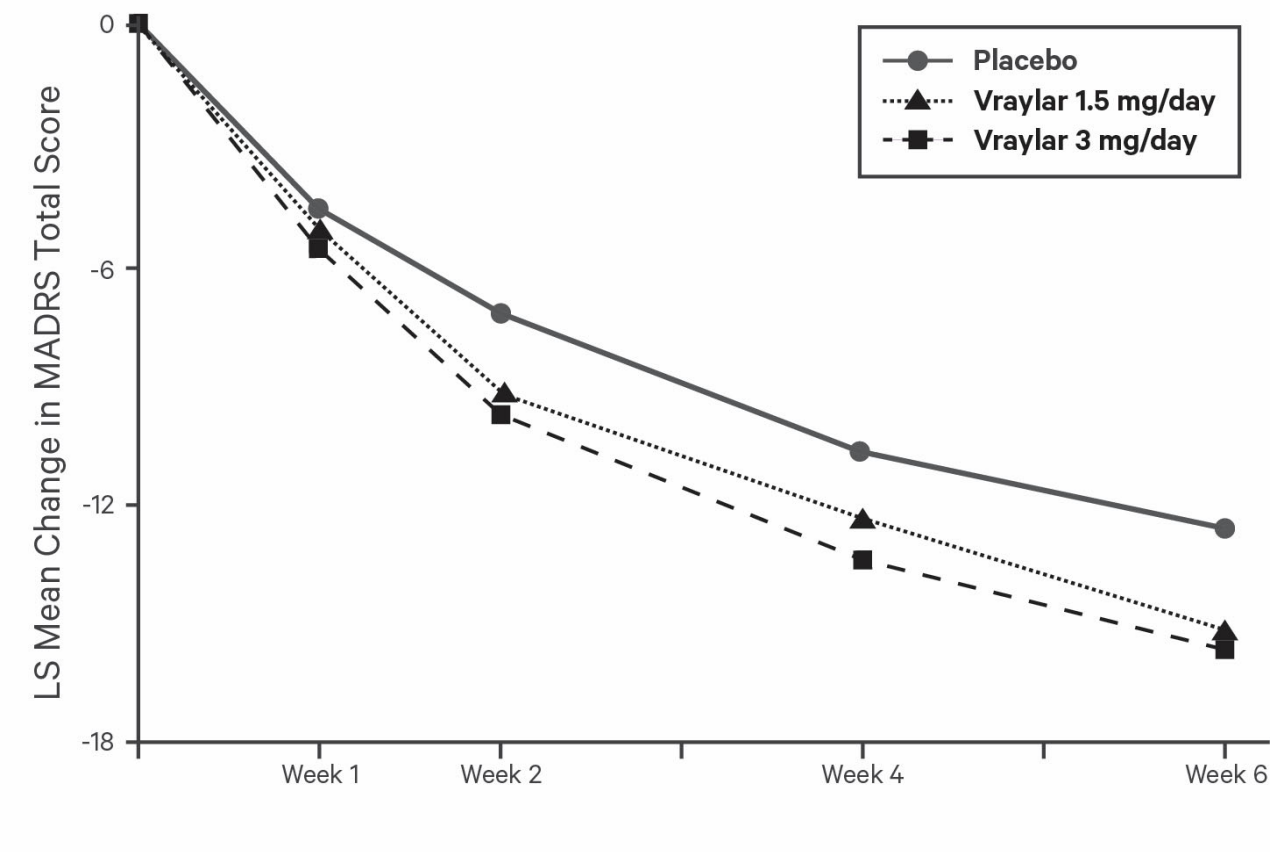
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 16. 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

14.4 Adjunctive Treatment of Major Depressive Disorder

The efficacy of VRAYLAR as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) was evaluated in 2 trials in adult patients (mean age of 45 years, range 18 to 65 years; 72% were female; and 85% were Caucasian) who met DSM-IV-TR or DSM-5 criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to 1 to 3 courses of prior antidepressant (ADT) therapy. Inadequate response during antidepressant treatment was defined as less than 50% improvement to antidepressant treatment of adequate dose and adequate duration.

In each study, the primary endpoint was change from baseline to Week 6 (Study 10) or Week 8 (Study 11) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, a 10-item clinician-rated scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms and 60 representing worst symptoms.

Study 10: In a 6-week, placebo-controlled trial (N = 751) involving two fixed doses of VRAYLAR (1.5 mg per day or 3 mg per day) + ADT, VRAYLAR 1.5 mg + ADT was superior to placebo + ADT at end of Week 6 on the MADRS total score. The treatment effect in the VRAYLAR 3 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Study 11: An 8-week, placebo-controlled trial (N = 808) involved flexible doses of VRAYLAR 1 to 2 mg per day + ADT or 2 to 4.5 mg per day + ADT. VRAYLAR 2 to 4.5 mg (mean dose was 2.6 mg) + ADT was superior to placebo + ADT at end of Week 8 on the MADRS total score. The treatment effect in the VRAYLAR 1 to 2 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Results from the primary efficacy parameters for both trials (Studies 10 and 11) are shown below in Table 17. Figure 6 below shows the time course of response based on the primary efficacy measure (MADRS total score) in Study 10.

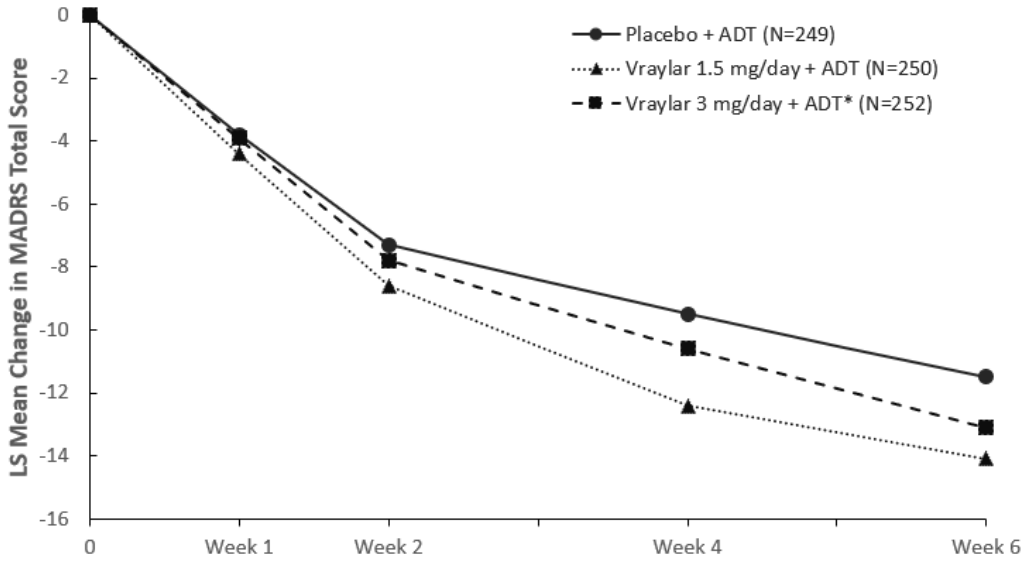
Table 17: Primary Analysis Results from Adjunctive Treatment of Major Depressive Disorder Trials

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: MADRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 10	VRAYLAR (1.5 mg/day) + ADT* (n=250)	32.8 (5.0)	-14.1 (0.7)	-2.5(-4.2, -0.9)
	VRAYLAR (3 mg/day) + ADT (n=252)	32.7 (4.9)	-13.1 (0.7)	-1.5 (-3.2, 0.1)
	Placebo + ADT (n=249)	31.9 (5.7)	-11.5 (0.7)	
Study 11	VRAYLAR (1 to 2 mg/day) + ADT (n=273)	29.0 (4.3)	-13.4 (0.5)	-0.9 (-2.4, 0.6)
	VRAYLAR (2 to 4.5 mg/day) + ADT* (n=271)	29.3 (4.1)	-14.6 (0.6)	-2.2 (-3.7, -0.6)
	Placebo + ADT (n=264)	28.9 (4.3)	-12.5 (0.5)	

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

Examination of population subgroups based on age, sex, and race did not suggest any clear evidence of differential responsiveness.

Figure 6. LS Mean‡ Change from Baseline to Week 6 in MADRS Total Score in Adjunctive Treatment of Major Depressive Disorder (Study 10)



Placebo + ADT (N)	249	246	246	238	231
Vraylar 1.5 mg/day+ADT (N)	250	250	242	237	231
Vraylar 3 mg/day+ADT* (N)	252	252	245	235	223

‡ LS Mean: least-squares mean
* Dose was not statistically significant.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VRAYLAR (cariprazine) capsules are supplied as follows:

Capsule Strength	Imprint Codes	Capsule Color	Package Configuration	NDC Code
1.5 mg	FL 1.5	White cap and body	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	Green to blue-green cap and white body	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	Green to blue-green cap and body	Bottle of 30	61874-145-30
			Bottle of 90	61874-145-90
6 mg	FL 6	Purple cap and white body	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).

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.

v5.0USPI115

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 and actions.** VRAYLAR and antidepressant medicines may increase suicidal thoughts or actions in some children and young adults **especially within the first few months of treatment or when the dose is changed.**
  - Depression and other mental illnesses are the most important causes of suicidal thoughts and 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 VRAYLAR or the 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, or if you develop suicidal thoughts or actions.
  - 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)
- along with antidepressant medicines to treat major depressive disorder (MDD)

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. Taking VRAYLAR during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. 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/clinical-and-research-programs/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.
- Take VRAYLAR 1 time each day with or without food.
- If you take too much VRAYLAR, call your healthcare provider or Poison Control Center at 1-800-222-1222 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.
  - **weight 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).**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See "What should I avoid while taking VRAYLAR?"
- **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, indigestion, constipation, feeling tired, trouble sleeping, increased appetite, and dizziness

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

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

Colorants include: black iron oxide, FD&C Blue 1, 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. Revised 12/2022

Proposed Package Insert

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----------

Indications and Usage (1)	12/2022
Dosage and Administration (2.5)	12/2022
Warnings and Precautions (5.7, 5.12)	12/2022

----------INDICATIONS AND USAGE----------
VRAYLAR is an atypical antipsychotic indicated for:
- 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)
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) 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
Adjunctive therapy to antidepressants for MDD (2.5)	1.5 mg daily	1.5 mg or 3 mg daily

- Schizophrenia and Bipolar Mania: Maximum recommended daily dosage is 6 mg. 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: Maximum recommended daily dosage is 3 mg (2.4)
- Adjunctive therapy for treatment of MDD: Maximum recommended daily dosage is 3 mg (2.5)

----------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 and Syncope*: 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
- Adjunctive treatment of MDD: akathisia, restlessness, fatigue, constipation, nausea, insomnia, increased appetite, dizziness, and extrapyramidal symptoms

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Strong CYP3A4 inhibitors: Reduce VRAYLAR dosage by half (2.6, 7.1)
- CYP3A4 inducers: Concomitant use is not recommended (2.6, 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: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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:

- 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)]*
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults *[see Clinical Studies (14.4)]*

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), Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage in Schizophrenia

The starting dosage of VRAYLAR is 1.5 mg once daily. The recommended dosage range is 1.5 mg to 6 mg once 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 Recommended Dosage in Manic or Mixed Episodes Associated with Bipolar I Disorder

The starting dosage of VRAYLAR is 1.5 mg once daily and should be increased to 3 mg once daily on Day 2. The recommended dosage range is 3 mg to 6 mg once daily. 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 Recommended Dosage in Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The starting dosage 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 Recommended Dosage for Adjunctive Therapy to Antidepressants in Treatment of Major Depressive Disorder

The starting dosage 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. In clinical trials, dosage titration at intervals of less than 14 days resulted in a higher incidence of adverse reactions *[see Adverse Reactions* (*6.1)*]. Maximum recommended dosage is 3 mg once daily.

2.6 Dosage Adjustments for CYP3A4 Inhibitors and Inducers

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)]*.

2.7 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 reactions 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 patients 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 reactions 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. There have been reports of hyperglycemia in patients treated with VRAYLAR. Although all 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%).

Adjunctive Treatment of Major Depressive Disorder

In two 6-week placebo-controlled trials of adult patients with major depressive disorder, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) was greatest in the VRAYLAR 3 mg per day + antidepressant therapy arm (3.2%) compared with those taking VRAYLAR 1.5 mg per day + antidepressant therapy (2%) or those placebo-treated (1.3%). The proportion of patients with shifts from normal to borderline (≥100 and <126 mg/dL) or from borderline to high were similar in patients treated with VRAYLAR and placebo. In a long-term, open-label adjunctive treatment of MDD study, 7% patients with normal hemoglobin A1c baseline values developed elevated levels (> 6%).

In one 8-week placebo-controlled trial of adult patients with major depressive disorder, the changes from baseline to end of the trial in fasting glucose were similar among the VRAYLAR and placebo + antidepressant therapy treatment groups. During the 8-week trial, serum insulin levels increased by 12 pmol/L in the VRAYLAR 1 mg to 2 mg per day group, 20 pmol/L in the VRAYLAR 2 mg to 4.5 mg per day group, and 8.5 pmol/L in the placebo group.

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.

Adjunctive Treatment of Major Depressive Disorder
In two 6-week placebo-controlled trials of adult patients with major depressive disorder, the proportion of patients with shifts in total cholesterol, fasting LDL, HDL, and fasting 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, 4, and 5 show the change in body weight occurring from baseline to endpoint in 6-week trials of schizophrenia, 3-week bipolar mania trials, 6-week and 8-week bipolar depression trials, and 6-week and 8-week trials of adjunctive treatment for major depressive disorder, 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%

Table 5. Change in Body Weight (kg) in two 6-Week and one 8-Week Adjunctive Treatment for Major Depressive Disorder Trials

		VRAYLAR	
6-week Trials	Placebo +ADT (N=503)	1.5 mg/day +ADT (N=502)	3 mg/day +ADT (N=503)
Mean Change at Endpoint	+0.2	+0.7	+0.7
Proportion of Patients with Weight Increase (≥7%)	1%	2%	2%
8-week Trial	Placebo + ADT (N=266)	1 to 2 mg/day + ADT (N=273)	2 to 4.5 mg/day + ADT (N=273)
Mean Change at Endpoint	0	+0.9	+0.9
Proportion of Patients with Weight Increase (≥7%)	2%	2%	3%

In the long-term, open-label adjunctive treatment of MDD trial, 2 patients (0.6%) discontinued due to weight increase. VRAYLAR was associated with mean change from baseline in weight of 1.7 kg at Week 26. In the long-term, open-label adjunctive treatment of MDD trial, 19% of patients demonstrated a ≥7% increase in body weight, and 5% demonstrated a ≥7% decrease in body weight.

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, may cause somnolence and 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. In two 6-week and one 8-week trials of depressive episodes of bipolar I disorder, VRAYLAR-treated patients reported 7% somnolence and 4% in the placebo-treated patients. In 6-week adjunctive treatment of major depressive disorder trials, somnolence was reported in 6% of VRAYLAR-treated patients compared to 4% of placebo-treated patients. In one 8-week adjunctive treatment of major depressive disorder trial, somnolence was reported in 11% of VRAYLAR-treated patients compared to 6% 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 6,722 adult patients exposed to one or more doses of VRAYLAR for the treatment of schizophrenia, manic or mixed episodes associated with bipolar I disorder, bipolar depression, and adjunctive treatment of major depressive disorder in placebo-controlled studies. This experience corresponds with a total experience of 1,182.8 patient-years. A total of 4,329 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 6.

Table 6. 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 to 3 mg/day (N=539) (%)	VRAYLAR* 4.5 to 6 mg/day (N=575) (%)	VRAYLAR* 9 to 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

Table 6. 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 to 3 mg/day (N=539) (%)	VRAYLAR* 4.5 to 6 mg/day (N=575) (%)	VRAYLAR* 9 to 12 mg/day (N=203) (%)
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
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 7.

Table 7. 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 to 6 mg/day (N=263) (%)	VRAYLAR* 9 to 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

Table 7. 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 to 6 mg/day (N=263) (%)	VRAYLAR* 9 to 12 mg/day° (N=360) (%)
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 8.

Table 8. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in Two 6-Week and One 8-Week Bipolar Depression Trials

	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

Adjunctive Therapy in Major Depressive Disorder

The following findings are based on two placebo-controlled, fixed-dose 6-week trials with VRAYLAR doses of 1.5 and 3 mg once daily plus an antidepressant and one placebo-controlled, flexible-dose 8-week trial with VRAYLAR doses of (1 to 2 mg) and (2 to 4.5 mg) once daily plus an antidepressant for adjunctive therapy in MDD.

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, 6% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 3% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): Akathisia, nausea, and insomnia occurred in two 6-week, fixed-dose trials. Akathisia, restlessness, fatigue, constipation, nausea, increased appetite, dizziness, insomnia, and extrapyramidal symptoms occurred in one 8-week flexible-dose trial.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 9.

Table 9. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in Two Fixed-Dose 6-Week

Placebo-Controlled Trials of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	Placebo + ADT (N=503) (%)	VRAYLAR 1.5 mg/day + ADT (N=502) (%)	VRAYLAR 3 mg/day + ADT (N=503) (%)
Eye Disorders			
Vision Blurred	<1	<1	2
Gastrointestinal Disorders			
Nausea	3	7	6
Dry Mouth	2	3	3
Constipation	1	2	2
Vomiting	1	1	2
General Disorders			
Fatigue	2	3	3
Investigations			
Weight increased	1	2	2
Nervous System Disorders			
Akathisia[a]	2	7	10
Somnolence[b]	4	5	7
Extrapyramidal Symptoms[c]	4	5	6
Psychiatric Disorders			
Insomnia[d]	5	9	10
Restlessness	2	4	4
Anxiety	1	2	1
Skin and Subcutaneous Tissue Disorders			
Hyperhidrosis	1	1	2

Note: Figures rounded to the nearest integer

[a] **Akathisia terms:** akathisia**,** psychomotor hyperactivity, feeling jittery, nervousness, tension

[b] **Somnolence terms**: hypersomnia, sedation, lethargy, somnolence

[c] **Extrapyramidal symptoms terms**: drooling, dyskinesia, extrapyramidal disorder, hypotonia, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, oromandibular

dystonia, parkinsonism, resting tremor, restless legs syndrome, stiff leg syndrome, salivary hypersecretion, stiff tongue, tardive dyskinesia, tremor, trismus

[d] **Insomnia terms**: initial insomnia, insomnia, middle insomnia, poor sleep quality, sleep disorder, terminal insomnia

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1 mg to 2 mg per day or 2 mg to 4.5 mg per day doses are shown in Table 10.

