- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*

## 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 ≥ 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 3.

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

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

*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 ≥ 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 4.

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

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

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

| System Organ Class / Preferred Term | Placebo (N= 442) (%) | VRAYLAR* 3 - 6 mg/day (N=263) (%) | VRAYLAR* 9 - 12 mg/day (N=360) (%) |
|---|---|---|---|

Note: Figures rounded to the nearest integer

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

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

*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) (%) | VRAYLAR* 4.5 - 6 mg/day (N=575) (%) | VRAYLAR* 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) (%) | VRAYLAR* 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**

| | | **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

**Table 8. Mean Change in Blood Pressure at Endpoint in 3-Week Bipolar Mania Trials**

| | | **VRAYLAR*** | |
|---|---|---|---|
| | Placebo (N=439) | 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*

### 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 9: 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 (2.3)]*. |
| *Examples:* | itraconazole, ketoconazole |
| **CYP3A4 Inducers** | |
| *Clinical Impact:* | CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the exposure of VRAYLAR has not been evaluated, and the net effect is unclear *[see Clinical Pharmacology (12.3)]*. |
| *Intervention:* | Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended *[see Dosage and Administration (2.1, 2.3)]*. |
| *Examples:* | 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 ≥ 30 mL/minute) renal impairment [*see Clinical Pharmacology 12.3)*].

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

### 8.8 Smoking

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

### 8.9 Other Specific Populations

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

## 9. DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

VRAYLAR is not a controlled substance.

### 9.2 Abuse

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

### 9.3 Dependence

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

## 10. OVERDOSAGE

### 10.1 Human Experience

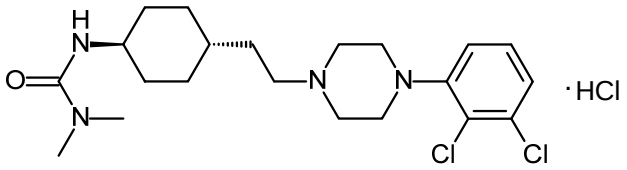
In pre-marketing clinical trials involving VRAYLAR in approximately 5000 patients or healthy subjects, accidental acute overdosage (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

### 10.2 Management of Overdosage

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

## 11. DESCRIPTION

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




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

## 12. CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

Cariprazine acts as a partial agonist at the dopamine $D_3$ and $D_2$ receptors with high binding affinity ($K_i$ values 0.085 nM, and 0.49 nM ($D_{2L}$) and 0.69 nM ($D_{2S}$), respectively) and at the serotonin 5-$HT_{1A}$ receptors ($K_i$ value 2.6 nM). Cariprazine acts as an antagonist at 5-$HT_{2B}$ and 5-$HT_{2A}$ receptors with high and

moderate binding affinity (Ki values 0.58 nM and 18.8 nM respectively) as well as it binds to the histamine $H_1$ receptors ($K_i$ value 23.2 nM). Cariprazine shows lower binding affinity to the serotonin 5-$HT_{2C}$ and $\alpha_{1A}$- adrenergic receptors ($K_i$ values 134 nM and 155 nM, respectively) and has no appreciable affinity for cholinergic muscarinic receptors ($IC_{50}$>1000 nM).

*Effect on QTc Interval*

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

### 12.3 Pharmacokinetics

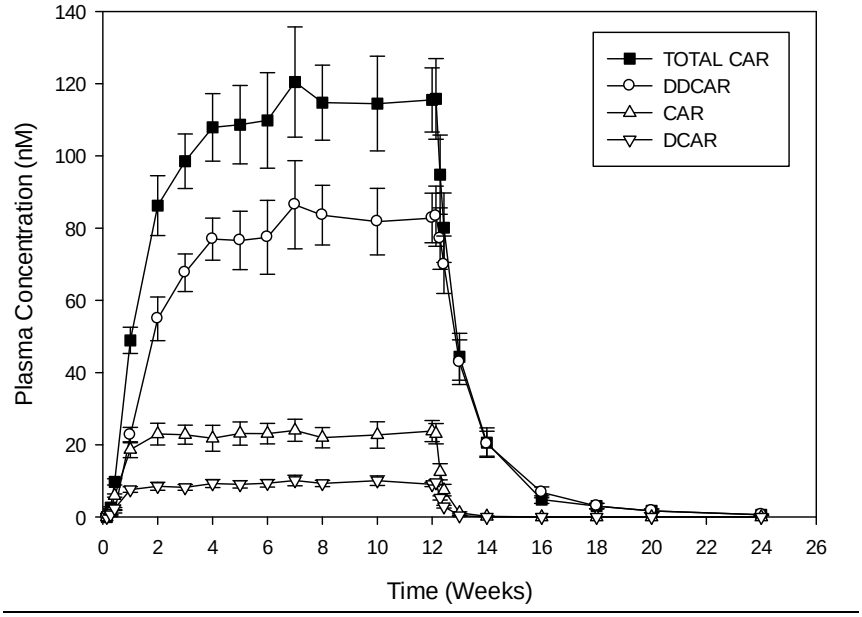
VRAYLAR activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

