

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

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)

INDICATIONS AND USAGE

VRAYLAR is an atypical antipsychotic indicated for the:

- Treatment of schizophrenia (1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder (1)

DOSAGE AND ADMINISTRATION

- Administer VRAYLAR once daily with or without food (2)

	Starting Dose	Recommended Dose
Schizophrenia (2.2)	1.5 mg/day	1.5 mg to 6 mg/day
Bipolar Mania (2.3)	1.5 mg/day	3 mg to 6 mg/day

- Doses above 6 mg daily do not confer significant benefit but increased the risk of dose-related adverse reactions.

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) (5.2)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia*: Discontinue if appropriate (5.4)
- *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 (5.5)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 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

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 inhibitors: reduce VRAYLAR dosage by half (2.4, 7.1)
- CYP3A4 inducers: do not recommend use with VRAYLAR (2.4, 7.1)

USE IN SPECIFIC POPULATIONS

- *Pregnancy*: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

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FULL PRESCRIBING INFORMATION

WARNING: 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 (cariprazine) is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.1)].

1. INDICATIONS AND USAGE

VRAYLAR™ is indicated for the:

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

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 (5.5)* and *Clinical Pharmacology (12.3)*].

The maximum recommended dose 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 Schizophrenia

The recommended dose range is 1.5 mg to 6 mg once daily. The starting dose of VRAYLAR is 1.5 mg. 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.

2.3 Manic or Mixed Episodes Associated with Bipolar I Disorder

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

2.4 Dosage Adjustments for CYP3A4 Inhibitors and Inducers

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

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

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

Dosage recommendation for patients concomitantly taking VRAYLAR with CYP3A4 inducers: Concomitant use of VRAYLAR and a CYP3A4 inducer has not been evaluated and is not recommended because the net effect on active drug and metabolites is unclear [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.5)*, *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

2.5 Treatment Discontinuation

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

3. DOSAGE FORMS AND STRENGTHS

VRAYLAR (cariprazine) capsules are available in four strengths.

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

4. CONTRAINDICATIONS

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

5. WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning, Warnings and Precautions (5.2)*].

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

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

5.3 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.

5.4 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.

There is no known treatment for tardive dyskinesia, although the syndrome 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.

5.5 Late-Occurring Adverse Reactions

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

Monitor for adverse reactions, including 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.

5.6 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

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

Schizophrenia

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

Bipolar Mania

In the 3-week, placebo-controlled trials of adult patients with bipolar disorder, 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 ($\geq 6.5\%$).

Dyslipidemia

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

Schizophrenia

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

Bipolar Mania

In the 3-week, placebo-controlled trials of adult patients with bipolar disorder, the proportion of patients with shifts in fasting total cholesterol, LDL, HDL and triglycerides were similar in patients treated with VRAYLAR and placebo.

Weight Gain

Weight gain has been observed with use of atypical antipsychotics, including VRAYLAR. Monitor weight at baseline and frequently thereafter. **Tables 1 and 2** show the change in body weight occurring from baseline to endpoint in 6-week schizophrenia and 3-week bipolar mania trials.

Table 1. Change in Body Weight (kg) in 6-Week Schizophrenia Trials

	Placebo (N=573)	VRAYLAR*		
		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 ($\geq 7\%$)	5%	8%	8%	17%

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

Table 2. Change in Body Weight (kg) in 3-Week Bipolar Mania Trials

	Placebo (N=439)	VRAYLAR*	
		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 ($\geq 7\%$)	2%	1%	3%

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

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.

5.7 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 $< 1000/\text{mm}^3$ and follow their WBC until recovery.

5.8 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.

5.9 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.

5.10 Potential for Cognitive and Motor Impairment

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

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

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

5.11 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.

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

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 the clinical trial database for VRAYLAR, consisting of 1733 patients with schizophrenia (aged 18 to 65) and 1025 patients with manic or mixed episodes associated with bipolar I disorder (aged 18 to 65) exposed to one or more doses with a total experience of 566.5 patient-years. Of these patients, 1317 participated in placebo-controlled, 6-week schizophrenia trials with doses ranging from 1.5 mg to 12 mg/day and 623 participated in placebo-controlled, 3-week bipolar mania trials with doses ranging from 3 mg to 12 mg/day. A total of 364 VRAYLAR-treated patients had at least 24 weeks of exposure and 239 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.