Table 10. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in a Flexible-dose 8-Week Placebo-Controlled Trial of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	**Placebo + ADT** (N=266) (%)	**VRAYLAR 1 to 2 mg/day + ADT** (N=273) (%)	**VRAYLAR 2 to 4.5 mg/day + ADT** (N=273) (%)
Cardiac disorders			
Palpitations	1	2	<1
Eye disorders			
Vision blurred	1	1	4
Gastrointestinal disorders			
Nausea	5	7	13
Constipation	2	2	5
Dry mouth	3	5	4
Vomiting	<1	1	3
General disorders			
Fatigue	4	7	10
Edema	<1	2	1
Infections			
Nasopharyngitis	2	4	1
Investigations			
Increased appetite	2	2	5
Weight increased	1	2	3
Musculoskeletal and Connective Tissue disorders			
Back pain	1	2	3
Myalgia	0	1	2
Nervous System disorders			
Akathisia[a]	3	8	23
Extrapyramidal symptoms[b]	5	12	18
Somnolence[c]	6	10	11
Dizziness	2	4	5
Psychiatric disorders			
Insomnia[d]	8	14	16
Restlessness	3	8	8
Agitation	<1	<1	3
Anxiety	<1	1	3

[a] **Akathisia terms:** akathisia, feeling jittery, nervousness, tension

[b] **Extrapyramidal symptoms terms**: cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypertonia, jaw stiffness, muscle contractions involuntary, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, nuchal rigidity, parkinsonism, psychomotor retardation, reduced facial expression, resting tremor, restless legs syndrome, sensation of heaviness, salivary hypersecretion, tremor

[c] **Somnolence terms**: hypersomnia, sedation, lethargy, somnolence

[d] **Insomnia terms**: initial insomnia, insomnia, middle insomnia, terminal insomnia, sleep disorder, poor sleep quality

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, bipolar depression and adjunctive treatment of major depressive disorder 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 adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness was 17% for VRAYLAR-treated patients versus 8% for placebo-treated patients. These reactions 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 reactions led to discontinuation in 0.5% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients.

In 3-week bipolar mania trials, the incidence of reported adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for VRAYLAR-treated patients versus 12% for placebo-treated patients. These reactions 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 reactions led to discontinuation in 2% of VRAYLAR-treated patients versus 0% of placebo-treated patients.

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

In the two 6-week adjunctive treatment of major depressive disorder trials, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 6% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 0.3% of VRAYLAR-treated patients versus 0.6% of placebo-treated patients. The combined incidence of akathisia and restlessness was 12% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 2% of VRAYLAR-treated patients versus 0.4% of placebo-treated patients.

In one 8-week adjunctive treatment of major depressive disorder trial, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 12% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These reactions led to discontinuation in 1% of VRAYLAR-treated patients versus 0.4% of placebo-treated patients. The incidence of akathisia and restlessness was 22% for VRAYLAR-treated patients versus 6% for placebo-treated patients. These reactions led to discontinuation in 3% of VRAYLAR-treated patients versus 0.0% of placebo-treated patients.

Cataracts

The development of cataracts was observed in nonclinical studies *[see Nonclinical Toxicology (13.2)]*. Cataracts were reported during the premarketing clinical trials of cariprazine; however, the duration of trials was too short to assess any association to cariprazine usage.

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)	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. VRAYLAR-treated patients' supine blood pressure increased by 0.1 to 0.3 mmHg; placebo-treated patients' supine blood pressure increased by 0.2 mmHg.

In two 6-week and one 8-week adjunctive treatment of major depressive disorder 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. At the end of the 6-week trials, VRAYLAR-treated patients' supine systolic blood pressure decreased by 0.1 to 0.7 mmHg; placebo-treated patients' supine systolic blood pressure decreased by 0.1 mmHg. VRAYLAR-treated patients' supine diastolic blood pressure increased by 0.1 mmHg and placebo-treated patients' supine diastolic blood pressure increased by 0.2 mmHg.

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 transaminase elevations of ≥3 times the upper limits of the normal reference range in two 6-week adjunctive treatment of major depressive disorder trials ranged between 0% and 1% for VRAYLAR-treated patients depending on dose group administered and 0% 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. The proportions of patients with elevations of CPK greater than 1000 U/L in two 6-week

adjunctive treatment of major depressive disorder trials ranged between 0.6% and 0.8% for VRAYLAR-treated patients versus 0% 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 5,763 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 1/1,000 patients (rare).

Gastrointestinal Disorders: ***Infrequent****: gastroesophageal reflux disease, gastritis*
Hepatobiliary Disorders: ***Rare:*** *hepatitis*
Metabolism and Nutrition Disorders: ***Frequent****: decreased appetite;* ***Rare****: hyponatremia*
Musculoskeletal and Connective Tissue Disorders: ***Rare****: rhabdomyolysis*
Nervous System Disorders: ***Rare****: ischemic stroke*
Psychiatric Disorders: ***Infrequent:*** *suicide ideation;* ***Rare****: completed suicide, suicide attempts*
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 13. 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 (2.6)]*.
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, 2.6)]*.

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 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.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. 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 $\geq$ 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

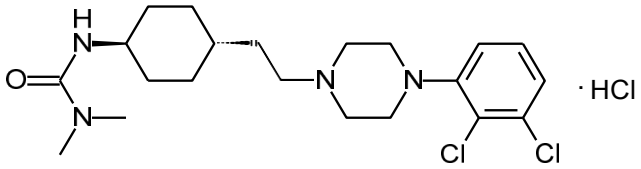
In pre-marketing clinical trials involving VRAYLAR in approximately 5000 patients or healthy subjects, accidental acute overdosage (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

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, an atypical antipsychotic, in hydrochloride salt form. 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 $C_{21}H_{32}Cl_2N_4O$•HCl 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 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, desmethylcariprazine (DCAR) and didesmethylcariprazine (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 α_{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

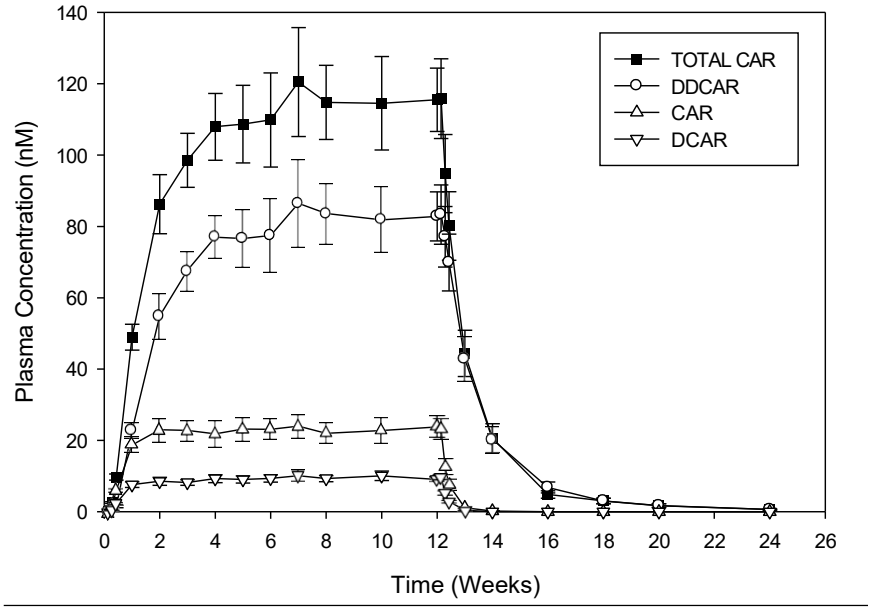
VRAYLAR activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

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 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

CYP3A4 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 (mean age of 37 years, aged 18 to 60 years; 31% were female; and 45% were Caucasian) who met Diagnostic and Statistical Manual of Mental Disorders 4th 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 14. 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.

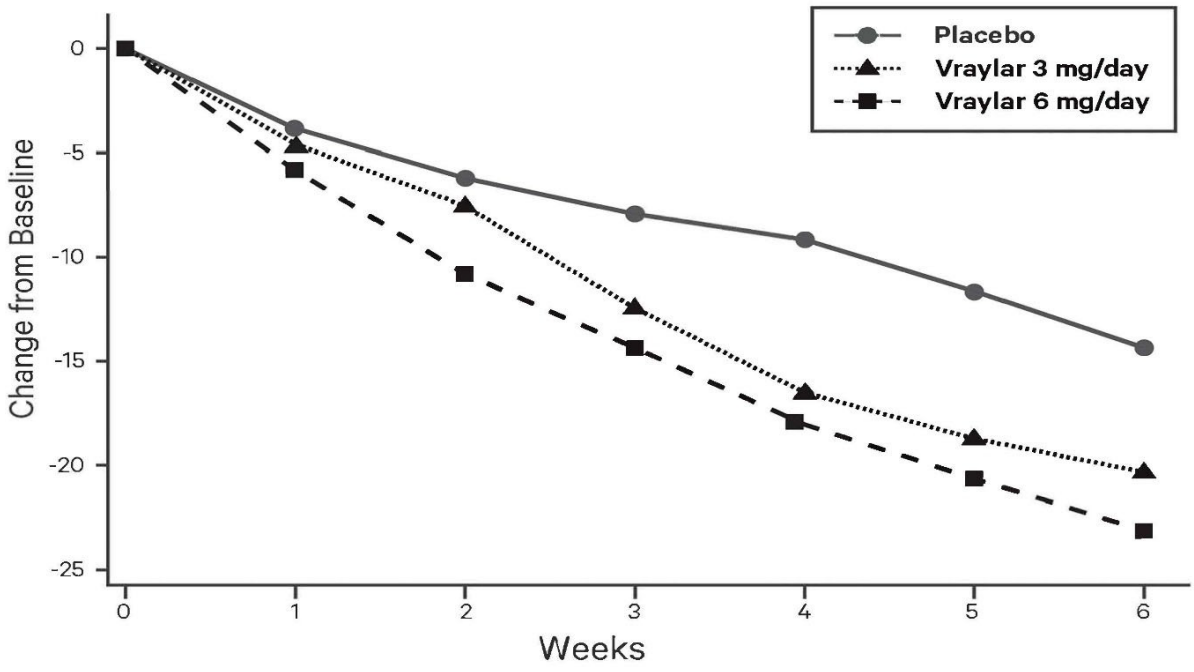
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 14. 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)

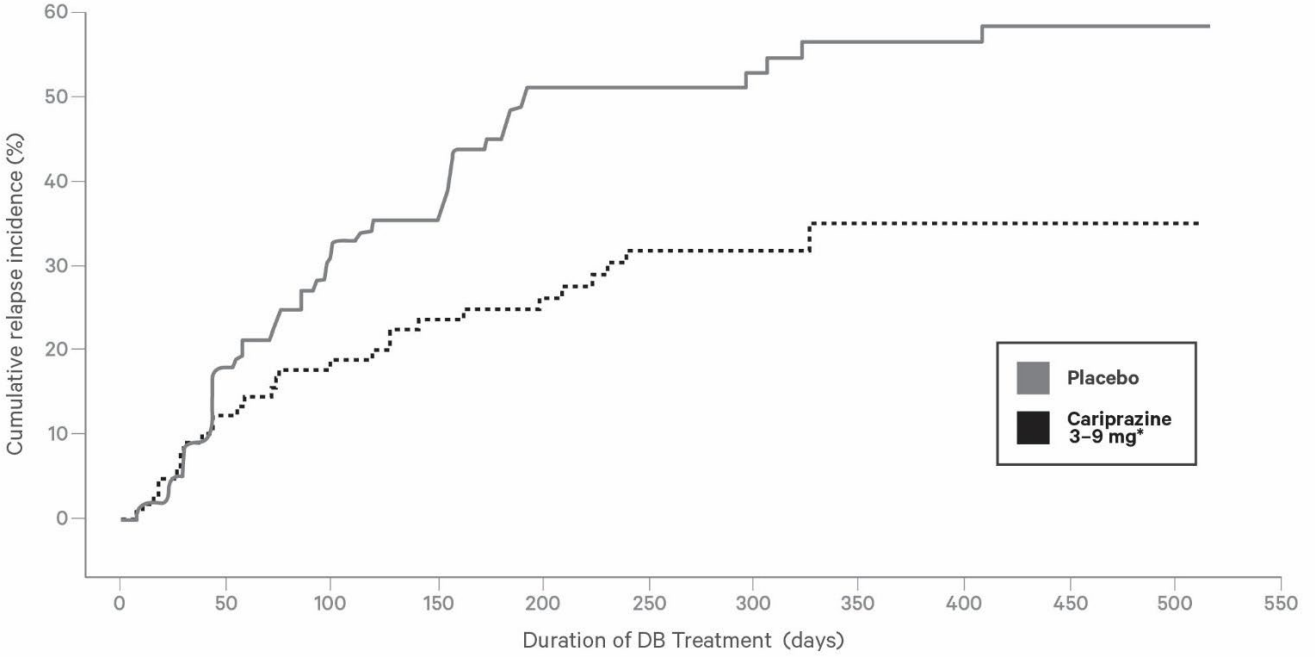


The safety and efficacy of VRAYLAR as maintenance treatment in adults with schizophrenia were demonstrated in a randomized withdrawal trial that included 200 patients meeting DSM-IV criteria for schizophrenia who were clinically stable following 20 weeks of open-label cariprazine at doses of 3 to 9 mg/day. 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; 40% were female; and 48% were Caucasian) 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 15. 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 15), and there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

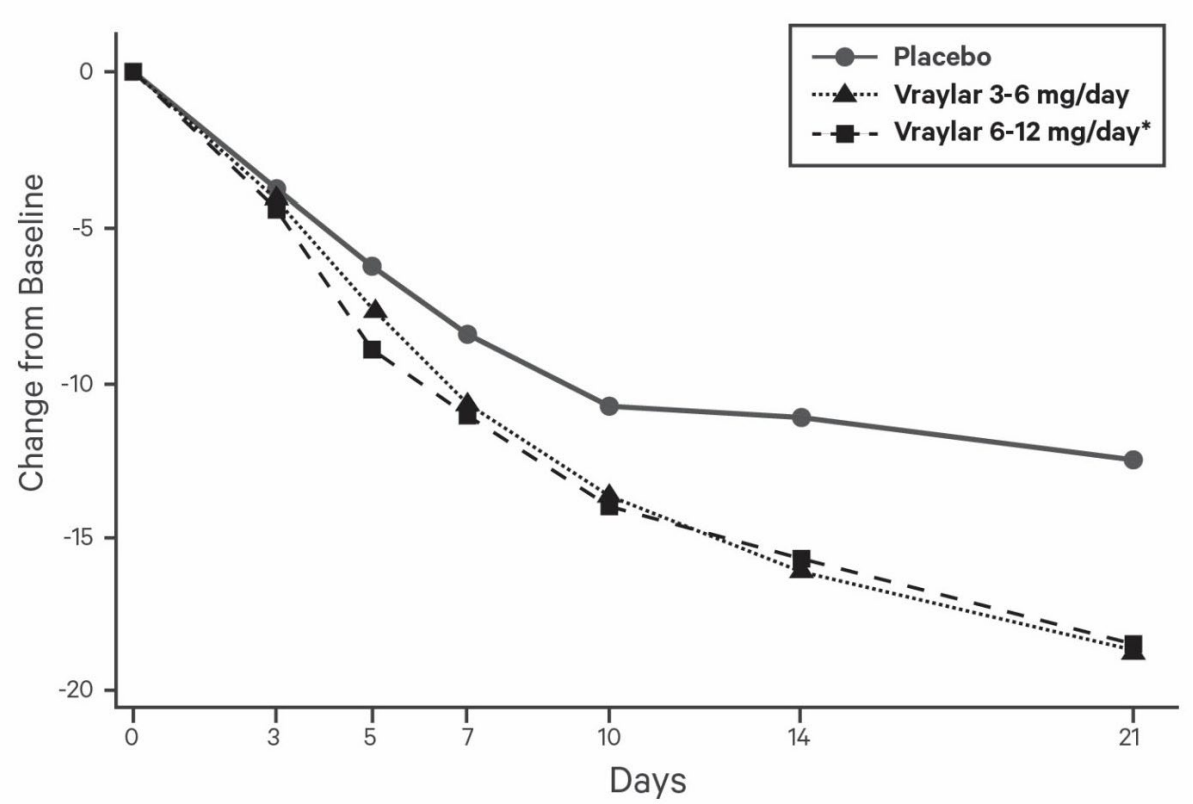
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 15. 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 43 years, range 18 to 65 years; 61% were female; and 75% were Caucasian) 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 16. 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.

