Vraylar® (cariprazine) capsules 1.5mg-3mg-4.5mg-6mg

Clinical Program Overview

Clinical Studies of VRAYLAR (cariprazine)[1]

The efficacy and safety of VRAYLAR have been proven in 12 clinical studies and 4 approved indications. VRAYLAR is approved in adults as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD), for the acute treatment of manic or mixed episodes associated with bipolar I disorder, for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression), and for the treatment of schizophrenia. VRAYLAR is the first and only dopamine and serotonin partial agonist approved for adjunctive therapy to antidepressants for the treatment of MDD and for the treatment of bipolar I depression. Although the exact way VRAYLAR works is unknown, the efficacy of VRAYLAR 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.

Adjunctive Treatment of Major Depressive Disorder:

VRAYLAR demonstrated improvement in two pivotal clinical trials based on mean reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at week 6 and week 8 in patients with major depressive disorder treated with VRAYLAR and an antidepressant (ADT). In the two pivotal efficacy studies, VRAYLAR was found to be effective as adjunctive treatment in adults with MDD who had an inadequate response to ADT

Major Depressive Disorder Trials

Study	Length of study	Measurement	Dose	Number of patients	Least-squares mean change from baseline	Significant *P*-value*
Study 10	Week 6	MADRS	1.5 mg/day+ ADT	250	-14.1	*P*<0.01
			3 mg/day + ADT	252	-13.1	NS
			Placebo+ ADT	249	-11.5	
Study 11	Week 8	MADRS	1-2 mg/day+ ADT	273	-13.4	NS
			2-4.5 mg/day + ADT	271	-14.6	*P*<0.05
			Placebo + ADT	264	-12.5	

NS= Not significant
**Adjusted P-values*

Bipolar I Disorder:

Manic and Mixed Episodes:

VRAYLAR demonstrated symptom improvement across 3 pivotal trials based on mean reduction in Young Mania Rating Scale (YMRS) total score at Week 3. VRAYLAR showed significant improvement in overall manic symptoms compared to patients who took placebo.

Bipolar I Disorder - Manic and Mixed Episodes Trials

Study	Length of study	Measurement	Dose	Number of patients	Least-squares mean change from baseline	Significant *P*-value*
Study 4	Week 3	YMRS	3-6 mg/day	165	-18.6	*P*<0.005
			6-12 mg/day†	167	-18.5	*P*<0.005
			Placebo	160	-12.5	
Study 5	Week 3	YMRS	3-12 mg/day†	118	-15.0	*P*<0.0001
			Placebo	117	-8.9	
Study 6	Week 3	YMRS	3-12 mg/day†	158	-19.6	*P*<0.001
			Placebo	152	-15.3	

**Adjusted P-values*

Bipolar Depression:

VRAYLAR demonstrated symptom improvement across 3 pivotal trials based on mean reduction in Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 6. In all three studies, the VRAYLAR 1.5 mg/day dose demonstrated statistical significance over placebo; additionally, in Study 8, the VRAYLAR 3 mg/day dose demonstrated statistical significance over placebo.

Bipolar I Disorder - Bipolar Depression Trials

Study	Length of study	Measurement	Dose	Number of patients	Least-squares mean change from baseline	Significant *P*-value*
Study 7	Week 8	MADRS	1.5 mg/day	145	-15.1	*P*<.0005
			3 mg/day	145	-13.7	NS
			Placebo	141	-11.1	
Study 8	Week 6	MADRS	1.5 mg/day	154	-15.1	*P*<0.05
			3 mg/day	164	-15.6	*P*<0.01
			Placebo	156	-12.6	
Study 9	Week 6	MADRS	1.5 mg/day	162	-14.8	*P*<0.05
			3 mg/day	153	-14.1	NS
			Placebo	163	-12.4	

NS= Not significant
**Adjusted P-values*

Schizophrenia:

VRAYLAR demonstrated symptom improvement across 3 pivotal trials based on mean reduction in Positive and Negative Syndrome Scale (PANSS) total score at Week 6. VRAYLAR showed significant improvement in overall schizophrenia symptoms compared to patients who took a placebo.

Schizophrenia Trials

Study	Length of study	Measurement	Dose	Number of patients	Least-squares mean change from baseline	Significant *P*-value*
Study 1	Week 6	PANSS	1.5 mg/day	140	-19.4	*P*<0.001
			3 mg/day	140	-20.7	*P*<0.001
			4.5 mg/day	145	-22.3	*P*<0.001
			Placebo	148	-11.8	
Study 2	Week 6	PANSS	3 mg/day	151	-20.2	*P*<0.01
			6 mg/day	154	-23.0	*P*<0.0001
			Placebo	149	-14.3	
Study 3	Week 6	PANSS	3-6 mg/day	147	-22.8	*P*<0.01
			6-9 mg/day†	147	-25.9	*P*<0.001
			Placebo	145	-16.0	

**Adjusted P-values*

IMPORTANT SAFETY INFORMATION

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

Elderly people with dementia-related psychosis (having lost touch with reality due to confusion and memory loss) taking medicines like VRAYLAR are at an increased risk of death. VRAYLAR is not approved for treating patients with dementia-related psychosis.