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

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

Adverse Reactions with an incidence of $\geq 2\%$ and greater than placebo, at any dose are shown in **Table 3**.

Table 3. Adverse Reactions Occurring in $\geq 2\%$ of VRAYLAR-treated Patients and $>$ Placebo-treated Adult Patients in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo (N= 584) (%)	VRAYLAR*		
		1.5 - 3 mg/day (N=539) (%)	4.5 - 6 mg/day (N=575) (%)	9 - 12 mg/day (N=203) (%)
Cardiac Disorders				
Tachycardia ^a	1	2	2	3
Gastrointestinal Disorders				
Abdominal pain ^g	5	3	4	7
Constipation	5	6	7	10
Diarrhea ^h	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 ^b	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 ⁱ	<1	1	1	2
Weight increased	1	3	2	3
Metabolism and nutrition disorders				
Decreased appetite	2	1	3	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1	2	1	2
Back pain	2	3	3	1
Pain in extremity	3	2	2	4
Nervous System Disorders				
Akathisia	4	9	13	14
Extrapyramidal Symptoms ^c	8	15	19	20
Headache ^j	13	9	11	18
Somnolence ^d	5	5	8	10
Dizziness	2	3	5	5
Psychiatric Disorders				
Agitation	4	3	5	3
Insomnia ^e	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 ^f	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**Fatigue terms:** asthenia, fatigue

^c**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

^d**Somnolence terms:** hypersomnia, sedation, somnolence

^e**Insomnia terms:** initial insomnia, insomnia, middle insomnia, terminal insomnia

^f**Hypertension terms:** blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension

^g**Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain

^h**Diarrhea terms:** diarrhea, frequent bowel movements

ⁱ**Hepatic enzyme increase terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased

^j**Headache terms:** headache, tension headache

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.

Adverse Reactions Associated with Discontinuation of Treatment: The only adverse reaction leading to discontinuation that occurred at a rate of $\geq 2\%$ 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 ($\geq 5\%$ and at least twice the rate of placebo): extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness.

Adverse Reactions with an incidence of $\geq 2\%$ and greater than placebo at any dose are shown in **Table 4**.

Table 4. Adverse Reactions Occurring in $\geq 2\%$ of VRAYLAR-treated Patients and $>$ Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo (N= 442) (%)	VRAYLAR*	
		3 - 6 mg/day (N=263) (%)	9 - 12 mg/day (N=360) (%)
Cardiac Disorders			
Tachycardia ⁱ	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 ^a	5	6	8
Diarrhea ^b	5	5	6
Toothache	2	4	3
General Disorders/Administration Site Conditions			
Fatigue ^c	2	4	5
Pyrexia ^j	2	1	4
Investigations			
Blood creatine phosphokinase increased	2	2	3
Hepatic enzymes increased ^d	<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 ^e	12	26	29
Headache ^k	13	14	13
Dizziness	4	7	6
Somnolence ^f	4	7	8
Psychiatric Disorders			
Insomnia ^g	7	9	8
Restlessness	2	7	7
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	1	3
Vascular Disorders			

Table 4. Adverse Reactions Occurring in $\geq 2\%$ of VRAYLAR-treated Patients and $>$ Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo (N= 442) (%)	VRAYLAR*	
		3 - 6 mg/day (N=263) (%)	9 - 12 mg/day (N=360) (%)
Hypertension ^h	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 **Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness,

^b **Diarrhea:** diarrhea, frequent bowel movements

^c **Fatigue terms:** asthenia, fatigue

^d **Hepatic enzymes increased terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased

^e **Extrapyramidal Symptoms terms:** bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism, salivary hypersecretion, tremor

^f **Somnolence terms:** hypersomnia, sedation, somnolence

^g **Insomnia terms:** initial insomnia, insomnia, middle insomnia

^h **Hypertension terms:** blood pressure diastolic increased, blood pressure increased, hypertension

ⁱ **Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia

^j **Pyrexia terms:** body temperature increased, pyrexia

^k **Headache terms:** headache, tension headache

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

In 6-week schizophrenia trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness was 17% for VRAYLAR-treated patients versus 8% for placebo-treated patients. These events led to discontinuation in 0.3% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 11% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These events led to discontinuation in 0.5% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of EPS is shown in **Table 5**.