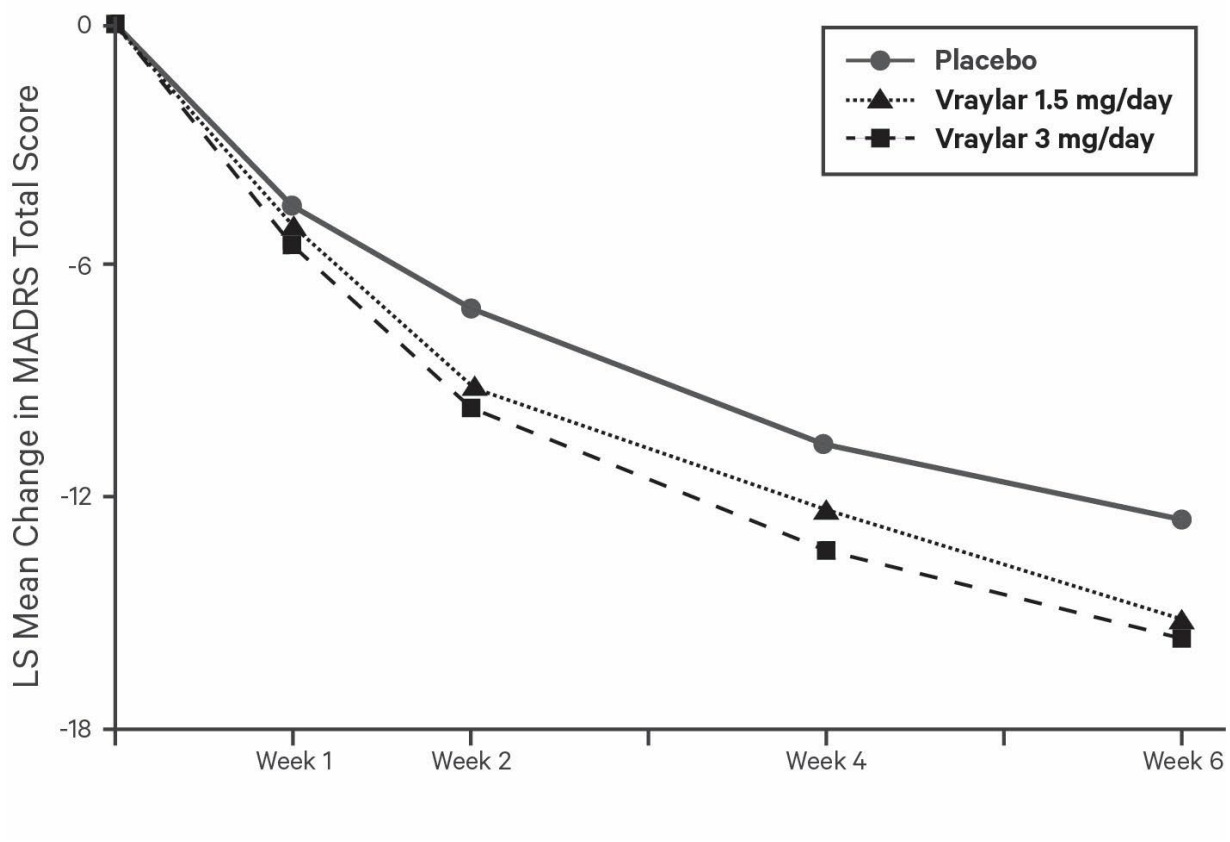
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 16. 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

14.4 Adjunctive Treatment of Major Depressive Disorder

The efficacy of VRAYLAR as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) was evaluated in 2 trials in adult patients (mean age of 45 years, range 18 to 65 years; 72% were female; and 85% were Caucasian) who met DSM-IV-TR or DSM-5 criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to 1 to 3 courses of prior antidepressant (ADT) therapy. Inadequate response during antidepressant treatment was defined as less than 50% improvement to antidepressant treatment of adequate dose and adequate duration.

In each study, the primary endpoint was change from baseline to Week 6 (Study 10) or Week 8 (Study 11) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, a 10-item clinician-rated scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms and 60 representing worst symptoms.

Study 10: In a 6-week, placebo-controlled trial (N = 751) involving two fixed doses of VRAYLAR (1.5 mg per day or 3 mg per day) + ADT, VRAYLAR 1.5 mg + ADT was superior to placebo + ADT at end of Week 6 on the MADRS total score. The treatment effect in the VRAYLAR 3 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Study 11: An 8-week, placebo-controlled trial (N = 808) involved flexible doses of VRAYLAR 1 to 2 mg per day + ADT or 2 to 4.5 mg per day + ADT. VRAYLAR 2 to 4.5 mg (mean dose was 2.6 mg) + ADT was superior to placebo + ADT at end of Week 8 on the MADRS total score. The treatment effect in the VRAYLAR 1 to 2 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Results from the primary efficacy parameters for both trials (Studies 10 and 11) are shown below in Table 17. Figure 6 below shows the time course of response based on the primary efficacy measure (MADRS total score) in Study 10.

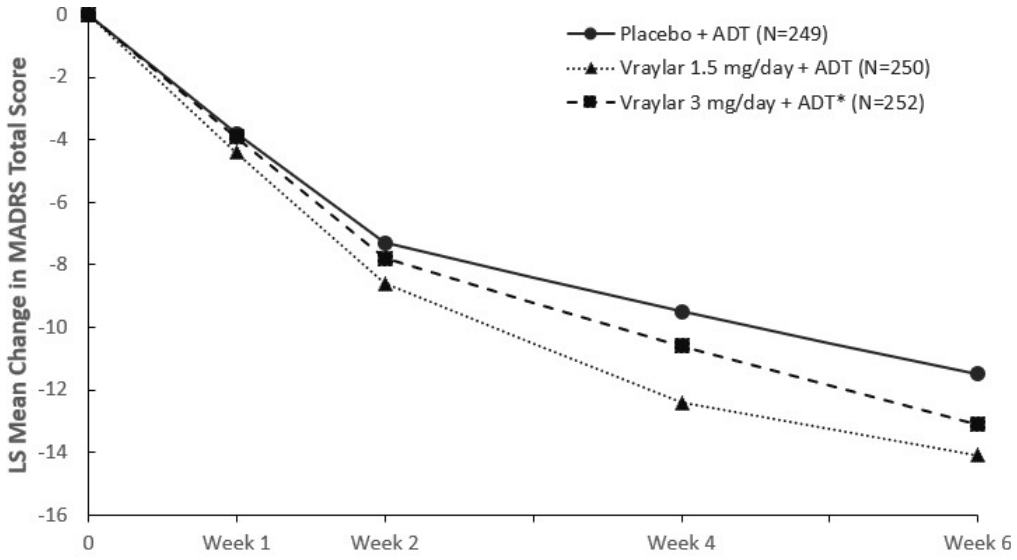
Table 17: Primary Analysis Results from Adjunctive Treatment of Major Depressive Disorder Trials

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: MADRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 10	VRAYLAR (1.5 mg/day) + ADT* (n=250)	32.8 (5.0)	-14.1 (0.7)	-2.5(-4.2, -0.9)
	VRAYLAR (3 mg/day) + ADT (n=252)	32.7 (4.9)	-13.1 (0.7)	-1.5 (-3.2, 0.1)
	Placebo + ADT (n=249)	31.9 (5.7)	-11.5 (0.7)	
Study 11	VRAYLAR (1 to 2 mg/day) + ADT (n=273)	29.0 (4.3)	-13.4 (0.5)	-0.9 (-2.4, 0.6)
	VRAYLAR (2 to 4.5 mg/day) + ADT* (n=271)	29.3 (4.1)	-14.6 (0.6)	-2.2 (-3.7, -0.6)
	Placebo + ADT (n=264)	28.9 (4.3)	-12.5 (0.5)	

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

Examination of population subgroups based on age, sex, and race did not suggest any clear evidence of differential responsiveness.

Figure 6. LS Mean‡ Change from Baseline to Week 6 in MADRS Total Score in Adjunctive Treatment of Major Depressive Disorder (Study 10)



Placebo + ADT (N)	249	246	246	238	231
Vraylar 1.5 mg/day+ADT (N)	250	250	242	237	231
Vraylar 3 mg/day+ADT* (N)	252	252	245	235	223

‡ LS Mean: least-squares mean
* Dose was not statistically significant.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VRAYLAR (cariprazine) capsules are supplied as follows:

Capsule Strength	Imprint Codes	Capsule Color	Package Configuration	NDC Code
1.5 mg	FL 1.5	White cap and body	Bottle of 30	42067-290-30
3 mg	FL 3	Green to blue-green cap and white body	Bottle of 30	42067-292-30
4.5 mg	FL 4.5	Green to blue-green cap and body	Bottle of 30	42067-294-30
6 mg	FL 6	Purple cap and white body	Bottle of 30	42067-296-30

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.

This drug was imported from Canada without the authorization of Allergan, USA, Inc. under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17. PATIENT COUNSELING INFORMATION

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

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.

v5.0USPI115

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 and actions.** VRAYLAR and antidepressant medicines may increase suicidal thoughts or actions in some children and young adults **especially within the first few months of treatment or when the dose is changed.**
  - Depression and other mental illnesses are the most important causes of suicidal thoughts and 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 VRAYLAR or the 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, or if you develop suicidal thoughts or actions.
  - 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)
- along with antidepressant medicines to treat major depressive disorder (MDD)

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. Taking VRAYLAR during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. 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/clinical-and-research-programs/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.
- Take VRAYLAR 1 time each day with or without food.
- If you take too much VRAYLAR, call your healthcare provider or Poison Control Center at 1-800-222-1222 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.
  - **weight 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).**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See "What should I avoid while taking VRAYLAR?"
- **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, indigestion, constipation, feeling tired, trouble sleeping, increased appetite, and dizziness

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

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

Colorants include: black iron oxide, FD&C Blue 1, 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. Revised 12/2022

This drug was imported from Canada without the authorization of Allergan, USA, Inc. under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

----------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
- Adjunctive treatment of MDD: akathisia, restlessness, fatigue, constipation, nausea, insomnia, increased appetite, dizziness, 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*.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VRAYLAR (cariprazine) capsules are supplied as follows:

Capsule Strength	Imprint Codes	Capsule Color	Package Configuration	NDC Code
1.5 mg	FL 1.5	White cap and body	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	Green to blue-green cap and white body	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	Green to blue-green cap and body	Bottle of 30	61874-145-30
			Bottle of 90	61874-145-90
6 mg	FL 6	Purple cap and white body	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.

What are the ingredients in VRAYLAR?
Active ingredient: cariprazine
Inactive ingredients: gelatin, magnesium stearate, pregelatinized starch, shellac, and titanium dioxide.
Colorants include: black iron oxide, FD&C Blue 1, 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. Revised 12/2022

FLSIP

----------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
- Adjunctive treatment of MDD: akathisia, restlessness, fatigue, constipation, nausea, insomnia, increased appetite, dizziness, and extrapyramidal symptoms

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VRAYLAR (cariprazine) capsules are supplied as follows:

Capsule Strength	Imprint Codes	Capsule Color	Package Configuration	NDC Code
1.5 mg	FL 1.5	White cap and body	Bottle of 30	42067-290-30
3 mg	FL 3	Green to blue-green cap and white body	Bottle of 30	42067-292-30
4.5 mg	FL 4.5	Green to blue-green cap and body	Bottle of 30	42067-294-30
6 mg	FL 6	Purple cap and white body	Bottle of 30	42067-296-30

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.

This drug was imported from Canada without the authorization of Allergan, USA, Inc. under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

What are the ingredients in VRAYLAR?
Active ingredient: cariprazine
Inactive ingredients: gelatin, magnesium stearate, pregelatinized starch, shellac, and titanium dioxide.
Colorants include: black iron oxide, FD&C Blue 1, 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 andDrug Administration. Revised 12/2022

This drug was imported from Canada without the authorization of Allergan, USA, Inc. under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	61874-115-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	42067-290-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	61874-130-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	42067-292-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	61874-145-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	42067-294-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	61874-160-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	42067-296-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	61874-115-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	42067-290-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	61874-130-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	42067-292-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	61874-145-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	42067-294-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	61874-160-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	42067-296-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	61874-115-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	42067-290-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	61874-130-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	42067-292-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	61874-145-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	42067-294-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	61874-160-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	42067-296-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	61874-115-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	42067-290-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	61874-130-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	42067-292-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	61874-145-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	42067-294-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	61874-160-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	42067-296-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)

CANADIAN TO FDA Comparison

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	61874-115-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	1.5 mg	42067-290-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	61874-130-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	3 mg	42067-292-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	61874-145-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	4.5 mg	42067-294-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)
12/21/2022	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	61874-160-30	204370	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	Aug-23	VRAYLAR	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)	6 mg	42067-296-30	LifeScience Logistics, LLC	Allergan USA, Inc.	Madison, NJ 07940	CARIPRAZINE (CARIPRAZINE HYDROCHLORIDE)

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **VRAYLAR®**

Cariprazine capsules

Capsules, 1.5 mg, 3 mg, 4.5 mg and 6 mg cariprazine (as cariprazine hydrochloride), oral

ATC Code: N05AX15

Antipsychotic agent

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, Quebec
H4S 1Z1

Date of Initial Authorization:
APR 22, 2022

Date of Revision:
SEP 07, 2022

Submission Control Number: 266582

RECENT MAJOR LABEL CHANGES

Not applicable

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Schizophrenia

VRAYLAR (cariprazine) is indicated for:

- the treatment of schizophrenia in adults.

In controlled clinical trials, VRAYLAR was found to improve both positive and negative symptoms.

Bipolar I disorder

VRAYLAR is indicated as monotherapy for:

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

The efficacy of VRAYLAR for long-term use has not been systematically evaluated in controlled studies for bipolar mania and depression (See 14 CLINICAL TRIALS). The physician who elects to use VRAYLAR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: VRAYLAR is not indicated in elderly patients with dementia. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX. The safety and efficacy of VRAYLAR have not been systematically evaluated in patients 65 years of age or older. Caution should be used when treating geriatric patients. See 7.1.4 Geriatrics and 10.3 Pharmacokinetics.

2 CONTRAINDICATIONS

VRAYLAR is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- With concomitant use of strong and moderate CYP3A4 inhibitors. See 9.4 Drug-Drug Interactions and 9.5 Drug-Food Interactions. Due to the slow elimination of cariprazine and its metabolites, treatment with strong and moderate CYP3A4 inhibitors must be initiated at least 2 weeks after VRAYLAR discontinuation.
- With concomitant use of strong and moderate CYP3A4 inducers. See 9.4 Drug-Drug Interactions and 9.6 Drug-Herb Interactions.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia:

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-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. See 7.1.4 Geriatrics. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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 7 WARNINGS AND PRECAUTIONS and 10.3 Pharmacokinetics.

Prior to initiating treatment with VRAYLAR, the following assessments should be done to guide patient selection and treatment.

Cardiac effects:

- Patients with pre-existing hypertension and other cardiovascular disease should be treated and stabilized before starting therapy with VRAYLAR. Blood pressure should be monitored. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

Hematologic effects:

- Complete blood count (CBC) should be tested in patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia. See 7 WARNINGS AND PRECAUTIONS, Hematologic.

Endocrine and metabolic effects:

- Baseline blood glucose, lipid profile and weight should be measured. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.

Hepatic effects:

- Transaminase and total bilirubin should be measured in patients with known or suspected abnormal hepatic function. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 8.2 Clinical Trial Adverse Reactions; 8.3 Less Common Clinical Trial Adverse Reactions; 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.

Ophthalmologic effects:

- Patients should undergo ophthalmologic examination prior to or shortly after initiating treatment with VRAYLAR. See 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.

Women of childbearing potential:

- It is not known if VRAYLAR reduces the effectiveness of systemically acting hormonal contraceptives. Therefore, alternative or concomitant methods of contraception must be used by female patients taking systemically acting hormonal contraceptives. See 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential and 7.1.1 Pregnant Women.

4.2 Recommended Dose and Dosage Adjustment

- **Schizophrenia**

The starting dosage of VRAYLAR is 1.5 mg daily. The recommended target dosage for VRAYLAR is 1.5 mg to 6 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased gradually in 1.5 mg increments. The maximum recommended dosage is 6 mg daily. Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability. Periodically reassess to determine the continued need and appropriate dosage for treatment.

In short-term controlled clinical trials, dosages above 6 mg/day did not confer increased efficacy to outweigh the dose-related treatment emergent adverse events.

- **Bipolar Mania (manic or mixed episodes associated with bipolar I disorder)**

The recommended dosage range is 1.5 mg to 6 mg once daily. The starting dose of VRAYLAR is 1.5 mg and can be increased thereafter by 1.5 mg increments, based on clinical response and tolerability. The lowest effective dose should be used. The maximum recommended dosage is 6 mg daily.

- **Bipolar Depression (depressive episodes associated with bipolar I disorder)**

The recommended 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. The lowest effective dose should be used. Maximum recommended dosage is 3 mg once daily.

	Starting dose	Recommended daily dose
Schizophrenia [1]	1.5 mg	1.5 mg to 6 mg
Bipolar Disorder – Mania [1]	1.5 mg	1.5 mg to 6 mg
Bipolar Disorder – Depression [2]	1.5 mg	1.5 mg or 3 mg
1. Doses > 6 mg/day did not confer increased efficacy in bipolar mania or schizophrenia 2. Doses > 3 mg/day were not evaluated for bipolar depression		

See also 4.2 Recommended Dose and Dosage Adjustment, Special Populations.

- **Special Populations**

  - Pediatrics (< 18 years of age):

No data are available to Health Canada: therefore, Health Canada has not authorized an indication for pediatric use.

  - Geriatrics (> 65 years of age):

VRAYLAR is not indicated in elderly patients with dementia. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7.1.4 Geriatrics.

The safety and efficacy of VRAYLAR in patients 65 years of age or older has not been established. 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 (see 10.3 Pharmacokinetics).

- Patients with Hepatic Impairment:

No dosage adjustment for VRAYLAR is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5 and 9).