After multiple dose administration of VRAYLAR, mean cariprazine and DCAR concentrations reached steady state at around Week 1 to Week 2 and mean DDCAR concentrations appeared to be approaching steady state at around Week 4 to Week 8 in a 12-week study (Figure 1). The half-lives based on time to reach steady state, estimated from the mean concentration-time curves, are 2 to 4 days for cariprazine, about 1 to 2 days for DCAR, and approximately 1 to 3 weeks for DDCAR. The time to reach steady state for the major active metabolite DDCAR was variable across patients, with some patients not achieving steady state at the end of the 12 week treatment *[see Dosage and Administration (2.1), Warnings and Precautions (5.5)]*. 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 ± SE)-Time Profile During and Following 12-weeks of Treatment with Cariprazine 6 mg/day[a]**




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

*Absorption*

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

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

*Distribution*

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

*Elimination*

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

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

*Studies in Specific Populations*

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

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

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

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

*Drug Interaction Studies*

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

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

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

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/m$^2$. In female rats, lower fertility and conception indices were observed at all dose levels which are equal to or higher than 1.6 times the MRHD of 6 mg/day based on mg/m$^2$. No effects on male fertility were noted at any dose up to 4.3 times the MRHD of 6 mg/day based on AUC of total cariprazine.

### 13.2 Animal Toxicology and/or Pharmacology

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

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

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

## 14. CLINICAL STUDIES

### 14.1 Schizophrenia

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

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

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

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

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

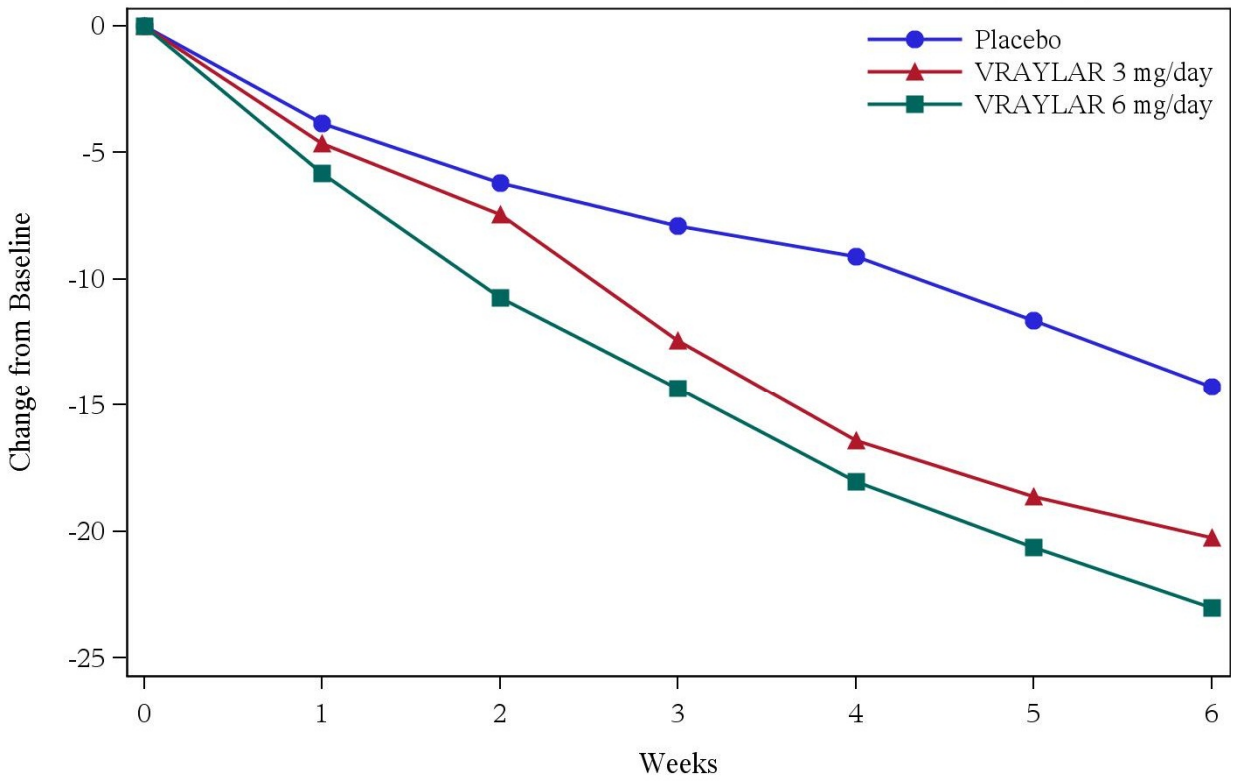
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