Table 5. Incidence of EPS Compared to Placebo in 6-Week Schizophrenia Studies

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

Note: Figures rounded to the nearest integer

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

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

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

In 3-week bipolar mania trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for VRAYLAR-treated patients versus 12% for placebo-treated patients. These events led to a discontinuation in 1% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 20% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These events led to discontinuation in 2% of VRAYLAR-treated patients versus 0% of placebo-treated patients. The incidence of EPS is provided in Table 6.

Table 6. Incidence of EPS Compared to Placebo in 3-Week Bipolar Mania Trials

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

Note: Figures rounded to the nearest integer

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

** **Dystonia includes adverse event terms:** dystonia, oromandibular dystonia

§ **Parkinsonism includes adverse event terms:** bradykinesia, drooling, dyskinesia, extrapyramidal disorder,

hypokinesia, muscle rigidity, muscle tightness, parkinsonism, salivary hypersecretion, tremor

Cataracts

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

Vital Signs Changes

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

Pooled data from 6-week schizophrenia and 3-week bipolar mania trials are shown in **Tables 7 and 8**.

Table 7. Mean Change in Blood Pressure at Endpoint in 6-Week Schizophrenia Trials

	Placebo (N=574)	VRAYLAR*		
		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

Table 8. 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

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 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 cariprazine and 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 database of 2758 VRAYLAR-treated patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions that appear elsewhere in the VRAYLAR label are not included.

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

*Gastrointestinal Disorders: **Infrequent:** gastroesophageal reflux disease, gastritis*

*Hepatobiliary Disorders: **Rare:** hepatitis*

*Metabolism and Nutrition Disorders: **Frequent:** decreased appetite; **Infrequent:** hyponatremia*

*Musculoskeletal and Connective Tissue Disorders: **Rare:** rhabdomyolysis*

*Nervous System Disorders: **Rare:** ischemic stroke*

*Psychiatric Disorders: **Infrequent:** suicide attempts, suicide ideation; **Rare:** completed suicide*

*Renal and Urinary Disorders: **Infrequent:** pollakiuria*

*Skin and Subcutaneous Tissue Disorders: **Infrequent:** hyperhidrosis*

7. DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with VRAYLAR

Table 9: Clinically Important Drug Interactions with VRAYLAR

Strong CYP3A4 Inhibitors	
<i>Clinical Impact:</i>	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)].
<i>Intervention:</i>	If VRAYLAR is used with a strong CYP3A4 inhibitor, reduce VRAYLAR dosage [see Dosage and Administration (2.3)].
<i>Examples:</i>	itraconazole, ketoconazole
CYP3A4 Inducers	

<i>Clinical Impact:</i>	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 <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention:</i>	Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended [see <i>Dosage and Administration (2.1, 2.3)</i>].
<i>Examples:</i>	rifampin, carbamazepine

7.2 Drugs Having No Clinically Important Interactions with VRAYLAR

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 [see *Clinical Pharmacology (12.3)*].

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. There are no available data on VRAYLAR use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. 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/kg/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 these 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. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [*see Use in Specific Populations (8.1)*]

8.5 Geriatric Use

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

or cardiac function, and of concomitant disease or other drug therapy.

Elderly patients with dementia-related psychosis treated with VRAYLAR are at an increased risk of death compared to placebo. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis [*see Boxed Warning and Warnings and Precautions (5.1, 5.2)*].

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 overdose (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

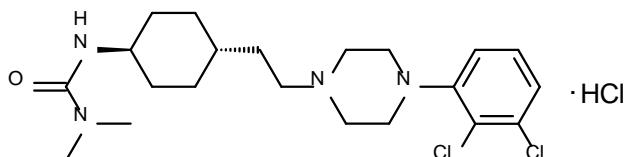
10.2 Management of Overdosage

No specific antidotes for VRAYLAR are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug

involvement. In case of an overdose, consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11. DESCRIPTION

The active ingredient of VRAYLAR is cariprazine HCl, an atypical antipsychotic. The chemical name is *trans*-N-{4-[2-[4-(2,3-dichlorophenyl)piperazine-1-yl]ethyl]cyclohexyl}-N',N'-dimethylurea hydrochloride; its empirical formula is C₂₁H₃₃Cl₃N₄O and its molecular weight is 463.9 g/mol. The chemical structure is:



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

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of cariprazine in schizophrenia and bipolar I disorder is unknown. However, the efficacy of cariprazine could be mediated through a combination of partial agonist activity at central dopamine D₂ and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors. Cariprazine forms two major metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), that have *in vitro* receptor binding profiles similar to the parent drug.