VRAYLAR should be used with caution in patients with moderate hepatic impairment.

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. See 10.3 Pharmacokinetics.

- Patients with Renal Impairment:

No dosage adjustment for VRAYLAR is required in patients with mild to moderate renal impairment (CrCL ≥ 30 mL/minute). 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.

- Concomitant use of CYP3A4 Inhibitors and Inducers:

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

Concomitant use with strong and moderate CYP3A4 inhibitors and strong and moderate CYP3A4 inducers is contraindicated. See 2 CONTRAINDICATIONS; 9.4 Drug-Drug Interactions; 9.5 Drug-Food Interactions; 9.6 Drug-Herb interactions.

Use VRAYLAR with caution in patients concomitantly taking weak CYP3A4 inhibitors (See 9.4 Drug-Drug Interactions).

- Other Specific Populations:

Dose adjustments are not necessary on the basis of race; however, use caution with doses higher than 4.5 mg in patients with low body weight (≤ 63 kg). See 10.3 Pharmacokinetics.

- Smoking:

No dosage adjustment for VRAYLAR is needed for patients who smoke. See 9.3 Drug-Behavioural Interactions.

- **Treatment Discontinuation**

There are no systematically collected data to specifically address switching patients from VRAYLAR to other antipsychotics, switching to VRAYLAR from another antipsychotic, or concerning concomitant administration with other antipsychotics.

When switching from another antipsychotic to VRAYLAR, gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while VRAYLAR is initiated.

When switching to another antipsychotic from VRAYLAR, the new antipsychotic should be initiated at its lowest dose while cariprazine is discontinued. 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 10.3 Pharmacokinetics.

In all cases the period of overlapping antipsychotic administration should be minimized.

4.4 Administration

VRAYLAR is given orally once daily and can be taken with or without food (see 9.5 Drug-Food Interactions).

4.5 Missed Dose

If a patient misses a dose by a few hours, the patient should be advised to take their dose as soon as he/she remembers. If most of the day has passed, he/she should be advised to wait until the next scheduled dose. Patients should be advised to not take 2 doses of VRAYLAR at once.

5 OVERDOSAGE

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.

Management of Overdosage

No specific antidotes for VRAYLAR are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and continuous electrocardiogram monitoring. The possibility of multiple drug involvement should be considered.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Capsule, 1.5 mg	Gelatin, magnesium stearate, pregelatinized starch and titanium dioxide. 3 mg & 4.5 mg: FD&C blue 1, FD&C red 40, yellow iron oxide. 6 mg: black iron oxide, FD&C blue 1, FD&C red 3 Printing ink: 1.5 mg, 3 mg & 6 mg: black iron oxide, propylene glycol, shellac 4.5 mg: povidone, propylene glycol, shellac, sodium hydroxide, titanium dioxide
	Capsule, 3 mg	
	Capsule, 4.5 mg	
	Capsule, 6 mg	

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.

1.5 mg capsule: Size # “4” white opaque capsule with a black “FL 1.5” imprint on the body of the capsule with a rectified radial orientation.

3 mg capsule: Size # “4” white opaque body and green to blue green opaque cap with a black “FL 3” imprint on the body of the capsule with a rectified radial orientation.

4.5 mg capsule: Size # “4” green to blue-green opaque capsule with a white “FL 4.5” imprint on the body of the capsule with a rectified radial orientation.

6 mg capsule: Size # “3” capsule with a white opaque body and a purple opaque cap with a black “FL 6” imprint on the body of the capsule with a rectified radial orientation.

Packaging: VRAYLAR will be supplied in following configurations:

Bottles of 30 capsules: 1.5 mg, 3 mg, 4.5 mg and 6 mg

Physician’s Sample available as a blister of 7 capsules: 1.5 mg, 3 mg, 4.5 mg and 6 mg

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Body Temperature Regulation:

Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing VRAYLAR for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Falls:

Atypical 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.

Late-Occurring Adverse Reactions:

Adverse events may first appear several weeks after the initiation of VRAYLAR treatment, likely 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 4.1 Dosing Considerations and 10.3 Pharmacokinetics.

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.

Carcinogenesis and Mutagenesis

For animal data, see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Hypertension and Tachycardia:

Cariprazine can cause hypertension and tachycardia. See 8.2 Clinical Trial Adverse Reactions; 10.2 Pharmacodynamics, Cardiac Electrophysiology and Hemodynamics.

Blood pressure should be measured prior to initiating treatment and periodically throughout treatment with VRAYLAR. Pre-existing hypertension and other cardiovascular disease should be treated and stabilized before starting therapy with VRAYLAR.

Orthostatic Hypotension and Syncope:

Atypical antipsychotics can cause orthostatic hypotension and syncope. Symptoms associated with orthostatic hypotension can include dizziness, light-headedness and tachycardia. 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 reported infrequently.

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.

ECG changes:

QT prolongation can develop in patients treated with antipsychotics.

With cariprazine, no QTc interval prolongation was detected compared to placebo-risperidone in a clinical trial designed to assess QT prolongation. See 10.2 Pharmacodynamics, Cardiac Electrophysiology and Hemodynamics.

In clinical trials, infrequent non-serious QT prolongations were reported with cariprazine.

Cariprazine should be used cautiously in patients with known cardiovascular disease or in patients with a family history of QT prolongation and in patients treated with medicinal products that might cause QT prolongation

Dependence/Tolerance

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

While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of VRAYLAR misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Driving and Operating Machinery

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

In the placebo-controlled clinical trials in patients with schizophrenia, bipolar mania and bipolar depression, somnolence (somnolence, sedation, hypersomnia) was a common treatment emergent adverse event that was reported more frequently in patients treated with VRAYLAR compared to patients that received placebo. See 8.2 Clinical Trial Adverse Reactions.

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.

Endocrine and Metabolism

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.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies, which did not include VRAYLAR, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because VRAYLAR was not marketed at the time these studies were performed, it is not known if VRAYLAR is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients should have baseline and periodic monitoring of blood glucose and body weight. See 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Schizophrenia

In the 6-week, placebo-controlled trials of adult patients with schizophrenia, the proportions 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. A shift from normal to high fasting glucose was reported for 7% of patients on placebo and 8% of patients on VRAYLAR and a shift from borderline to high was reported for 24% of patients on placebo and 16% of patients on VRAYLAR. The proportions of patients with shifts in fasting glucose increased over time during the longer-term open-label studies. At 48 weeks, 14% of patients had a shift from normal (< 100 mg/dL) to high (≥ 126 mg/dL) and 58% of patients had a shift from borderline (≥ 100 and < 126 mg/dL) to high. In the long-term, open-label schizophrenia studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥ 6.5%).

Bipolar Disorder

In three placebo-controlled 3-week bipolar mania trials there was a low-level imbalance in the percentage of patients with shifts from normal (< 100 mg/dL) to high (≥ 126 mg/dL) fasting glucose. No dose response was observed. In the 16-week open-label study, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥ 6.5%).

In three placebo-controlled 6- to 8-week bipolar depression trials, the proportion of patients with shifts in fasting glucose from normal (< 100 mg/dL) to high (≥ 126 mg/dL), borderline (≥ 100 and < 126 mg/dL) to high and normal/impaired (< 126 mg/dL) to high were similar in patients treated with VRAYLAR and placebo.

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. See 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

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. During longer-term open-label treatment with VRAYLAR, the proportions of patients with shifts in fasting and non-fasting HDL and fasting triglycerides increased over time and showed a marked increase relative to what was observed in the 6-week controlled trials. A shift in fasting and non-fasting HDL from normal (≥ 40 mg/dL) to low (< 40 mg/dL) was reported in 4.7% of patients on placebo and 3.8% on VRAYLAR in the 6-week trials and in 44% of patients treated with VRAYLAR for 48 weeks in longer-term open-label trials. A shift in fasting triglycerides from normal (< 150 mg/dL) to high (≥ 200 mg/dL) was reported in 8.3% of patients on placebo and 7.6% of patients treated with VRAYLAR in the 6-week trials and in 29% of patients that received open-label treatment with VRAYLAR for 48 weeks.

Bipolar Disorder

In three placebo-controlled 3-week bipolar mania trials and in three placebo-controlled 6- to 8-week bipolar depression trials in adults, 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. See 8.2 Clinical Trial Adverse Reactions .

Genitourinary

Rare cases of priapism have been reported with antipsychotic use. This adverse reaction is generally not found to be dose-dependent or correlated with the duration of treatment.

Hematologic

Leukopenia, Neutropenia, and Agranulocytosis:

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis has also been reported. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting VRAYLAR and then periodically throughout treatment.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of VRAYLAR should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue VRAYLAR in patients with severe neutropenia (absolute neutrophil count < $1x10^9$/L) and follow their WBC counts until recovery.

Thromboembolism:

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including VRAYLAR, in case reports and/or observational studies. When prescribing VRAYLAR, all potential risk factors for VTE should be identified and preventative measures undertaken.

Hepatic/Biliary/Pancreatic

See 8.2 Clinical Trial Adverse Reactions; 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Findings.

Monitoring and Laboratory Tests

The following assessments should be done before and periodically during treatment with VRAYLAR.

- Monitor blood pressure. See 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
- Monitor complete blood count (CBC). See 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Hematologic.
- Monitor blood glucose, lipid profile and weight. See 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.
- Monitor transaminase and bilirubin levels in patients with known or suspected abnormal hepatic function. See 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Findings.
- Ophthalmologic examination in patients who develop changes in vision during treatment See 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.

Neurologic

Neuroleptic Malignant Syndrome (NMS):

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with administration of antipsychotic drugs, including VRAYLAR.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status 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.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both

serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of all antipsychotic drugs, including VRAYLAR, and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Extrapyramidal Symptoms (EPS)/Akathisia/Restlessness:

Akathisia and restlessness are frequently occurring adverse reactions of antipsychotics. Akathisia is a movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. As cariprazine causes akathisia and restlessness, it should be used cautiously in patients who are prone to or already exhibit symptoms of akathisia. Akathisia develops early in treatment. Therefore, close monitoring in the first phase of treatment is important. Prevention includes slow up-titration; treatment measures include slight down-titration of cariprazine or anti-EPS medication. The dose can be modified based on individual response and tolerability. See 4.2. Recommended dose and dosage adjustment; 8.2 Clinical Trial Adverse Reactions.

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.

Seizures:

Like other atypical antipsychotic drugs, VRAYLAR may cause seizures and should be used cautiously 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 patients 65 years or older.

Ophthalmologic

The development of cataracts and retinal toxicity was observed in association with cariprazine treatment in chronic dog studies at approximately 4 times the maximum recommended human dose (MRHD) of 6 mg/day. Lens changes and cataracts have also been observed in patients during long-term VRAYLAR treatment, but a causal relationship to VRAYLAR use has not been established. The possibility of lenticular changes during long-term use of VRAYLAR in human, thus cannot be excluded at this time. An ophthalmologic examination prior to or shortly after initiating treatment with VRAYLAR is recommended. Patients who develop symptoms such as blurred vision or other changes in vision during treatment should undergo an ophthalmologic examination. If clinically significant ocular changes associated with VRAYLAR use are observed, discontinuation of VRAYLAR should be considered.

Psychiatric

Suicide/ suicidal thoughts or clinical worsening:

Depressive episodes are associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission of depression occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition to depressive episodes associated with bipolar disorder, depression may be co-morbid with schizophrenia.

Schizophrenia as well as manic episodes associated with bipolar disorder, can also be associated with an increased risk of suicide-related events, and thus close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Patients with a history of suicide-related events are also known to be at a greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare professional. 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.

Prescriptions for VRAYLAR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Reproductive Health: Female and Male Potential

Women of childbearing potential/contraception:

Women of childbearing potential must be advised to avoid pregnancy while treated with VRAYLAR. See 7.1.1 Pregnant Women. Female patients of childbearing potential must use highly effective contraceptive methods during treatment and for at least 12 weeks following treatment discontinuation. It is not known if VRAYLAR reduces the effectiveness of systemically acting hormonal contraceptives.

Therefore, alternative or concomitant methods of contraception must be used by female patients taking systemically acting hormonal contraceptives.

Respiratory

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.

Skin

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life-threatening adverse drug reactions that have been reported with atypical antipsychotic exposure. SCARs commonly present as a combination of the following symptoms: malaise, mucosal ulceration, extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. Discontinue VRAYLAR if severe cutaneous adverse reactions occur. See 8.5 Post-Market Adverse Reactions.

7.1 Special Populations

7.1.1 Pregnant Women

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 10.3 Pharmacokinetics.

Teratogenic effects
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 16 NON-CLINICAL TOXICOLOGY.

Non-teratogenic effects
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Women of childbearing potential must be advised to avoid pregnancy while being treated with VRAYLAR. See 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential.

The use of VRAYLAR during pregnancy is not recommended unless the expected benefits outweigh the potential risks to the fetus. Patients should be advised to notify their physician if they become pregnant during treatment with VRAYLAR.

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/research/pregnancyregistry/atypicalantipsychotic/.

7.1.2 Breastfeeding

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. See 16 NON-CLINICAL TOXICOLOGY, Lactational Transfer. 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of VRAYLAR have not been established in patients less than 18 years of age.

7.1.4 Geriatrics

Clinical trials of VRAYLAR in the treatment of schizophrenia and bipolar mania did not include enough patients aged 65 and older to determine whether the safety and efficacy of VRAYLAR are different in elderly patients compared to 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Use in Geriatric Patients with Dementia

Overall Mortality: Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. VRAYLAR is not indicated in elderly patients with dementia (e.g., dementia-related psychosis). See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Cerebrovascular Adverse Events, including Stroke: In placebo-controlled trials with some atypical antipsychotics in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. VRAYLAR is not approved for the treatment of patients with dementia (e.g., dementia-related psychosis). See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including VRAYLAR. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. VRAYLAR is not indicated for the treatment of dementia-related psychosis and should not be used in patients at risk for aspiration pneumonia.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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.

Treatment Emergent Adverse Events Associated with Discontinuation of Treatment: A total of 9% (118/1317) of patients treated with VRAYLAR (1.5 mg/day to 12 mg/day) and 12% (71/584) of patients that received placebo in 6-week clinical trials discontinued due to adverse events. 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. Akathisia, insomnia, restlessness, aggression, headache and hypertension were the only treatment emergent adverse events that led to discontinuation of treatment for ≥ 2 patients treated with VRAYLAR and more frequently than in patients that received placebo.

Most common treatment emergent adverse events: The most common treatment emergent adverse events, reported in ≥ 5% of patients treated with VRAYLAR and at least twice the rate of placebo in the 6-week schizophrenia clinical trials were extrapyramidal symptoms and akathisia.

Treatment emergent adverse events with an incidence of ≥ 2% and greater than placebo, at any dose are shown below in Table 2.

Table 2 Treatment Emergent Adverse Events Occurring in ≥ 2% of VRAYLAR-treated Patients and Placebo-treated Adult Patients in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	VRAYLAR*			Placebo n = 584 (%)
	1.5 - 3 mg/day n = 539 (%)	4.5 - 6 mg/day n = 575 (%)	9 - 12 mg/day** n = 203 (%)	
Cardiac Disorders				
Tachycardia[a]	2	2	3	1
Eye Disorders				
Vision blurred	1	2	2	< 1
Gastrointestinal Disorders				
Abdominal pain[b]	3	4	7	5
Constipation	6	7	10	5
Diarrhea[c]	2	4	5	3
Dry Mouth	1	2	3	2
Dyspepsia	4	5	5	4
Nausea	5	7	8	5
Toothache	3	4	6	4
Vomiting	4	5	5	3
General Disorders/Administration Site Conditions				
Fatigue[d]	2	3	2	1
Infections and Infestations				
Nasopharyngitis	1	1	3	1
Urinary tract infection	1	< 1	3	1
Investigations				
Blood creatine phosphokinase increased	1	2	3	1
Hepatic enzyme increased[e]	1	2	3	< 1
Weight increased	3	2	3	1
Metabolism and Nutrition Disorders				
Decreased appetite	1	3	2	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	2	1	3	1
Back pain	3	3	2	2
Joint stiffness	0	1	2	0
Myalgia	1	1	2	1
Pain in extremity	2	2	4	3

System Organ Class / Preferred Term	VRAYLAR*			Placebo n = 584 (%)
	1.5 - 3 mg/day n = 539 (%)	4.5 - 6 mg/day n = 575 (%)	9 - 12 mg/day** n = 203 (%)	
Nervous System Disorders				
Akathisia	9	13	14	4
Extrapyramidal symptoms[f]	15	19	20	8
Headache[g]	9	11	18	13
Somnolence[h]	5	8	10	6
Dizziness	3	5	5	2
Psychiatric Disorders				
Agitation	3	5	3	4
Insomnia[i]	12	13	11	11
Restlessness	4	6	5	3
Anxiety	6	5	3	4
Respiratory, Thoracic and Mediastinal Disorders				
Cough	1	2	4	2
Reproductive system and breast disorders				
Dysmenorrhea[j]	1	1	6	2
Skin and Subcutaneous Disorders				
Rash	< 1	1	3	1
Vascular Disorders				
Hypertension[k]	2	3	6	1

* 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.

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. Percentages for sex-specific AEs are relative to the number of patients of the appropriate sex.

k. Hypertension terms: blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension

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.

Treatment Emergent Adverse Events Associated with Discontinuation of Treatment: The adverse events 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 event, compared with 7% of placebo-treated patients in these trials.

Most common treatment emergent adverse events (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness.

Treatment emergent adverse events with an incidence of ≥ 2% and greater than placebo at any dose are shown below in Table 3.