**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
[a]Difference (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)**

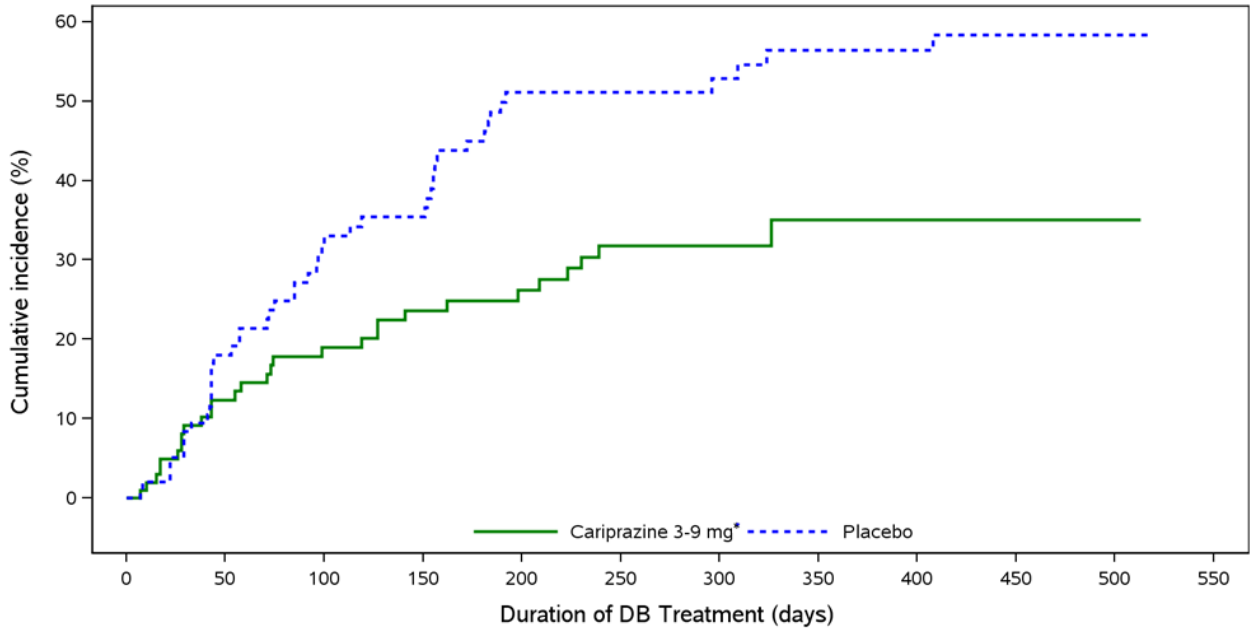



The safety and efficacy of VRAYLAR as maintenance treatment in adults with schizophrenia were demonstrated in a randomized withdrawal trial that included 200 patients meeting DSM-IV criteria for schizophrenia who were clinically stable following 20 weeks of open-label cariprazine at doses of 3 to 9 mg/day.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

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

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

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




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

DB = double-blind

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

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

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

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

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

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

In each study, the primary endpoint was decrease from baseline in YMRS total score at the end of week 3. The change from baseline for each VRAYLAR dose group was compared to placebo. The results of the trials are shown in Table 11. The time course of efficacy results is shown in Figure 4.