12.2 Pharmacodynamics

Cariprazine acts as a partial agonist at the dopamine D₃ and D₂ 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 (K_i values 0.58 nM and 18.8 nM respectively) as well as it binds to the histamine H₁ 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 (IC₅₀>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

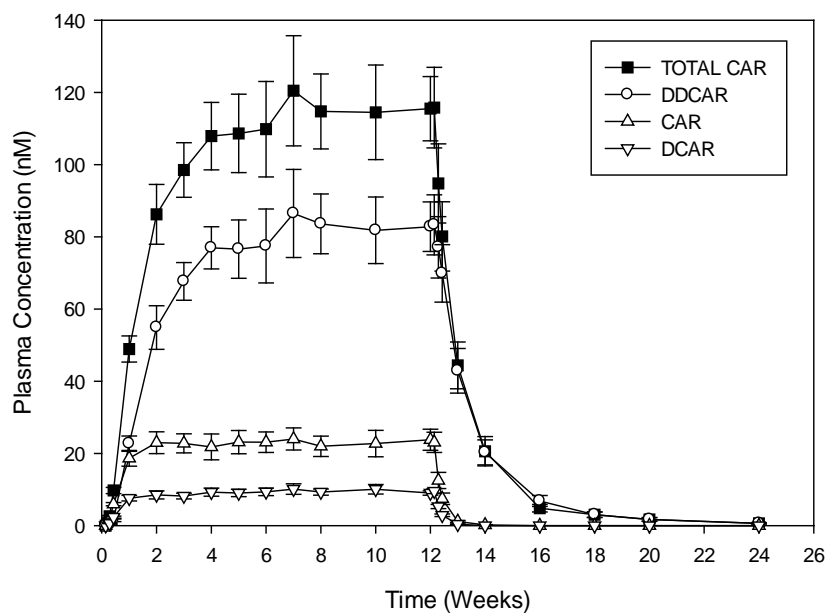
VRAYLAR activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

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, 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 (5.5)*]. 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 \pm SE)-Time Profile During and Following 12-weeks of Treatment with Cariprazine 6 mg/day^a



^aTrough concentrations shown during treatment with cariprazine 6 mg/day.

SE: standard error; TOTAL CAR: sum concentration of cariprazine, DCAR and DDCAR; CAR: cariprazine

Absorption

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

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

Distribution

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

Elimination

Metabolism

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

Excretion

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

Studies in Specific Populations

Hepatic Impairment

Compared to healthy subjects, patients with either mild or moderate hepatic impairment (Child-Pugh score between 5 and 9) had approximately 25% higher exposure (C_{max} and AUC) for cariprazine and approximately 45% lower exposure for the major active metabolites, DCAR and DDCAR, following a single dose of 1 mg cariprazine or 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 polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), and 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*.

CYP 3A4 inhibitors

Coadministration 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.

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/m². 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/m². No effects on male fertility were noted at any dose up to 4.3 times the MRHD of 6 mg/day based on AUC of total cariprazine.

13.2 Animal Toxicology and/or Pharmacology

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

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

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

14. CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of VRAYLAR for the treatment of schizophrenia was established in three, 6-week, randomized, double-blind, placebo-controlled trials in patients (aged 18 to 60 years) who met Diagnostic and Statistical Manual of Mental Disorders 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 10**. 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 10. Primary Analysis Results from Schizophrenia Trials