Table 3 Treatment Emergent Adverse Events Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	VRAYLAR*		Placebo n = 442 (%)
	3 - 6 mg/day n = 263 (%)	9 - 12 mg/day** n = 360 (%)	
Cardiac Disorders			
Tachycardia[a]	2	1	1
Eye Disorders			
Vision blurred	4	4	1
Gastrointestinal Disorders			
Nausea	13	11	8
Constipation	6	11	5
Vomiting	10	8	4
Dry mouth	3	2	2
Dyspepsia	7	9	4
Abdominal pain[b]	6	8	5
Diarrhea[c]	5	6	5
Toothache	4	3	2
General Disorders/Administration Site Conditions			
Fatigue[d]	4	5	2
Pyrexia[e]	1	4	2
Investigations			
Blood creatine phosphokinase increased	5	4	4
Hepatic enzymes increased[f]	1	3	< 1
Weight increased	2	3	2
Metabolism and Nutrition Disorders			
Decreased appetite	3	4	3

System Organ Class / Preferred Term	VRAYLAR*		Placebo n = 442 (%)
	3 - 6 mg/day n = 263 (%)	9 - 12 mg/day** n = 360 (%)	
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	4	2	2
Back pain	1	3	1
Nervous System Disorders			
Akathisia	20	21	5
Extrapyramidal Symptoms[g]	26	29	12
Headache[h]	14	13	13
Dizziness	7	6	4
Somnolence[i]	7	8	4
Psychiatric Disorders			
Insomnia[j]	9	8	7
Restlessness	7	7	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1	3	2
Vascular Disorders			
Hypertension[k]	5	4	1

* 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.

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

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.

Treatment Emergent Adverse Events Associated with Discontinuation of Treatment: There were no adverse events leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo. Overall, 7% of the patients who received VRAYLAR discontinued treatment due to an adverse event, compared with 5% of placebo-treated patients in these trials.

Most common treatment emergent adverse events (≥ 5% and at least twice the rate of placebo): nausea, akathisia, restlessness, and extrapyramidal symptoms.

Treatment emergent adverse events with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 4.

Table 4 Treatment Emergent Adverse Events Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in two 6-week trials and one 8-week trial Bipolar Depression Trials

System Organ Class / Preferred Term	VRAYLAR		Placebo n = 468 (%)
	1.5 mg/day n = 470 (%)	3 mg/day n = 469 (%)	
Gastrointestinal Disorders			
Nausea	7	8	3
General Disorders /Administration Site Conditions			
Fatigue[a]	4	3	2
Weight increase	2	2	<1
Metabolism and Nutrition Disorders			
Increased appetite	3	3	2
Nervous System Disorders			
Akathisia	6	10	2
Extrapyramidal symptoms[b]	4	6	2
Dizziness	4	3	2
Somnolence[c]	7	6	4
Psychiatric Disorders			
Insomnia[d]	7	10	7
Restlessness	2	7	3

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

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).

Schizophrenia:

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 majority (97.7%) of akathisia and EPS AEs were mild or moderate in severity and less than 1% led to discontinuation. The incidence of EPS based on Adverse Events is shown in Table 5. The incidences of parkinsonism and akathisia based on the SAS and BARS, respectively, are shown in Table 6.

Table 5 Incidence of Treatment Emergent EPS Adverse Events Compared to Placebo in 6-Week Schizophrenia Studies

Adverse Event Term	VRAYLAR*			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	24	32	33	14
All EPS Events, excluding Akathisia / Restlessness	15	19	20	8
Akathisia	9	13	14	4
Dystonia[a]	2	1	2	< 1
Parkinsonism[b]	13	16	18	7
Restlessness	4	6	5	3
Musculoskeletal stiffness	1	3	1	1

* 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.

a. Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, trismus, torticollis

b. Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, parkinsonism, tremor, salivary hypersecretion

In the long-term study, the rate of new cases of akathisia did not continue to escalate over time. Akathisia was manageable; 99.7% events were mild to moderate in severity and approximately 1% led to discontinuation.

Table 6 Incidence of Parkinsonism and Akathisia Compared to Placebo in 6-Week Schizophrenia Studies Based on Shifts from Baseline in SAS or BARS Scores

Incidence	VRAYLAR			Placebo n = 584 (%)
	1.5 - 3 mg/day n = 539 (%)	4.5 - 6 mg/day n = 575 (%)	9-12 mg/day n = 203 (%)	
Shifts from Baseline in SAS score (Parkinsonism)	8.2	11.2	12.9	4.2
Shifts from Baseline in BARS score (Akathisia)	14.7	15.8	14.8	5.8

SAS: Simpson Angus Scale; BARS: Barnes Akathisia Rating Scale

Bipolar Mania:

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 akathisia and extrapyramidal disorder was lower in patients who received a modal dose of 3 to 6 mg VRAYLAR compared to patients who received a modal dose of 9 to 12 mg VRAYLAR. The majority (93.6%) of akathisia and extrapyramidal symptoms AEs were mild or moderate severity. The incidence of EPS is provided in Table 7. The incidences of parkinsonism and akathisia based on the SAS and BARS, respectively, are shown in Table 8.

Table 7 Incidence of EPS Compared to Placebo in 3-Week Bipolar Mania Trials

Adverse Event Term	**VRAYLAR***		Placebo n = 442 (%)
	3 - 6 mg/day n = 263 (%)	9 - 12mg/day** n = 360 (%)	
All EPS Events	41	45	18
All EPS Events, excluding Akathisia / Restlessness	26	29	12
Akathisia	20	21	5
Dystonia[a]	5	3	1
Parkinsonism[b]	21	26	10
Restlessness	7	7	2
Musculoskeletal stiffness	2	2	1

* 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.

a. Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia

b. Parkinsonism includes adverse event terms: bradykinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, parkinsonism, salivary hypersecretion, tremor

The onset of akathisia and EPS events occurred mostly during the initial 2-weeks of treatment and then the number of new cases decreased thereafter. This pattern was also observed in the 16 week study.

Table 8 Incidence of Parkinsonism and Akathisia Compared to Placebo in three 3-Week Bipolar Mania Trials Based on Shifts from Baseline in SAS or BARS Scores

Incidence	VRAYLAR		Placebo n = 442 (%)
	3 - 6 mg/day n = 263 (%)	9 - 12mg/day n = 360 (%)	
Shifts from Baseline in SAS score (Parkinsonism)	11.2	17.8	2.3
Shifts from Baseline in BARS score (Akathisia)	22.0	21.9	5.3
SAS: Simpson Angus Scale; BARS: Barnes Akathisia Rating Scale			

Bipolar Depression:

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 majority (97.2%) of akathisia AEs were mild or moderate in severity. The overall rate of akathisia was lower in bipolar depression studies compared with other indications, possibly due to the slower titration schemes and lower doses used in the bipolar depression studies. The incidence of EPS is shown in Table 9. The incidences of parkinsonism and akathisia based on the SAS and BARS, respectively, are shown in Table 10.

Table 9 Incidence of EPS Compared to Placebo in two 6-Week and one 8-Week Bipolar Depression Trials

Adverse Event Term	**VRAYLAR**		Placebo n = 468 (%)
	1.5 mg/day n = 470 (%)	3 mg/day n = 469 (%)	
All EPS Events	10	19	7
All EPS Events, excluding Akathisia / Restlessness	3	6	2
Akathisia	6	10	2
Dystonia[a]	< 1	< 1	< 1
Parkinsonism [b]	3	4	2
Restlessness	2	7	3
Musculoskeletal stiffness	< 1	1	< 1
Tardive Dyskinesia	0	< 1	0
a. Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia b. Parkinsonism includes adverse event terms: bradykinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, parkinsonism, salivary hypersecretion, tremor			

Table 10 Incidence of Parkinsonism and Akathisia Compared to Placebo in two 6-Week and one 8-Week Bipolar Depression Trials Based on Shifts from Baseline in SAS or BARS Scores

Incidence	VRAYLAR		Placebo n = 468 (%)
	1.5 mg/day n = 470 (%)	3 mg/day n = 469 (%)	
Shifts from Baseline in SAS score (Parkinsonism)	1.1	3.5	0.4
Shifts from Baseline in BARS score (Akathisia)	8.5	13.8	4.3
SAS: Simpson Angus Scale; BARS: Barnes Akathisia Rating Scale			

Additional Safety Evaluations:

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 16 NON-CLINICAL TOXICOLOGY. The possibility of lenticular changes or cataracts cannot be excluded at this time.

Vital Signs Changes

In general, at the recommended doses for VRAYLAR, there were no clinically meaningful differences between VRAYLAR-treated patients and patients on placebo in mean change from baseline to endpoint in supine blood pressure parameters in the short-term schizophrenia, bipolar mania or bipolar depression clinical trials. However, increases in blood pressure and heart rate were observed with VRAYLAR in the ECG assessment study. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 10.2 Pharmacodynamics, Cardiac Electrophysiology and Hemodynamics.

Weight

Weight gain has been observed with use of atypical antipsychotics, including VRAYLAR. Monitor weight at baseline and frequently thereafter. TablesTable 11, Table 12 and Table 13 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.

Schizophrenia:

Table 11 shows the change in body weight occurring from baseline to endpoint in 6-week schizophrenia trials.

Table 11 Change in Body Weight (kg) in 6-Week Schizophrenia Trials

	Placebo n = 584 (%)	VRAYLAR*		
		1.5 - 3 mg/day n = 539 (%)	4.5 - 6 mg/day n = 575 (%)	9-12 mg/day** n = 203 (%)
Mean Change at Endpoint	+0.3	+0.8	+1	+2
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.

Bipolar Mania

Table 12 show the change in body weight occurring from baseline to endpoint in 3-week bipolar mania trials.

Table 12 Change in Body Weight (kg) in 3-Week Bipolar Mania Trials

	Placebo n = 442 (%)	VRAYLAR*	
		3 - 6 mg/day n = 263 (%)	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.

There was a slight difference in mean weight gain between VRAYLAR and placebo patients (+0.5 kg vs. 0.2 kg, respectively).

Bipolar Depression

Table 13 shows the change in body weight occurring from baseline to endpoint in the two 6-week and one 8-week bipolar depression trials.

Table 13 Change in Body Weight (kg) in two 6-Week and one 8-Week Bipolar Depression Trials

	Placebo n = 463 (%)	VRAYLAR	
		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%

There was a slight difference in mean weight gain between VRAYLAR and placebo patients (+0.6 kg vs. -0.1 kg, respectively).

8.3 Less Common Clinical Trial Adverse Reactions

Adverse events 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 events listed are those that could be of clinical importance, as well as those that are plausibly drug-related on pharmacologic or other grounds. Adverse events 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

Investigations: Infrequent: blood triglycerides increased; blood glucose increased

Metabolism and Nutrition Disorders: Infrequent: hyponatremia; hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders: Rare*:* rhabdomyolysis

Nervous System Disorders: Infrequent: dysarthria; 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

Vascular Disorders: Infrequent: orthostatic hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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. Most cases of transaminase elevation were asymptomatic, and the majority of cases had confounds such as, recent prior or concomitant medications, history of transaminase elevation, mild baseline elevations or positive baseline serology for hepatitis, history of alcohol use/abuse. See 4.1 Dosing Considerations; 7 WARNINGS AND PRECAUTIONS Monitoring and Laboratory Tests.

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 proportion of patients with elevations of CPK greater than 1000 U/L in the long-term open-label 48-week studies was 8.7%. 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.

8.5 Post-Market Adverse Reactions

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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

The co-administration of therapeutic doses of cariprazine with strong and moderate CYP3A4 inhibitors or inducers has not been investigated and may lead to significant changes in cariprazine exposure.

- Concomitant use of strong and moderate CYP3A4 inhibitors is contraindicated during treatment with VRAYLAR and for at least 2 weeks after VRAYLAR discontinuation. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions, and 9.5 Drug-Food Interactions.
- Concomitant use of strong and moderate inducers is contraindicated during treatment with VRAYLAR. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions and 9.6 Drug-Herb Interactions.

9.2 Drug Interactions Overview

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

Based on *in vitro* results, cariprazine has the potential to act as a CYP3A4/3A5 inducer at the intestinal level. At clinically relevant concentrations, cariprazine and its metabolites, DCAR and DDCAR, are not expected to induce hepatic CYP3A4/3A5, CYP1A2 and CYP2B6 or to inhibit the activity of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/3A5.

Based on *in vitro* results, cariprazine has the potential to act as a weak P-glycoprotein (P-gp) inhibitor at the intestinal level. At clinically relevant concentrations, cariprazine and its metabolites, DCAR and DDCAR, are not expected to inhibit the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), breast cancer resistance protein (BCRP), organic cation transporter 2 (OCT2), and organic anion transporter 1 and 3 (OAT1 and OAT3).

In vitro results showed that cariprazine and its metabolites, DCAR and DDCAR, are not substrates of P-gp, OATP1B1, OATP1B3 and BCRP. Therefore, no interaction is expected between VRAYLAR and inhibitors of P-gp, OATP1B1, OATP1B3 and BCRP.

9.3 Drug-Behavioural Interactions

Alcohol / CNS Drugs

Given the primary central nervous system effects of cariprazine, VRAYLAR should be used with caution in combination with other centrally acting medicinal products and alcohol.

Smoking

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

9.4 Drug-Drug Interactions

Table 14 Established or Potential Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Strong CYP3A4 Inhibitors itraconazole, ketoconazole, clarithromycin, protease inhibitors **Moderate CYP3A4 Inhibitors** diltiazem, erythromycin **Weak CYP3A4 inhibitors** cimetidine, ranitidine	CT	Concomitant use of VRAYLAR (0.5 mg/day) with a strong CYP3A4 inhibitor, ketoconazole, caused a two-fold increase in total cariprazine plasma concentration (cariprazine and its active metabolites) during short-term co-administration (4 days). Concomitant use of therapeutic doses at steady state with CYP3A4 inhibitors has not been evaluated and, it is not known if further increases in total cariprazine exposure may occur during longer co-administration, due to the long half-life of the cariprazine active moieties.	Concomitant use of a strong and moderate CYP3A4 inhibitor is contraindicated during treatment with VRAYLAR and for at least 2 weeks after VRAYLAR discontinuation. Caution should be exercised when VRAYLAR is co-administered with a weak CYP3A4 inhibitor. See 2 CONTRAINDICATIONS.
Strong and Moderate CYP3A4 Inducers rifampin, carbamazepine, phenytoin, phenobarbital, efavirenz, bosentan, St. John's Wort	T	CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The co-administration of VRAYLAR with strong or moderate inducers of CYP3A4 may therefore lead to a significant decrease in total cariprazine exposure. The net effect on active drug and metabolites is not known as the effect of CYP3A4 inducers on the exposure of VRAYLAR has not been evaluated.	Concomitant use of a strong or moderate CYP3A4 inducer is contraindicated during treatment with VRAYLAR. See 2 CONTRAINDICATIONS.
CYP3A4 substrates midazolam, triazolam	T	Based on *in vitro* results, cariprazine has the potential to act as a CYP3A4 inducer at the intestinal level. The effect of VRAYLAR on the exposure to CYP3A4 substrates has not been evaluated.	Caution should be exercised if VRAYLAR is co-administered with CYP3A4 substrates. Additional monitoring and dose adjustments may be required.
Oral contraceptives	T	It is not known whether VRAYLAR reduces the effectiveness of systemically acting hormonal contraceptives.	Alternative or concomitant methods of contraception must be used by female patients taking systemically acting hormonal contraceptives. See

Proper/Common name	Source of Evidence	Effect	Clinical comment
			7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential.
P-glycoprotein substrates dabigatran, digoxin	T	Based on *in vitro* results, cariprazine has the potential to act as a P-gp inhibitor at the intestinal level. The effect of VRAYLAR on the exposure to P-gp substrates has not been evaluated.	Caution should be exercised if VRAYLAR is co-administered with P-gp substrates. Additional monitoring and dose adjustments may be required.
Proton pump inhibitors pantoprazole	CT	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}.	Concomitant use of proton pump inhibitors is not expected to decrease the efficacy of VRAYLAR.
Legend: C = Case Study; CT = Clinical Trial; T = Theoretical			

CYP2D6 inhibitors:

In vitro results showed that the CYP2D6-mediated pathway plays a minor role in cariprazine metabolism. Therefore, CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR.

9.5 Drug-Food Interactions

In clinical studies, VRAYLAR was administered without regard to food.

A dedicated drug-food interaction study demonstrated that food had no significant effect on C_{max} or AUCT. However, administration of 1.5 mg VRAYLAR with a high-fat, high-calorie meal delayed median (minimum-maximum) time to C_{max} (T_{max}) to 9.0 (2.0-12.0) hours from 4.0 (3.0-9.0) hours following administration of 1.5 mg VRAYLAR under fasting conditions.

Grapefruit is a known CYP3A4 inhibitor. Co-administration of VRAYLAR with strong and moderate CYP3A4 inhibitors is contraindicated. See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions. Patients must be instructed to avoid consumption of grapefruit or grapefruit-containing products while being treated with VRAYLAR and for at least 2 weeks after treatment discontinuation.

9.6 Drug-Herb Interactions

St John's Wort is a known CYP3A4 inducer. Co-administration of VRAYLAR with strong and moderate CYP3A4 inducers is contraindicated. See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of cariprazine in schizophrenia and bipolar I disorder is unknown. However, the therapeutic effect of cariprazine may be mediated through a combination of partial agonist activity at central dopamine D_3, D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Cariprazine forms two major metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), that have *in vitro* receptor binding and functional activity profiles similar to the parent drug.