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.

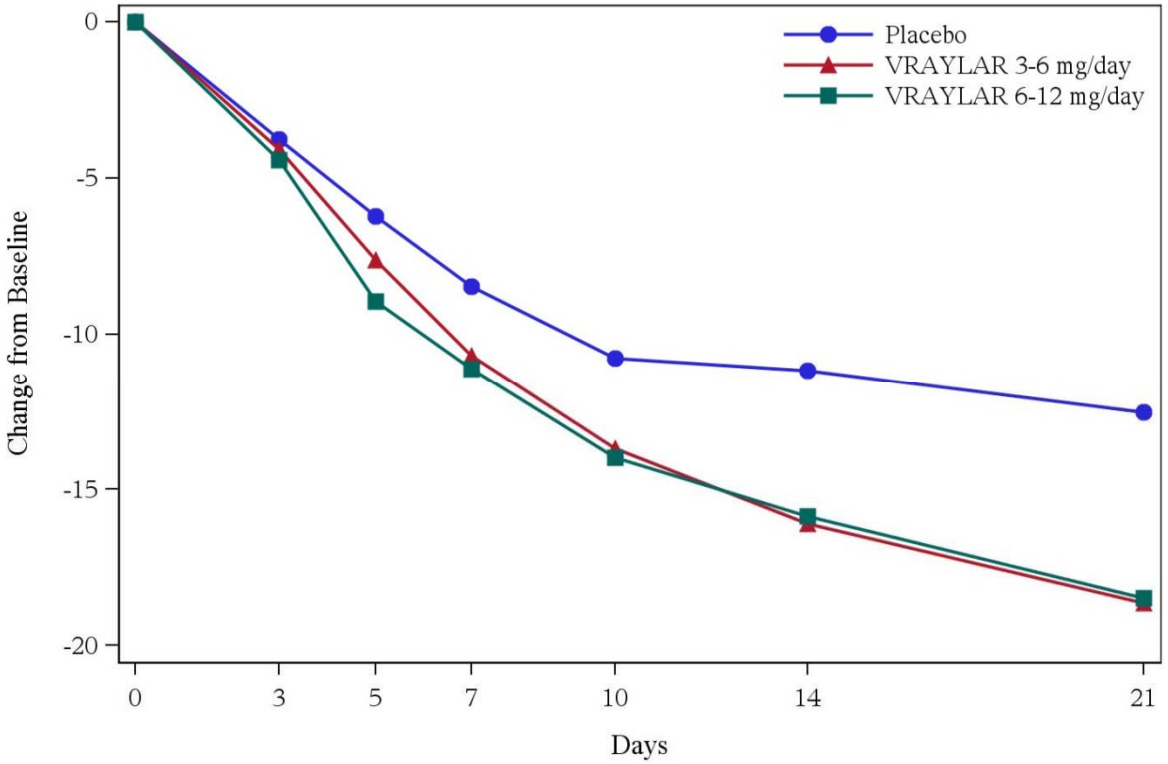
Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

**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
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo

**Figure 4. 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 20 (Hospital Unit Dose) | 61874-115-20 |
| 3 mg | FL 3 | Bottle of 30 | 61874-130-30 |
| | | Bottle of 90 | 61874-130-90 |
| | | Box of 20 (Hospital Unit Dose) | 61874-130-20 |
| 4.5 mg | FL 4.5 | Bottle of 30 | 61874-145-30 |
| | | Bottle of 90 | 61874-145-90 |
| | | | |
| 6 mg | FL 6 | Bottle of 30 | 61874-160-30 |
| | | Bottle of 90 | 61874-160-90 |
| | | | |
| (1) 1.5 mg, (6) 3 mg | FL 1.5<br>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 (5.6)]*.

*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 (5.7)]*.

*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 (5.8)]*.

*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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Forest Laboratories Ireland Limited
Dublin, IE.

Distributed by:
Allergan USA, Inc.
Irvine, CA 92612

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