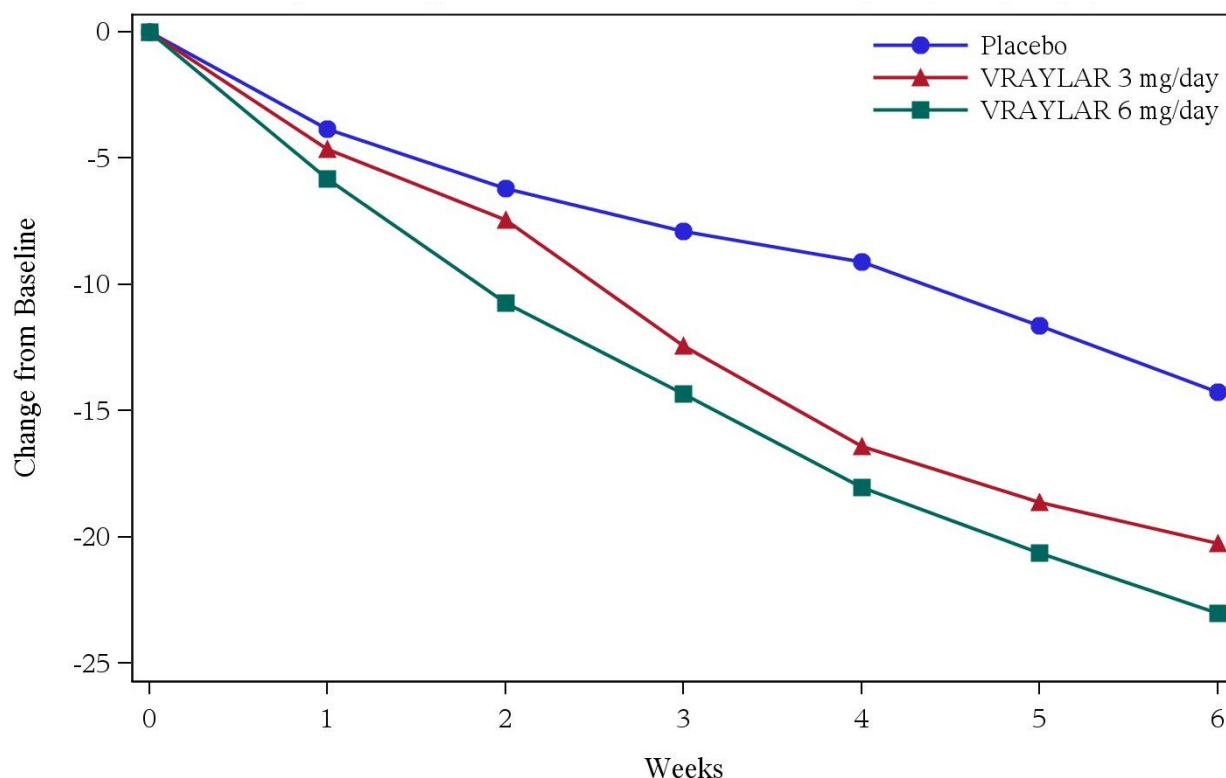
Study Number	Treatment Group (# ITT subjects)	Primary Efficacy Endpoint: PANSS Total		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference ^a (95% CI)
Study 1	VRAYLAR (1.5 mg/day)* (n=140)	97.1 (9.1)	-19.4 (1.6)	-7.6 (-11.8, -3.3)
	VRAYLAR (3 mg/day)* (n=140)	97.2 (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)* (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

^aDifference (drug minus placebo) in least-squares mean change from baseline

*Doses that are statistically significantly superior to placebo

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



14.2 Manic or Mixed Episodes Associated with Bipolar I Disorder

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

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

- The YMRS is an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology. YMRS total score may range from 0 to 60 with a higher score reflecting greater severity.
- The CGI-S is validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In each study, the primary endpoint was decrease from baseline in YMRS total score at the end of week 3. The change from baseline for each VRAYLAR dose group was compared to placebo. The results of the trials are shown in **Table 11**. The time course of efficacy results is shown in Figure 3.

Study 1: 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 2: 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 3: 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 11**) 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 11. Primary Analysis Results from Manic or Mixed Episodes Associated with Bipolar I Disorder Trials