VRAYLAR and antidepressants may increase suicidal thoughts or actions in some children and young adults especially within the first few months of treatment or when the dose is changed. Depression and other mental illnesses are the most important causes of suicidal thoughts and actions. Patients on antidepressants and their families or caregivers should watch for new or worsening depression symptoms, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when VRAYLAR or the antidepressant is started or when the dose is changed. Report any change in these symptoms immediately to the doctor.

VRAYLAR may cause serious side effects, including:

- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death**
- **Neuroleptic malignant syndrome (NMS):** Call your healthcare provider or go to the nearest hospital emergency room right away if you have high fever, stiff muscles, confusion, increased sweating, or changes in breathing, heart rate, and blood pressure. These can be symptoms of a rare but potentially fatal side effect called NMS. VRAYLAR should be stopped if you have NMS.
- **Uncontrolled body movements (tardive dyskinesia or TD):** VRAYLAR may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking VRAYLAR. Tardive dyskinesia may also start after you stop taking VRAYLAR.
- **Late-occurring side effects:** VRAYLAR stays in your body for a long time. Some side effects may not happen right away and can start a few weeks after starting VRAYLAR, or if your dose increases. Your healthcare provider should monitor you for side effects for several weeks after starting or increasing dose of VRAYLAR.
- **Problems with your metabolism, such as:**
  - **High blood sugar and diabetes:** Increases in blood sugar can happen in some people who take VRAYLAR. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before or soon after starting VRAYLAR and regularly during treatment. Tell your healthcare provider if you have symptoms such as feeling very thirsty, very hungry, or sick to your stomach, urinating more than usual, feeling weak, tired, confused, or your breath smells fruity.
  - **Increased fat levels (cholesterol and triglycerides) in your blood:** Your healthcare provider should check fat levels in your blood before or soon after starting VRAYLAR and during treatment.
  - **Weight gain:** Weight gain has been reported with VRAYLAR. You and your healthcare provider should check your weight before and regularly during treatment.
- **Low white blood cell count:** Low white blood cell counts have been reported with antipsychotic drugs, including VRAYLAR. This may increase your risk of infection. Very low white blood cell counts, which can be fatal, have been reported with other antipsychotics. 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 blood pressure when changing position (orthostatic hypotension), and can slow thinking and motor skills, which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions)**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities:** Do NOT drive, operate machinery, or do other dangerous activities until you know how VRAYLAR affects you. VRAYLAR may make you drowsy.
- **Increased body temperature:** Do not become too hot or dehydrated during VRAYLAR treatment. Do not exercise too much. In hot weather, stay inside in a cool place if possible. Stay out of the sun. Do not wear too much clothing or heavy clothing. Drink plenty of water.
- **Difficulty swallowing** that can cause food or liquid to get into your lungs

Who should not take VRAYLAR?

Do not take VRAYLAR if you are allergic to any of its ingredients. Get emergency medical help if you are having an allergic reaction (eg, rash, itching, hives, swelling of the tongue, lip, face or throat).

What should I tell my healthcare provider before taking VRAYLAR?

Tell your healthcare provider about any medical conditions and if you:

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar in you or your family
- have or have had high levels of total cholesterol, LDL-cholesterol, or triglycerides; or low levels of HDL-cholesterol
- have or have had seizures (convulsions)
- have or have had kidney or liver problems
- have or have had low white blood cell count
- are pregnant or plan to become pregnant. VRAYLAR may harm your unborn baby. Taking VRAYLAR during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. Talk to your healthcare provider about the risk to your unborn baby if you take VRAYLAR during pregnancy. If you become pregnant or think you are pregnant during treatment, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or http://www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. It is not known if VRAYLAR passes into breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with VRAYLAR.

Tell your healthcare provider about all medicines that you take, including prescriptions, over-the-counter medicines, vitamins, and supplements. VRAYLAR may affect the way other medicines work, and other medicines may affect how VRAYLAR works. Do not start or stop any medicines while taking VRAYLAR without talking to your healthcare provider.

What are the most common side effects of VRAYLAR?

- The most common side effects include difficulty moving or slow movements, tremors, uncontrolled body movements, restlessness and feeling like you need to move around, sleepiness, nausea, vomiting, indigestion, constipation, feeling tired, trouble sleeping, increased appetite, and dizziness.

These are not all the possible side effects of VRAYLAR.

Please see the full Prescribing Information, including Boxed Warnings, and Medication Guide.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

If you are having difficulty paying for your medicine, AbbVie may be able to help. Visit www.AbbVie.com/myAbbVieAssist to learn more.

Visit www.VRAYLAR.com for more information.

Reference: VRAYLAR. Package insert. Allergan USA, Inc; 2022

Maintenance Treatment of Schizophrenia:

VRAYLAR was approved by the FDA in November 2017 for the maintenance treatment of schizophrenia in adults. This approval was based on positive results from a withdrawal study in the prevention of relapse in adult patients with schizophrenia in 200 adult patients with acute exacerbation of schizophrenia who were found to respond to VRAYLAR, and who met stabilization criteria. The study duration was up to 92 weeks, with a 20-week open-label phase where patients with schizophrenia were treated with VRAYLAR 3, 6, or 9 mg/day. Patients were then randomized either to continue their VRAYLAR dose or be switched to placebo for up to 72 weeks or until a relapse occurred. VRAYLAR was shown to significantly delay the time to relapse compared to placebo.

†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.

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