10.2 Pharmacodynamics

Cariprazine acts as a dopamine D_3/D_2 receptor partial agonist with high *in vitro* binding affinity at the dopamine D_3 (K_i = 0.085-0.3 nM), and D_2 receptors (K_i values, D_{2L}= 0.49-0.71 nM and D_{2S} = 0.69). Cariprazine acts as a partial agonist at the serotonin 5-HT_{1A} receptor with high *in vitro* binding affinity (K_i = 1.4- 2.6 nM) and acts as an antagonist at 5-HT_{2B} and 5-HT_{2A} receptors as well as histamine H_1 receptors with high to moderate binding affinities (Ki values, 5-HT_{2B} =0.58 -1.1 nM; 5-HT_{2A} = 18.8 nM; H_1 = 23.2 nM respectively). Cariprazine shows lower binding affinity to 5-HT_{2C} and α_{1A}- adrenergic receptors (K_i values, $5HT_{2C}$ = 134 nM and α_{1A} = 155 nM, respectively) and has no appreciable binding affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM).

Cardiac Electrophysiology and Hemodynamics

In a double-blind, placebo- and positive-controlled, parallel group ECG assessment study, patients with schizophrenia or schizoaffective disorder were randomized to receive supratherapeutic doses of cariprazine 9 mg/day and 18 mg/day (n = 63) or placebo-risperidone (n = 66). To attain cariprazine, DCAR and DDCAR plasma concentrations with the supratherapeutic doses that would be similar to steady-state concentrations at the maximum recommended dose of 6 mg/day within a short timeframe, patients in the cariprazine group received placebo from days 1-5, were upward titrated from 1.5 mg/day to 6 mg/day from days 6-9, received 9 mg/day from days 10-20, were upward titrated from 12 mg/day to 15 mg/day from days 21-24, and received 18 mg/day from days 25-35. The mean C_{max} values for CAR (22.8 ng/mL) and DCAR (4.8 ng/mL) reported for the supratherapeutic 9 mg/day dose on day 20 were similar to those reported for the therapeutic 6 mg/day dose at steady-state in other trials, whilst the mean C_{max} for DDCAR (23.1 ng/mL) was lower. The mean C_{max} values achieved with the supratherapeutic 18 mg/day dose on day 34 were twice those achieved with the therapeutic 6 mg/day dose at steady-state in other trials.

In the placebo-risperidone group, patients received placebo from days 1-5, risperidone 4 mg/day from days 7-15, placebo from days 16-20, risperidone 4 mg/day from days 21-29, and placebo from days 30-34. A positive control or placebo was administered on days 6 and 35, according to a nested crossover design.

ECG assessments were performed on day 20 and day 34 and compared with day 5 baseline. Blood pressure was measured daily.

Blood Pressure:

Cariprazine caused increases in systolic and diastolic blood pressure.

On day 20, the mean change from baseline in systolic blood pressure ranged from -3.7 mmHg to -2.9 mmHg for placebo-risperidone and from 5.3 mmHg to 5.4 mmHg for cariprazine 9 mg/day, whilst the mean change from baseline in diastolic blood pressure ranged from -2.6 mmHg to -0.8 mmHg for placebo-risperidone and from 4.9 mmHg to 5.2 mmHg for cariprazine 9 mg/day.

On day 34, the mean change from baseline in systolic blood pressure ranged from -3.8 mmHg to -3.3 mmHg for placebo-risperidone and from 5.2 mmHg to 5.4 mmHg for cariprazine 18 mg/day, whilst the mean change from baseline in diastolic blood pressure ranged from -2.3 mmHg to -1.4 mmHg for placebo-risperidone and from 4.3 mmHg to 5.8 mmHg for cariprazine 18 mg/day.

Heart Rate:

Cariprazine was associated with an increase in heart rate. The maximum difference from placebo-risperidone in mean change from baseline heart rate was 7.2 bpm (90% CI 4.1, 10.4) on day 20 during treatment with cariprazine 9 mg/day and 8.2 bpm (90% CI 4.8, 11.6) on day 34 during treatment with cariprazine 18 mg/day.

QTc Interval:

Risperidone and its active metabolite, paliperidone, cause QTc prolongation. On day 20, the mean change from baseline QTcF ranged from 6.2 ms to 10.4 ms in the placebo-risperidone group and from 1.7 ms to 5.6 ms in the cariprazine group during treatment with the 9 mg/day dose. On day 34, the mean change from baseline QTcF ranged from 4.5 ms to 8.3 ms in the placebo-risperidone group and from 1.0 ms to 5.3 ms in the cariprazine group during treatment with the 18 mg/day dose.

According to a concentration-response model of the relationship between mean change from baseline QTcF and total cariprazine (the combination of the parent compound and its two major active metabolites, DCAR and DDCAR), no meaningful effect on the QTcF interval was predicted for total cariprazine concentrations up to 200 nmol/L. The mean C_{max} for total cariprazine at steady-state during treatment with the 6 mg/day maximum recommended therapeutic dose is expected to be approximately 100-150 nmol/L.

Because of the upward titration design, comparisons between the 9 mg/day and 18 mg/day doses are not controlled for time and sequence effects.

10.3 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.

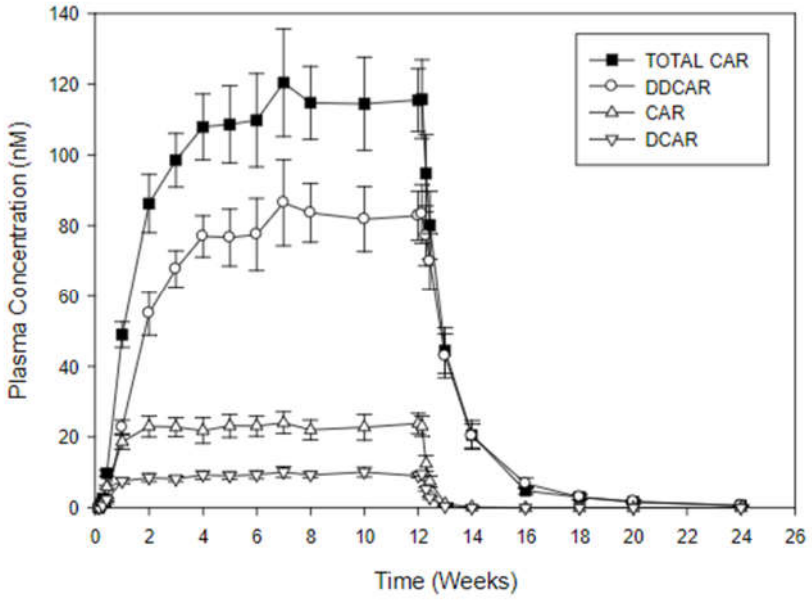
After multiple dose administration of VRAYLAR, mean cariprazine and DCAR concentrations reached steady state at around Week 1 to Week 2 and mean DDCAR concentrations appeared to be approaching steady state at around Week 4 to Week 8 in a 12-week study (Figure 1). The functional half-lives based on time to reach 90% 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 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS, Late-Occurring Adverse Reactions. 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.

Based on a population pharmacokinetic analysis, terminal elimination half-lives (mean ± SD) are 10.1 ± 0.66 days for cariprazine, 5.9 ± 2.8 days for DCAR, 19.1 ± 9.25 days for DDCAR, and 8.9 ± 9.19 days for total CAR.

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,b]



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

b. The presented plasma-concentration vs. time profile was based on the Study A002-A11. Cariprazine tablets were orally administered once a day for 12 weeks to Japanese schizophrenia patients (n = 16) starting with an initial dose of 1.5 mg/day on Day 1, followed by daily up-titration dosages for 1 to 4 days to a fixed final dose of 6 mg/day for 12 weeks (See Special Populations and Conditions).

Absorption

After single dose administration of VRAYLAR, the peak plasma cariprazine concentration occurred in approximately 3-6 hours. See 9.5 Drug-Food Interactions.

Distribution

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

Metabolism

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

Elimination

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.

Special Populations and Conditions

- **Pediatrics**

VRAYLAR is not approved for use in pediatric patients.

- **Geriatrics**

In a population pharmacokinetic analysis, age did not significantly affect the pharmacokinetics of cariprazine, DCAR, or DDCAR in patients aged 18 to 65 years. Dose adjustments are not necessary on the basis of age for adults 18 to 65 years of age. The effect of age for elderly patients (> 65 years of age) on cariprazine pharmacokinetics, efficacy and safety was not evaluated. Caution should be used when treating geriatric patients. See 1.2 Geriatrics; 4.1 Dosing Considerations; 7.1.4 Geriatrics.

- **Sex**

In a population pharmacokinetic analysis, gender did not have clinically relevant effects on the pharmacokinetics of cariprazine, DCAR, or DDCAR. Dose adjustments are not necessary on the basis of gender.

- **Genetic Polymorphism**

Based on the final population PK analysis, there were no statistically significant differences in cariprazine, DCAR, DDCAR, and TOTAL cariprazine exposures between extensive and poor metabolizers of CYP2D6.

- **Ethnic Origin**

Based on a population pharmacokinetic analysis (n = 2036), total cariprazine AUC was 45% higher in Asian patients (n = 312) and 24% lower in Black patients (n = 689) compared to that in Caucasian patients (n = 961). These differences were due to the combined effect of race and weight on cariprazine PK. The subjects with lower body weight (33-63 kg) had 36% higher total cariprazine AUC compared to the reference group with weight ranging from 74 to 82 kg. Dose adjustments are not necessary on the basis of race, however, use caution for dose increase higher than 4.5 mg in patients with low body weight (≤ 63 kg).

- **Hepatic Insufficiency**

Compared to healthy subjects, total cariprazine exposure (C_{max} and AUC) in subjects with either mild or moderate hepatic impairment (Child-Pugh score between 5 and 9) was decreased by 16 to 20% and by 11 to 14%, respectively, following daily doses of 0.5 mg cariprazine (a subtherapeutic dose) for 14 days. In this study, no subject was exposed to therapeutic doses of cariprazine and full effect on cariprazine exposure could not be determined as one of the metabolites, DDCAR, had not reached steady-state.

In a population pharmacokinetic analysis (n = 2036), no clinically significant differences in the PK of cariprazine and its metabolites were observed in patients with mild hepatic impairment (n = 290), whereas the effect of moderate hepatic impairment remains unclear due to the very small sample size (n = 4) and other confounding variables. VRAYLAR should therefore be used with caution in patients with moderate hepatic impairment.

The effect of severe hepatic impairment on the pharmacokinetics of cariprazine and its metabolites has not been evaluated. Therefore, the use of VRAYLAR in patients with severe hepatic impairment is not recommended.

- **Renal Insufficiency**

Cariprazine and its major active metabolites are minimally excreted in urine. Pharmacokinetic analyses indicated no significant relationship between plasma clearance and creatinine clearance. Based on a population pharmacokinetic analysis (n = 2036), no clinically significant differences in the PK of cariprazine and its metabolites were observed in subjects with mild (n = 353) and moderate (n = 20) renal impairment. The effect of severe renal impairment on pharmacokinetics of cariprazine and its metabolites has not been evaluated. Therefore, the use of VRAYLAR in patients with severe renal impairment is not recommended.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 and 30°C. Protect 3 mg and 4.5 mg capsules from light to prevent potential color fading.

Keep out of reach and sight of children.

Disposal of VRAYLAR capsules should be in keeping with recommendations governing the disposal of pharmaceutical biohazardous waste.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

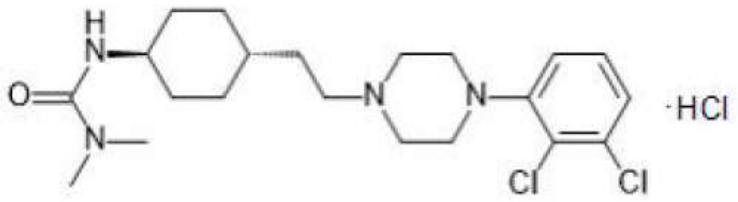
Common name: cariprazine HCl

Chemical name: trans-N-{4-[2-[4-(2,3-dichlorophenyl)piperazine-1-yl]ethyl]cyclohexyl}-N',N'-dimethylurea hydrochloride;

Molecular formula and: $C_{21}H_{33}Cl_3N_4O$

molecular mass: 463.9 g/mol

Structural formula:



Physicochemical properties: White to almost white crystalline powder. The polymorph Form I of cariprazine HCl is the most stable and relevant form which can be unequivocally differentiated from the polymorph Form III by FT-IR.

Practically insoluble in Isopropanol and N,N-Dimethylformamide
Very slightly soluble in Acetone, Acetonitrile, and Water
Slightly soluble in Dichloromethane and Ethanol
Freely soluble in Methanol
Cariprazine HCl exhibits maximum solubility at approximately pH 3

The following table provides the solubilities over the physiological pH range (1.2-6.8) for the drug substance Cariprazine HCl.

pH	Media	Solubility (average, mg/ml)
1	0.1N HCl	3.5
3	USP phthalate buffer	6.0
4.5	EP phosphate buffer	13.8
5.5	EP phosphate buffer	0.27
6.8	EP phosphate buffer	0.005
7.5	EP phosphate buffer	0.001

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Schizophrenia

The efficacy of VRAYLAR for the treatment of schizophrenia was established in three, 6-week, randomized, double-blind, placebo-controlled trials and one longer-term randomized withdrawal trial. All trials included patients (aged 18 to 60 years) who met Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision (DSM-IV-TR) criteria for schizophrenia who were experiencing an acute exacerbation of psychotic symptoms. Details of study designs and patient demographics are provided in Table 15 for the short-term trials and in Table 17 for the randomized withdrawal trial. Results are presented in Table 16 for the short-term trials and Table 18 for the randomized withdrawal trial.

Trial Design and Study Demographics in 6-week Trials for Schizophrenia

Studies RGH-MD-16 and RGH-MD-04 used a fixed-dose regimen to compare VRAYLAR 1.5 mg/day, 3 mg/day or 4.5 mg/day to placebo (Study RGH-MD-16) and VRAYLAR 3 mg/day and 6 mg/day to placebo (Study RGH-MD-04). Both studies included an active control arm (risperidone or aripiprazole) to assess assay sensitivity. In both trials, patients who were randomized to VRAYLAR initiated treatment at 1.5 mg/day and in Study RGH-MD-16, one treatment group received VRAYLAR 1.5 mg/day for the duration of the study. For patients assigned to dosages above 1.5 mg/day, the dosage was increased by 1.5 mg increments each day. On Day 2 the dosage increased to 3 mg for patients assigned to 3 mg/day or higher; on Day 3 the dosage increased to 4.5 mg for patients assigned to 4.5 mg/day or higher; and, on Day 4 the dosage increased to 6 mg for patients assigned to 6 mg/day. Once assigned dosages were reached, patients remained on these doses for the duration of the trial.

Study RGH-MD-05 used a fixed-flexible dose regimen, comparing VRAYLAR 3 to 6 mg/day (low dose group) and 6 to 9 mg/day (high dose group) to placebo. All patients who were randomized to VRAYLAR initiated treatment at 1.5 mg/day. The dosage was increased to 3 mg/day on Day 2 for all patients in both VRAYLAR dose groups and maintained at 3 mg/day for the first 2 weeks in the low dose group. In the high dose group the dosage was increased to 4.5 mg/day on Day 3, to 6 mg/day starting on Day 4 and maintained at 6 mg/day for the first 2 weeks in this group. On Day 14 patients in either VRAYLAR group with an inadequate response, defined as < 20% improvement in Positive and Negative Syndrome Scale (PANSS) total score from baseline to end of Week 2 and a Clinical Global Impressions-Severity (CGI-S) score $\geq$ 4, and who did not have significant tolerability issues had the dose increased by 1.5 mg increments. In the low dose group, the dosage was increased to 4.5 mg/day for Days 14 and 15, and to 6 mg/day thereafter. In the high dose group, the dosage was increased to 7.5 mg/day for Days 14 and 15, and to 9 mg/day thereafter. Dosages were fixed from the end of Week 3 to Week 6.

The 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.

Table 15 Summary of patient demographics in 6-week clinical trials in Schizophrenia (Intent-to-Treat Population)

Study #	Trial design	Dosage, duration (oral daily dosing)	Study subjects (n)	Median age (Range)	Sex
Study RGH-MD-16	Phase 2b. randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose	VRAYLAR 1.5 mg or 3 mg or 4.5 mg or risperidone 4 mg or placebo 6 weeks	Placebo (148) VRAYLAR 1.5 mg (140) 3 mg (140) 4.5 mg (145) Risperidone 4 mg/day (138)	35.0 (18-61)	n = 711 491 M / 220 F
Study RGH-MD-04	Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed- dose, efficacy and safety study	VRAYLAR 3 mg or 6 mg or aripiprazole 10 mg or placebo 6 weeks	Placebo (149) VRAYLAR 3 mg (151) 6 mg (154) Aripiprazole 10 mg/day (150)	38.0 (18-63)	n = 604 378 M / 226 F
Study RGH-MD-05	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose	VRAYLAR 3-6 mg or 6-9 mg or placebo 6 weeks	Placebo (145) VRAYLAR 3–6 mg (147) 6–9 mg (147)	35.0 (18-60)	n = 439 335 M / 104 F

Results of 6-week trials for Schizophrenia

Study RGH-MD-16: In a 6-week, placebo-controlled trial (n = 711) using three fixed doses of VRAYLAR (1.5, 3, or 4.5 mg/day) and an active control (risperidone), improvements in PANSS total score and CGI-S score from baseline to study endpoint were statistically significant with all VRAYLAR doses and the active control compared to placebo.

The active reference confirmed the assay sensitivity of the study.

Study RGH-MD-04: In a 6-week, placebo-controlled trial (n = 604) using two fixed doses of VRAYLAR (3 or 6 mg/day) and an active control (aripiprazole), improvements in PANSS total score and CGI-S score from baseline to study endpoint were statistically significant with both VRAYLAR doses and the active control

compared to placebo. Adjusted p-values for the primary and secondary endpoints were based on matched parallel gatekeeping procedure.

The active reference confirmed the assay sensitivity of the study.

