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

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

Cataracts

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

Vital Signs Changes

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

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

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

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

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

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

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

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

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

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

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

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

Changes in Laboratory Tests

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

Skin and Subcutaneous Tissue Disorders – Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with VRAYLAR

Table 14. Clinically Important Drug Interactions with VRAYLAR

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

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

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

These are not all the possible side effects of VRAYLAR.

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

How should I store VRAYLAR?

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

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

General information about the safe and effective use of VRAYLAR.

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

What are the ingredients in VRAYLAR?

Active ingredient: cariprazine hydrochloride

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

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

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

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

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