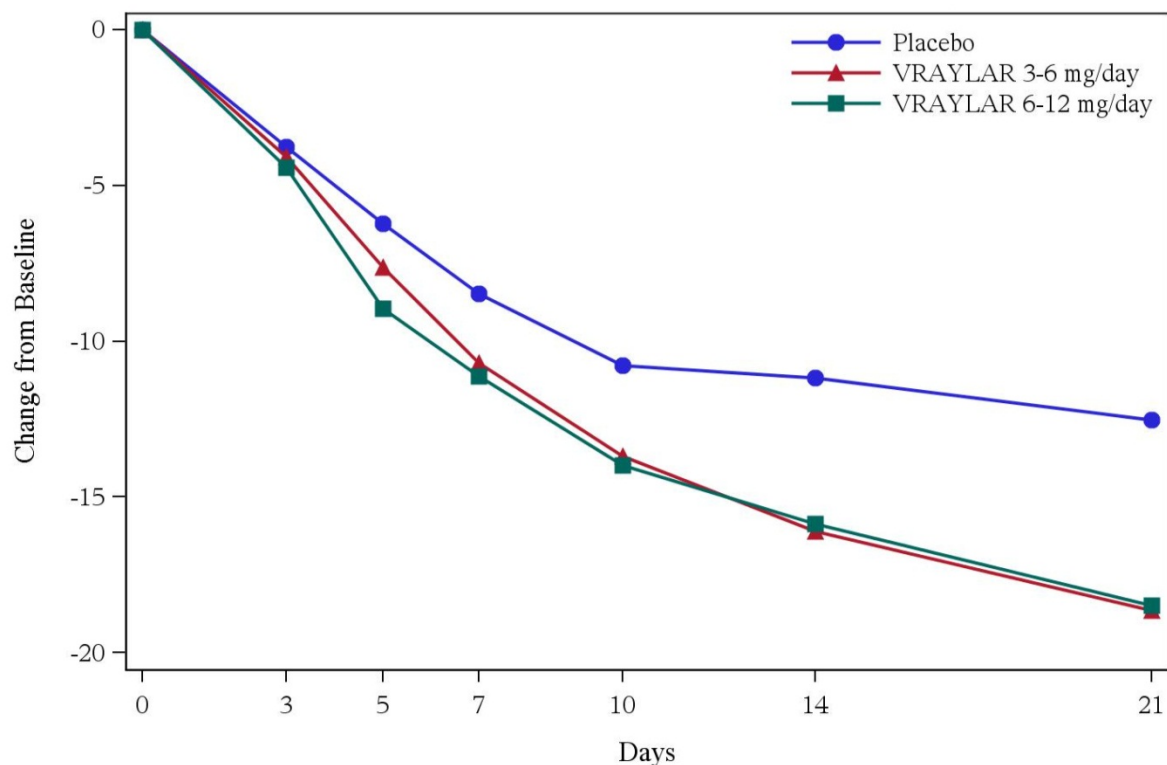
Study Number	Treatment Group (# ITT subjects)	Primary Efficacy Endpoint: YMRS Total		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference ^a (95% CI)
Study 1	VRAYLAR (3-6 mg/day)* (n=165)	33.2 (5.6)	-18.6 (0.8)	-6.1 (-8.4, -3.8)
	VRAYLAR (6-12 mg/day)* (n=167)	32.9 (4.7)	-18.5 (0.8)	-5.9 (-8.2, -3.6)
	Placebo (n=160)	32.6 (5.8)	-12.5 (0.8)	--
Study 2	VRAYLAR (3-12 mg/day)* (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 3	VRAYLAR (3-12 mg/day)* (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

^aDifference (drug minus placebo) in least-squares mean change from baseline

*Doses that are statistically significantly superior to placebo

Figure 3 Change from Baseline in YMRS total score by study visit (Study 1)



16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VRAYLAR capsules are supplied as follows:

Capsule Strength	Imprint Codes	Package Configuration	NDC Code
1.5 mg	FL 1.5	Blister pack of 7	61874-115-17
		Bottle of 30	61874-115-30
		Bottle of 90	61874-115-90
		Box of 100 (Hospital Unit Dose)	61874-115-63
3 mg	FL 3	Bottle of 30	61874-130-30
		Bottle of 90	61874-130-90
		Box of 100 (Hospital Unit Dose)	61874-130-63
4.5 mg	FL 4.5	Bottle of 30	61874-145-30
		Bottle of 90	61874-145-90
		Box of 100 (Hospital Unit Dose)	61874-145-63
6 mg	FL 6	Bottle of 30	61874-160-30
		Bottle of 90	61874-160-90
		Box of 100 (Hospital Unit Dose)	61874-160-63
(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

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

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 [see *Warnings and Precautions (5.3)*].

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 (5.4)*].

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

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 (5.11)*].

Heat Exposure and Dehydration

Educate patients regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions (5.12)*].

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)*].

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