Study RGH-MD-05: In a 6-week, placebo-controlled trial (n = 439) using two flexible-dose ranges of VRAYLAR (3 to 6 mg/day or 6 to 9 mg/day), improvements in PANSS total score and CGI-S score from baseline to study endpoint were statistically significant with both VRAYLAR dose ranges compared to placebo. Adjusted p-values for the primary and secondary endpoints were based on matched parallel gatekeeping procedure.
Results are summarized in Table 16. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

Table 16 Primary Analysis Results of 6-week trials for Schizophrenia

Treatment Group (ITT patients)	Primary Efficacy Endpoint: PANSS Total			
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Treatment Comparison vs Placebo	
			LSMD[a] (95% CI)	Adjusted p-value[b]
Study RGH-MD-16				
VRAYLAR 1.5 mg* (n = 140)	97.1 (9.1)	-19.4 (1.6)	-7.6 (-11.8, -3.3)	0.0005
VRAYLAR 3 mg* (n = 140)	97.2 (8.7)	-20.7 (1.6)	-8.8 (-13.1, -4.6)	< 0.0001
VRAYLAR 4.5 mg* (n = 145)	96.7 (9.0)	-22.3 (1.6)	-10.4 (-14.6, -6.2)	< 0.0001
Placebo (n = 148)	97.3 (9.2)	-11.8 (1.5)	--	--
Study RGH-MD-04				
VRAYLAR 3 mg* (n = 151)	96.1 (8.7)	-20.2 (1.5)	-6.0 (-10.1, -1.9)	0.0044
VRAYLAR 6 mg* (n = 154)	95.7 (9.4)	-23.0 (1.5)	-8.8 (-12.9, -4.7)	< 0.0001
Placebo (n = 149)	96.5 (9.1)	-14.3 (1.5)	--	--
Study RGH-MD-05				
VRAYLAR 3-6 mg* (n = 147)	96.3 (9.3)	-22.8 (1.6)	-6.8 (-11.3, -2.4)	0.0029
VRAYLAR 6-9 mg*[c] (n = 147)	96.3 (9.0)	-25.9 (1.7)	-9.9 (-14.5, -5.3)	< 0.0001
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

b. Study RGH-MD-16: Adjusted p-value based on closed testing procedure between 3mg and 4.5mg, and then serial gatekeeping procedure from 3mg/4.5mg to 1.5mg. The primary analysis for change from baseline used an Analysis of Covariance (ANCOVA) model and Last Observation Carried Forward (LOCF), with treatment group and study center as factors and baseline value as a covariate.
Study RGH-MD-04 / RGH-MD-05: Adjusted p-values based on matched parallel gatekeeping procedure. The primary analysis was a Mixed effects Model for Repeated Measures (MMRM) with treatment groups, study

Treatment Group (ITT patients)	Primary Efficacy Endpoint: PANSS Total			
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Treatment Comparison vs Placebo	
			LSMD[a] (95% CI)	Adjusted p-value[b]
center, visit, and treatment group by visit interaction as fixed effects, and baseline and baseline-by-treatment as covariates. c. 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. *Doses that are statistically significantly superior to placebo				

Trial Design and Study Demographics in Longer-term trial (up to 92 weeks) for Schizophrenia (RGH-MD-06)

Study RGH-MD-06 was a randomized withdrawal, double-blind, placebo-controlled trial to evaluate the efficacy, safety and tolerability of VRAYLAR in adults with schizophrenia. The trial included patients meeting DSM-IV-TR criteria for schizophrenia who were experiencing an acute exacerbation of psychotic symptoms at study entry. Patients who completed 20 weeks of open-label treatment with cariprazine and met criteria for stability could be randomized to either cariprazine or placebo for observation of relapse, for up to 72 weeks during the double-blind phase of the study.

A total of 751 patients entered the study and received open-label treatment with VRAYLAR at doses of 3 to 9 mg/day for 20 weeks. During the open-label phase all patients received VRAYLAR 1.5 mg on Day 1 and had an increase in dosage to 3 mg/day on Day 2. The dosage could have been increased based on response and tolerability to 4.5 mg/day (Day 4), 6 mg/day (Day 6) or to a maximum dose of 9 mg/day (Day 10). For the first 6 weeks of open-label treatment dose adjustments were allowed; thereafter, patients remained on a stable dose within the range of 3 to 9 mg/day. Patients who did not tolerate VRAYLAR 3 mg/day were discontinued from the study. A total of 200 patients who completed 20 weeks of open-label treatment on a stable dose of VRAYLAR (3 to 9 mg/day) and met protocol-defined criteria for stability were randomized to receive either placebo or cariprazine (1:1) at the same dose for observation of relapse during the double-blind phase of the study. The total study duration was 92 weeks. Details on patient demographics are provided in Table 17.

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).

Table 17 Summary of patient demographics in longer-term Schizophrenia Trial

Study #	Trial design	Dosage, duration (oral daily dosing)	Study subjects (n)	Median age (Range)	Sex
Study RGH-MD-06	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of cariprazine for prevention of relapse of schizophrenia symptoms after stabilization.	Open-label Phase (20 weeks): VRAYLAR 3 mg or 6 mg or 9 mg Double-blind Phase (72 weeks): VRAYLAR 3 mg or 6 mg or 9 mg or placebo	Open-label Phase (20 weeks): VRAYLAR (751) Double-blind Phase (72 weeks): VRAYLAR (101) Placebo (99)	38.0 (18 - 60)	Open-label Phase (20 weeks): 544 M / 221 F Double-blind Phase (72 weeks): 132 M / 68 F

Results of Longer-term trial (up to 92 weeks), Schizophrenia (Study RGH-MD-06)

After 20-weeks of open-label treatment with VRAYLAR, patients who were clinically stable and continued to receive VRAYLAR 3 to 9 mg/day had a statistically significant longer time to relapse than patients who were randomized to placebo (p=0.0010).

Table 18 Primary Efficacy Analysis: Survival Analysis Summary of Time to First Relapse During the Double-blind Treatment Period (Double-blind Intent-to-Treat Population) in Study RGH-MD-06

	Placebo (n = 99)	**Cariprazine 3-9 mg[a] (n = 101)**
Number censored	52	76
Number of events	47	25
Crude rate of event, %	47.5	24.8
Time to relapse days[b]		
25% percentile (95% CI)	92 (44, 151)	224 (99, -)
50% percentile (95% CI)	296 (157, -)	—
75% percentile (95% CI)	—	—
P-value[c]	—	0.0010
Hazard ratio[d] (95% CI)	—	0.45

Note: Time to first relapse (days) is calculated as the date of the first relapse – the date of randomization + 1. Patients who did not meet relapse criteria are considered censored at the time of completion or discontinuation from the double-blind phase of the study.

a. 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.

b. Percentiles (95% CI) are based on Kaplan-Meier estimates.

c. P-value is based on the log-rank test.

d. Hazard ratio (cariprazine 3-9 mg versus placebo) is based on Cox proportional hazards regression model, with treatment group as an explanatory variable.
CI = confidence interval.

Bipolar Mania

Bipolar Mania Trial Design and Study Demographics

Summary of patient demographics for clinical trials in Manic or Mixed Episodes Associated with Bipolar I Disorder (Bipolar Mania)

The efficacy of VRAYLAR in the acute management 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 I disorder with manic or mixed episodes with or without psychotic features. Details on patient demographics are provided in Table 19. In all three trials, VRAYLAR was statistically 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.

In each study, the primary endpoint was change 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 20.

Table 19 Summary of patient demographics for clinical trials in patients with Manic or Mixed Episodes Associated with Bipolar I Disorder Trials (Bipolar Mania) (Intent-to-Treat Population)

Study #	Trial design	Dosage, duration (oral daily dosing)	Study subjects (n)*	Median age (Range)	Sex
Study RGH-MD-31	Phase 2, randomized, double-blind, placebo controlled, parallel-group, flexible-dose, efficacy and safety study	VRAYLAR 3-12 mg/day or placebo 3 weeks	Placebo (117) VRAYLAR 3 -12 mg (118)	39.0 (18 - 60)	n = 235 156 M / 79 F
Study RGH-MD-32	Phase 3, randomized, double-blind, placebo controlled, parallel-group, flexible-dose, efficacy and safety study	VRAYLAR 3-12 mg/day or placebo 3 weeks	Placebo (152) VRAYLAR 3 -12 mg (158)	35.0 (18 - 60)	n = 310 199 M / 111 F

Study #	Trial design	Dosage, duration (oral daily dosing)	Study subjects (n)*	Median age (Range)	Sex
Study RGH-MD-33	Phase 3, randomized, double-blind, placebo controlled, parallel-group, fixed/flexible dose, efficacy and safety study	VRAYLAR 3-6 mg/day or 6-12 mg/day or placebo 3 weeks	Placebo (160) VRAYLAR 3-6 mg/day (165) 6-12 mg/day (167)	43.0 (18 - 65)	n = 492 262 M / 230 F

Study Results

Results of studies 31, 32 and 33 in patients with Manic or Mixed Episodes Associated with Bipolar I Disorder (Bipolar Mania)

Study RGH-MD-31: In a 3-week, placebo-controlled trial (n = 235) involving a flexible-dose range of VRAYLAR (3 to 12 mg/day), VRAYLAR was statistically superior to placebo on the YMRS total score and CGI-S.

Study RGH-MD-32: In a 3-week, placebo-controlled trial (n = 310) involving a flexible-dose range of VRAYLAR (3 to 12 mg/day), VRAYLAR was statistically superior to placebo on the YMRS total score and CGI-S.

Study RGH-MD-33: 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 statistically superior to placebo on the YMRS total score and the CGI-S. The 6 to 12 mg/day dose group showed no additional advantage.

The efficacy of VRAYLAR was established at doses ranging from 3 to 12 mg/day. Doses above 6 mg did not confer additional benefit over lower doses (Table 20) while there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

Table 20 Primary Analysis Results from Manic or Mixed Episodes Associated with Bipolar I Disorder Trials (Bipolar Mania)

Treatment Group (ITT patients)	Primary Efficacy Endpoint: YMRS Total Score			
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Treatment Comparison vs Placebo	
			LSMD[a] (95% CI)	Adjusted p-value[b]
Study RGH-MD-31				
VRAYLAR (3-12 mg/day)*[b]	30.6 (5.0)	-15.0 (1.1)	-6.1 (-8.9, -3.3)	< 0.0001
Placebo	30.2 (5.2)	-8.9 (1.1)	--	--
Study RGH-MD-32				
VRAYLAR (3-12 mg/day)*	32.3 (5.8)	-19.6 (0.9)	-4.3 (-6.7, -1.9)	0.0004
Placebo	32.1 (5.6)	-15.3 (0.9)	--	--
Study RGH-MD-33				

Treatment Group (ITT patients)	Primary Efficacy Endpoint: YMRS Total Score			
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Treatment Comparison vs Placebo	
			LSMD[a] (95% CI)	Adjusted p-value[b]
VRAYLAR (3-6 mg/day)*	33.2 (5.6)	-18.6 (0.8)	-6.1 (-8.4, -3.8)	< 0.001
VRAYLAR (6-12 mg/day)*[bc]	32.9 (4.7)	-18.5 (0.8)	-5.9 (-8.2, -3.6)	< 0.001
Placebo	32.6 (5.8)	-12.5 (0.8)	--	--

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. Study RGH-MD-33: Adjusted p-value based on matched parallel gatekeeping procedure. Study RGH-MD-31 and Study RGH-MD-32: Adjusted p-value based on serial gatekeeping procedure.

c. 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.

Bipolar Depression

Trial Design and Study Demographics in clinical trials in Depressive Episodes Associated with Bipolar I Disorder

The efficacy of VRAYLAR in the management 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. Details on patient demographics is provided in Table 21.

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 22.

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.

Table 21 Summary of patient demographics for clinical trials in Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression) (Intent-to-Treat Population)

Study #	Trial design	Dosage, duration (oral daily dosing)	Study subjects (n)	Median age (Range)	Sex
Study RGH-MD-53	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group	VRAYLAR 1.5 mg or 3 mg or placebo 6 weeks	Placebo (163) VRAYLAR 1.5 mg (162) 3 mg (153)	46 (18-65)	n = 478 179 M / 299 F

Study #	Trial design	Dosage, duration (oral daily dosing)	Study subjects (n)	Median age (Range)	Sex
Study RGH-MD-54	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group	VRAYLAR 1.5 mg or 3 mg or placebo 6 weeks	Placebo (156) VRAYLAR 1.5 mg (154) 3 mg (164)	43 (18-65)	n = 474 195 M / 279 F
Study RGH-MD-56	Phase 2b, multicenter, randomized, double-blind, placebo controlled, parallel-group	VRAYLAR 0.75 mg or 1.5 mg or 3 mg or placebo 8 weeks (primary analysis at 6 weeks)	Placebo (141) VRAYLAR 0.75 mg (140) 1.5 mg (145) 3 mg (145)	42 (18-65)	n = 571 214 M / 357 F

Results of Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

Study RGH-MD-53: 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. VRAYLAR 3 mg was not statistically superior to placebo for the primary and secondary endpoints.

Study RGH-MD-54: 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 but not on the CGI-S score.

Study RGH-MD-56: 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. VRAYLAR 0.75 mg and 3 mg were not statistically superior to placebo for the primary and secondary endpoints.

Table 22 Primary Analysis Results for clinical trials in Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

Treatment Group (ITT patients)	Primary Efficacy Endpoint: MADRS Total Scores			
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Treatment Comparison vs Placebo	
			LSMD[a] (95% CI)	Adjusted p-value[b]
Study RGH-MD-53				
VRAYLAR (1.5 mg/day)*	31.5 (4.3)	-14.8 (0.8)	-2.5 (-4.6, -0.4)	0.0417
VRAYLAR (3 mg/day)	31.5 (4.8)	-14.1 (0.8)	-1.8 (-3.9, 0.4)	0.1051
Placebo	31.4 (4.5)	-12.4 (0.8)	--	--
Study RGH-MD-54				
VRAYLAR (1.5 mg/day)*	30.7 (4.3)	-15.1 (0.8)	-2.5 (-4.6, -0.4)	0.0331
VRAYLAR (3 mg/day)*	31.0 (4.9)	-15.6 (0.8)	-3.0 (-5.1, -0.9)	0.0103
Placebo	30.2 (4.4)	-12.6 (0.8)	--	--
Study RGH-MD-56				
VRAYLAR (1.5 mg/day)*	30.3 (4.4)	-15.1 (0.8)	-4.0 (-6.3, -1.6)	0.0030
VRAYLAR (3 mg/day)	30.6 (4.7)	-13.7 (0.9)	-2.5 (-4.9, -0.1)	0.1122
Placebo	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

b. Adjusted p-values: adjustment was performed using matched parallel gatekeeping procedure to control the overall type I error rate for multiple comparisons

*Doses that are statistically significantly superior to placebo

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Cariprazine is metabolized to the major human metabolites DCAR and DDCAR in rats, mice, rabbits, and dogs. Comparisons of systemic exposure at adverse effect dose levels, no effect dose levels (NOEL), and no adverse effect dose levels (NOAEL) in animals to that at the maximal recommended human dose (MRHD) are on the basis of total cariprazine (cariprazine + DCAR + DDCAR). In patients, total cariprazine exposure based on $AUC_{0\text{-}24h}$ was 1273 ng·h/mL at the 6 mg MRHD.

Neurological and behavioral clinical signs attributed to the pharmacological effects of cariprazine were noted in dogs, rats, and mice. Clinical signs decreased in incidence and severity with repeated dosing. In

dogs, decreased spontaneous motor activity, tremor, staring into space, vocalization, and/or disorientation were noted with dose related increases in frequency and severity.

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 3 mg/kg/day in a 13 week study and 4 mg/kg/day in the 52 week study. At 3 mg/kg/day in the dog, AUC of total cariprazine was 10.2 (male) and 6.0 (female) times that of patients at the MRHD. In the dog, electroretinography (ERG) evaluations conducted in a 13-week study did not indicate any cariprazine related functional effects on the outer retina at doses up to 8 mg/kg/day. The NOEL for cataract and retinal toxicity in the dog is 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. Increased incidence and severity of retinal degeneration/atrophy in the rat occurred at all doses tested (≥ 0.75 mg/kg/day and thus, at total cariprazine exposures less than that at the MRHD. Cataract was not observed in other repeat dose studies in pigmented mice or albino rats and retinal degeneration in the 2-year rat study appeared to be exacerbation of an age-related process.

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 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 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 based on AUC of total cariprazine. The relevance of these findings to patients is unknown.

Cariprazine-related changes indicative of pseudopregnancy were observed in the female mammary gland at all dose levels of all studies conducted in mice and rats and in the reproductive organs in all mouse studies and shorter term rat studies. These findings are known class effects of antipsychotics that cause increases in circulating prolactin. Cariprazine oral doses of 0.1 and 1 mg/kg/day given for 14 days to female rats resulted in increases in serum prolactin of 87- and 256-fold, respectively, compared to controls. The female mammary gland and reproductive organ findings observed in the rodent were not observed in the dog. They are considered rodent specific and, thus, unlikely to be relevant for patients.

Genotoxicity:

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.

Carcinogenicity:

There was no treatment-related 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.

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 resulted in exposures that were 0.2 to 1.8 (males)/ 0.8 to 4.1 (females) times that at the MRHD based on the 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 resulted in exposures that were 0.2 to 7.9 (males)/2.6 to 19 (females) times the MRHD based on AUC of total cariprazine.

Reproductive and Developmental Toxicology:

- Fertility and early embryonic development

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 while at 10 mg/kg/day, numbers of delivered pups and implantation sites were reduced with concomitant decreases in live litter size. The NOAEL for female reproductive toxicity was < 1 mg/kg/day and the NOAEL for F1 developmental toxicity was 3 mg/kg/day. 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.

Embryo fetal development

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 AUC of total cariprazine at the MRHD caused fetal developmental toxicity at all doses. Reduced fetal body weight and decreased male anogenital distance were noted at all doses, and external and skeletal malformations as well as increased incidences of visceral and skeletal variations were seen at 2.5 and 7.5 mg/kg/day. 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 based on AUC of total cariprazine. At these doses, cariprazine caused fetal external malformations (localized fetal thoracic edema), skeletal malformations (bent limb bones, scapular and humerus), 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.

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

- Perinatal and postnatal reproductive toxicity

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 based on AUC of total cariprazine, did not cause maternal toxicity. Reduced postnatal survival and body weights occurred throughout the pre-weaning and post-weaning periods of first generation pups at 1 mg/kg/day. 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.

- Lactational Transfer

Cariprazine was administered to pregnant rats during pregnancy and lactation at 0.1, 0.3, and 1 mg/kg/day. Cariprazine concentrations in dams at 2 h post-dose on lactation day 10 increased proportionally with dose and decreased approximately 1.5-fold by 4 h post-dose. Cariprazine milk concentrations determined 2 h post-dose increased with dose and were between 1.6- and 2.9-fold higher than plasma concentrations. Plasma analysis in F1 pups showed little to no exposure to cariprazine, and no detectable exposure to cariprazine metabolites DCAR and DDCAR.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]VRAYLAR®

Cariprazine capsules

Read this carefully before you start taking **VRAYLAR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VRAYLAR**.

Serious Warnings and Precautions

- VRAYLAR belongs to a group of medicines called atypical antipsychotics. These medicines have been linked to a higher rate of death when used in elderly patients with dementia (loss of memory and other mental abilities).
- VRAYLAR is not to be used if you are elderly and have dementia.

What is VRAYLAR used for?

VRAYLAR is used to treat symptoms of schizophrenia in adults. Not all people with this disorder have the same symptoms. Some of the most common symptoms of schizophrenia may include:

- hallucinations (seeing, feeling, hearing or smelling things that are not there)
- delusions (believing things that are not true)
- paranoia (not trusting others or feeling very suspicious)
- avoiding family members and friends and wanting to be alone
- feeling depressed, anxious or tense

VRAYLAR is also used to manage symptoms in adults who suffer from manic or depressive episodes in bipolar disorder. Bipolar disorder is a condition with symptoms such as:

- bipolar mania (feeling invincible or an all-powerful inflated self-esteem, having racing thoughts, easily losing train of thought, overreacting to what you see or hear, speeding-up your activities, talking very quickly, too loudly, or more than usual, needing less sleep, having poor judgment, severe irritability)
- bipolar depression (feeling sad or hopeless, loss of interest and enjoyment, feeling tired, loss of energy, changes in appetite, sleeping too much, difficulty concentrating)

VRAYLAR is not a cure for your condition, but it can help manage your symptoms and help you feel better.

How does VRAYLAR work?

Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain may be due to certain chemicals (dopamine and serotonin) in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Exactly how VRAYLAR works is unknown. However, it seems to adjust the balance of these chemicals.

What are the ingredients in VRAYLAR?

Medicinal ingredients: cariprazine (as cariprazine hydrochloride)

Non-medicinal ingredients: black iron oxide (1.5 mg, 3 mg and 6 mg only), FD&C Blue 1 (3 mg, 4.5 mg and 6 mg only), FD&C Red 3 (6 mg only), FD&C Red 40 (3 mg and 4.5 mg only), gelatin, magnesium stearate, povidone (4.5 mg only), pregelatinized starch, propylene glycol, shellac, sodium hydroxide (4.5 mg only), titanium dioxide and yellow iron oxide (3 mg and 4.5 mg only).

VRAYLAR comes in the following dosage forms:

Capsules: 1.5 mg, 3 mg, 4.5 mg and 6 mg.

Do not use VRAYLAR if:

- you are allergic to cariprazine or to any of the ingredients in VRAYLAR or its container.
- you are taking:
  - strong or moderate CYP3A4 inhibitors. Strong or moderate CYP3A4 inhibitors should also not be taken for at least 2 weeks after your treatment with VRAYLAR has stopped.
  - Strong or moderate CYP3A4 inducers.

  Ask your healthcare professional if you are unsure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VRAYLAR. Talk about any health conditions or problems you may have, including if you:

- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- exercise vigorously or work in hot or sunny places.
- have low or high blood pressure.
- get dizzy, especially upon standing, or have a history of fainting or feeling sleepy.
- have or are prone to akathisia. It is a movement disorder that includes symptoms such as feelings of restlessness and inability to stay still. VRAYLAR may cause or worsen your symptoms of akathisia.
- have had a stroke or are at risk for stroke.
- have or have a family history of:
  - heart problems
  - any problems with the way your heart beats
  - heart disease
- drink alcohol or use street drugs.
- have a history of alcohol or drug abuse.
- have diabetes or a family history of diabetes as VRAYLAR may increase your blood sugar levels.
- have or have had liver or kidney problems.
- know that you have or have had a low white blood cell count in the past.
- have risk factors for developing blood clots such as:
  - a family history of blood clots
  - being over the age of 65
  - smoking
  - being overweight
  - have a recent major surgery (such as hip or knee replacement)
  - not being able to move due to air travel or other reasons
  - taking oral birth control (“The Pill”)
- have a history of seizures (fits).
- are at risk for aspiration pneumonia.
- are pregnant, think you may be pregnant or plan to become pregnant.
- are breastfeeding or are planning to breastfeed.

Other warnings you should know about:

You may experience side effects several weeks after starting treatment with VRAYLAR, or a dose increase. This is due to the fact that it takes a few weeks for the medicine to accumulate in your body. VRAYLAR can also stay in the body for at least 12 weeks after your treatment has stopped. Your healthcare professional will regularly monitor your overall health while you are taking VRAYLAR. Tell your healthcare professional if you notice any side effects.

VRAYLAR can cause serious side effects, including:

- **Extrapyramidal Symptoms (EPS)**: They are a group of symptoms that can occur in people taking antipsychotic medicines such as VRAYLAR. They include:
  - abnormal muscle movements
  - feeling restless
  - inability to stay still (e.g., rocking back and forth while standing or sitting, pacing or marching in place, shifting your weight from foot to foot, crossing and uncrossing your legs while sitting, squirming or fidgeting)
  - shaking
  - muscle stiffness without pain

  EPS may appear early during your treatment with VRAYLAR. Tell your healthcare professional if you experience these symptoms. They may adjust your dose or prescribe you medicines that will help stop these symptoms.
- **Tardive Dyskinesia:** It is a disorder that mainly affects your facial movements and may be irreversible. Your risk of experiencing this serious side effect increases:
  - if you are elderly, especially elderly women;
  - if you take VRAYLAR for a long period of time;
  - the higher the amount of VRAYLAR you take.
- **Suicidal Thoughts or Actions**: If you have thoughts of harming or killing yourself at any time, contact your healthcare professional or go to a hospital **right away**. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses. Ask them to read this leaflet. You might ask them to tell you if they:
  - think your depression or mental illness is getting worse.
  - are worried about changes in your behaviour.
- **Hypotension** (low blood pressure): Some people may faint, or get lightheaded and dizzy while taking VRAYLAR, especially when getting up from a lying or sitting position. This is more likely to happen when you start taking VRAYLAR or as your dose increases. Certain medications, diseases or conditions can make this worse. This will usually pass on its own but if it does not, tell your healthcare professional.
- **Hypertension** (high blood pressure) and **Tachycardia** (abnormally fast heartbeat): You may be at a higher risk of experiencing these serious side effects as your dose of VRAYLAR increases.

See the "**Serious side effects and what to do about them**" table, for more information on these and other serious side effects.

Dehydration and Overheating: VRAYLAR may interfere with your body's ability to adjust to heat. It is important not to become too hot or dehydrated while you are taking 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.

Falls: The following symptoms have been reported with the use of antipsychotic medicines, such as VRAYLAR:

- feeling sleepy
- a fall in blood pressure when you stand up from sitting or lying down
- vision problems
- poor balance or lack of coordination

This can lead to falls that may cause fractures or other fall-related injuries. Certain medications, diseases or conditions can make this worse.

Driving and Using Machines: VRAYLAR may affect your judgement, thinking or motor skills, and make you feel sleepy. Give yourself time after taking VRAYLAR to see how you feel before driving a vehicle or using machinery.

Pregnancy and Birth Control:

- Avoid becoming pregnant while you are taking VRAYLAR and for at least 12 weeks after your treatment has stopped. VRAYLAR may harm an unborn baby. Your healthcare professional will discuss the potential risks with you.
- Use a highly effective birth control method while you are taking VRAYLAR and for at least 12 weeks after your treatment. Do not have unprotected sex. It is not known if VRAYLAR changes how well birth control pills work. If you use birth control pills, use an additional form of birth control while you are taking VRAYLAR.
- If you discover that you are pregnant while taking VRAYLAR or within 12 weeks of stopping your treatment, contact your healthcare professional **as soon as possible**. If you are currently taking VRAYLAR, you and your healthcare professional will decide if you should continue to take it while you are pregnant.
- **Pregnancy Registry:** If you become pregnant while taking VRAYLAR, talk to your healthcare professional about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can enroll in this registry by calling 1-866-961-2388. The purpose of this registry is to collect information about the safety of antipsychotic medicines during pregnancy. Information about the registry can also be found at the website: http://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

Effects in Newborns: In some cases, babies born to mothers taking VRAYLAR during pregnancy have symptoms of withdrawal that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may get better on their own. Be ready to seek emergency medical help for your newborn if they:

- have trouble breathing.
- are overly sleepy.
- have muscle stiffness or floppy muscles (like a rag doll).
- are shaking.
- are having trouble feeding.

Breastfeeding:

- It is not known if VRAYLAR can pass into your breast milk and harm a breastfed baby. Therefore, VRAYLAR is not recommended during breastfeeding.

- Talk to your healthcare professional about the best way to feed your baby while you take VRAYLAR.

Check-ups and testing: Your healthcare professional may do check-ups and tests before you start VRAYLAR and during your treatment. These tests may include:

- blood tests to monitor:
  - blood sugar
  - red and white blood cell count
  - amount of platelets
  - lipid levels (a type of fatty substance in your body)
  - that your liver or kidneys are working properly
- blood pressure checks to monitor any changes.
- body weight checks to monitor any weight gain.
- eye examinations to monitor any changes in your vision.

Your healthcare professional may also regularly monitor you for signs of misuse and abuse.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take VRAYLAR with:

- strong or moderate CYP3A4 inhibitors. Strong or moderate CYP3A4 inhibitors should also not be taken for at least 2 weeks after your treatment with VRAYLAR has stopped.
- strong or moderate CYP3A4 inducers.

Strong and moderate CYP3A4 inhibitors or inducers include but are not limited to:

- medicines used to treat fungal infections (e.g., ketoconazole, itraconazole)
- certain medicines used to treat bacterial infections (e.g., rifampin, erythromycin, clarithromycin)
- medicines used to treat viral infections, including HIV infections and AIDS (e.g., efavirenz)
- medicines used to treat high blood pressure, or chest pain (e.g., bosentan, diltiazem)
- certain medicines used to treat depression
- medicines used to treat seizures (e.g., carbamazepine, phenytoin, phenobarbital)
- certain medicines used to treat inflammation
- St. John's Wort, a herbal remedy
- grapefruit, grapefruit juice, or products containing grapefruit extract

Ask your healthcare professional if you are unsure you are taking them.

The following may also interact with VRAYLAR:

- midazolam, used before surgery to cause sleepiness, relieve anxiety and prevent any memory of the event.
- triazolam, used to treat insomnia.
- digoxin, used to treat various heart conditions.
- dabigatran, used to prevent blood clots.
- cimetidine and ranitidine, used to treat ulcers of the stomach and intestines.
- birth control pills.

- alcohol. This includes prescription and non-prescription medications that contain alcohol.

Taking VRAYLAR with other medicines may cause possible serious side effects. It can also affect how VRAYLAR or your other medicines work. Therefore, while you are taking VRAYLAR it is important that you:

- only take medicines prescribed by your healthcare professional.
- talk to your healthcare professional first before starting or stopping any medicines.

How to take VRAYLAR:

- The dose prescribed to you will depend on your medical condition. Your healthcare professional will prescribe you the lowest dose possible needed for your treatment and may increase your dose depending on how you respond to VRAYLAR. Take VRAYLAR exactly as your healthcare professional tells you to take it.
- Even if you feel better, do **NOT** change your dose or stop taking VRAYLAR without talking to your healthcare professional.
- Take VRAYLAR once a day, with or without food.
- Try taking VRAYLAR at the same time each day.

Usual dose:

The usual starting dose is 1.5 mg, once a day.

Schizophrenia

The recommended dose range is 1.5 mg to 6 mg, once a day. The maximum recommended dose is 6 mg per day.

Bipolar mania

The recommended dose range is 1.5 mg to 6 mg, once a day. The maximum recommended dose is 6 mg per day.

Bipolar depression

Your healthcare professional may increase your dose to 3 mg once a day on Day 15 of your treatment. The maximum recommended dose is 3 mg per day.

Overdose:

Symptoms of an overdose with VRAYLAR may include:

- dizziness or light-headedness when standing up
- feeling sleepy

If you think you, or a person you are caring for, have taken too much VRAYLAR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose by only a few hours, take it as soon as possible. If most of the day has passed since your missed dose, skip that dose and wait until your next scheduled dose. Never take two doses at once.

What are possible side effects from using VRAYLAR?

These are not all the possible side effects you may have when taking VRAYLAR. If you experience any side effects not listed here, tell your healthcare professional.

You may experience side effects several weeks after starting treatment with VRAYLAR, or a dose increase. This is due to the fact that it takes a few weeks for the medicine to accumulate in your body.

Side effects may include:

- back or abdominal pain
- changes in vision
- diarrhea, constipation, indigestion, nausea or vomiting
- excessive sweating
- falls and fractures
- feeling agitated
- feeling tired or sleepy, trouble falling or staying asleep
- headache
- joint pain or stiffness
- painful menstrual periods (women)
- pain in arms, legs, feet or hands
- toothache
- stuffy or runny nose
- frequent urination
- weight gain, changes in appetite (loss or increase)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Extrapyramidal Symptoms (EPS): abnormal muscle movements, including difficulty starting muscle movements, shaking, restlessness or muscle stiffness without pain.		√	
UNCOMMON			
Hyperglycemia (high blood sugar): increased thirst, frequent urination, excessive hunger, headache, blurred vision and fatigue.	√		
Blood clots: swelling, pain and redness in an arm or leg that can be warm to the touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations.		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up).		√	
Tachycardia (abnormally fast heartbeat)		√	
RARE			
Suicidal Thoughts or Actions: thoughts or attempts to hurt or kill yourself.			√
Neuroleptic Malignant Syndrome: pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion, or reduced consciousness.			√
Tardive Dyskinesia: muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body.		√	
Seizures (fits): loss of consciousness with uncontrollable shaking.			√
Dysphagia: difficulty swallowing that can cause food or liquid to get into your lungs, problems with your esophagus.		√	
Allergic Reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hepatitis (inflammation of liver): abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin.			√
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine.			√
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance.			√
Severe Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine.			√
VERY RARE			
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 15 - 30°C. Protect the 3 mg and 4.5 mg capsules from light to prevent the colour of the capsules from fading.
- Keep out of reach and sight of children.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about VRAYLAR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

Last Revised SEP 07, 2022

Licensed from Gedeon Richter Plc.

Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 204370

Collapse All

VRAYLAR (CARIPRAZINE HYDROCHLORIDE)
EQ 1.5MG BASE
Marketing Status: Prescription

Active Ingredient: CARIPRAZINE HYDROCHLORIDE
Proprietary Name: VRAYLAR
Dosage Form; Route of Administration: CAPSULE; ORAL
Strength: EQ 1.5MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N204370
Product Number: 001
Approval Date: Sep 17, 2015
Applicant Holder Full Name: ABBVIE INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=204370&Appl_type=N)

VRAYLAR (CARIPRAZINE HYDROCHLORIDE)
EQ 3MG BASE
Marketing Status: Prescription

Active Ingredient: CARIPRAZINE HYDROCHLORIDE
Proprietary Name: VRAYLAR
Dosage Form; Route of Administration: CAPSULE; ORAL
Strength: EQ 3MG BASE
Reference Listed Drug: Yes

Reference Standard: No
TE Code:
Application Number: N204370
Product Number: 002
Approval Date: Sep 17, 2015
Applicant Holder Full Name: ABBVIE INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=204370&Appl_type=N)

VRAYLAR (CARIPRAZINE HYDROCHLORIDE)
EQ 4.5MG BASE
Marketing Status: Prescription

Active Ingredient: CARIPRAZINE HYDROCHLORIDE
Proprietary Name: VRAYLAR
Dosage Form; Route of Administration: CAPSULE; ORAL
Strength: EQ 4.5MG BASE
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N204370
Product Number: 003
Approval Date: Sep 17, 2015
Applicant Holder Full Name: ABBVIE INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=003&Appl_No=204370&Appl_type=N)

VRAYLAR (CARIPRAZINE HYDROCHLORIDE)
EQ 6MG BASE
Marketing Status: Prescription

Active Ingredient: CARIPRAZINE HYDROCHLORIDE
Proprietary Name: VRAYLAR
Dosage Form; Route of Administration: CAPSULE; ORAL
Strength: EQ 6MG BASE
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N204370
Product Number: 004
Approval Date: Sep 17, 2015
Applicant Holder Full Name: ABBVIE INC
Marketing Status: Prescription

Patent and Exclusivity Information (patent_info.cfm?Product_No=004&Appl_No=204370&Appl_type=N)