Brand Name: Vraylar

Generic Name: Cariprazine

Manufacturer[5]: Actavis Pharma, Inc.

Drug Class[5]: Second Generation (Atypical) Antipsychotic

Uses:

Labeled[1,2,3,4,5]: Indicated for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder
Unlabeled: None reported

Mechanism of Action[1,2,3,4,5]:

The exact mechanism of cariprazine is unknown. It is thought that drug efficacy is related to the result of partial agonist activity at central dopamine D-2 and serotonin 5-HT1A receptors, and antagonist activity at serotonin 5-HT2A receptors. Cariprazine is a partial agonist at D-2 and D-3 with high binding affinity, an antagonist at 5-HT2B with high binding affinity, an antagonist at 5-HT2A with moderate binding affinity, and it acts as a moderate antagonist at H-2 receptors. There is a lower binding affinity at serotonin 5-HT2C and alpha-1 adrenergic receptors. There is no appreciable affinity for muscarinic receptors.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max}	3-6 hours
V_d	Not reported
$T_{1/2}$	2-4 days
Clearance	Not reported
Protein binding	91-97% (% albumin not reported)
Bioavailability	Not reported

Metabolism: Cariprazine is extensively metabolized in the liver primarily by CYP3A4 and to a lesser extent CYP2D6 to desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Both metabolites are pharmacologically equipotent to cariprazine. DCAR is metabolized to DDCAR by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite.

Elimination: Cariprazine is primarily excreted through the kidneys into urine (21%). 1.2 % was excreted in urine as unchanged cariprazine.

Efficacy:

Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, Nemeth G, Durgam S. Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. Journal of affective disorders. 2015;174:296-302.

Study Design: Multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible dose study.

Description of Study: *Methods:* 312 patients with acute manic or mixed episodes associated with bipolar I disorder were randomized to receive either cariprazine or placebo. The study comprised three phases: a no-drug washout period of 4-7 days, a 3-week treatment phase, and a 2-week safety follow-up period. Patients randomized to receive cariprazine started with a dose of 1.5 mg/day (day 0) with a dose increase to 3.0 mg/day on day 1; on day 2, dosage could be increased to 6 mg/day for 2 days based on patient response and tolerability. Patients were voluntarily hospitalized during the washout period and for at least 14 days of the 3-week treatment phase. Efficacy was assessed using the YMRS, CGI-S, MADRS, and Positive and Negative Syndrome Scale (PANSS). Safety evaluations included the recording of adverse events, clinical laboratory tests, 12-lead electrocardiogram, weight, vital signs, and the Columbia-Suicide Rating Scale (C-SSRS). Extrapyramidal symptoms were assessed with the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS). Efficacy analyses were based on the Intent-to-Treat population. *Outcome Results:* At week three, the YMRS total score was reduced by an average of 19.6 in the cariprazine group. A total of 6 (4%) placebo-treated patients and 30 (19%) cariprazine treated patients experienced treatment-emergent EPS. 8 placebo treated patients and 36 cariprazine treated patients experienced treatment-emergent akathisia.

Limitations: Since this study is active drug versus placebo, there is a lack of active comparison. Also, the duration of this study was short. Longer studies are needed to better characterize the metabolic effects of cariprazine. The study was funded by Forest Laboratories, which is a subsidiary of Vraylar's manufacturer, Actavis. Forest Laboratories was involved in the study design, collection, analysis, interpretation of data, and the decision to present these results. There were several conflicts of interest related to the authors of the study. The study excluded patients that had been treated with clozapine within the last 10 years. This makes the results difficult to extrapolate to patients that had been previously treated with clozapine. The study's drug

wash out period is not sufficient for patients that had previously been on an antipsychotic medication.

Conclusion: The study showed that cariprazine was generally well tolerated in the treatment of acute manic or mixed episodes associated with bipolar I disorder. Cariprazine treatment response was greater than placebo. Since this study included only three weeks of treatment, further studies would be needed to further evaluate adverse effects.

Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, Laszlovszky I. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord 2015; 17: 63-75.

Study Design: Multinational, randomized, double-blind, placebo-controlled, parallel group, flexible-dose study.

Description of Study: *Methods:* A total of 238 patients were randomized to receive either placebo or cariprazine (3-12 mg/day) in the treatment of acute manic or mixed episodes associated with bipolar I disorder. The study consisted of a drug washout period of up to four days, a three-week treatment period, and a two-week safety follow up. Cariprazine was initiated at 1.5 mg/day and then increased to dose assigned. The scales used to assess primary and secondary efficacy were the YMRS and CGI-S, respectively. Both YMRS and CGI-S were administered at screening, baseline, and days 2, 4, 7, 11, 14, and 21. Additionally, the Clinical Global Impressions—Improvement (CGI-I) scale, MADRS, and Positive and Negative Syndrome Scale (PANSS) were administered. Adverse events reports, laboratory tests, 12-lead ECG, and vital signs evaluated safety and tolerability. *Outcome Results:* On average, cariprazine decreased the YMRS total score by 15, compared to placebo's 8.9. Only extrapyramidal disorder and akathisia occurred at a significantly higher incidence in cariprazine relative to placebo patients.

Limitations: Similar to other mania studies, the short duration of the trial and the lack of a comparing agent are considered to be limitations of the study. The study excluded patients with other DSM-IV Axis I diagnoses (dementia, schizophrenia, schizoaffective disorder, etc). Further studies would need to be done to determine use of cariprazine in those disorders. The differences between the groups at baseline were recorded but the significance was not expressed. The drug wash out period of up to 4 days would not be appropriate for patients currently taking an antipsychotic drug. The study was supported by funding from Forest Laboratories, Inc. and Gedeon Richter Plc.

Conclusion: The study demonstrated that cariprazine was effective in the treatment of adult patients with acute manic or mixed episodes associated with bipolar I disorder. Cariprazine demonstrated improvement on all

measures with the exception of MADRS, which measured depression symptoms. Further studies are needed to determine long-term adverse effects of cariprazine since this study only included three weeks of treatment.

Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Nemeth G, Vieta E, Calabrese J, Yatham L. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry. 2016; 173: 271-281.

Study Design: Multinational, randomized, double-blind, placebo-controlled, parallel group, fixed dose study.

Description of Study: *Methods:* In the study, 584 patients were randomized to receive placebo or three doses of cariprazine (0.75 mg/day, 1.5 mg/day, or 3 mg/day). The study included a screening period (up to 14 days, including a no-drug 1-week washout), 8-week treatment, and 1-week safety follow-up. The primary analysis endpoint was week 6, but patients continued double-blind treatment through week 8 to assess the persistence of efficacy. All patients receiving cariprazine were started on a dose of 0.5 mg/day and titrated up to their assignment dosing. Efficacy was evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S, and the HAM-D, all of which were administered at screening, at baseline, and at weeks 1, 2, 4, 6, and 8. Physical examination and clinical laboratory monitoring were conducted at screening and at week 8. Adverse events and vital sign parameters were recorded at each study visit; ECG was performed at screening and at weeks 1, 4, and 8. The Young Mania Rating Scale (YMRS) was administered at screening and at all visits. The Columbia-Suicide Severity Rating Scale and extrapyramidal symptom scales were administered at all study visits. The Columbia-Suicide Severity Rating Scale was also administered at follow up. *Outcome Results:* Cariprazine 0.75 mg/day had an average decrease of 13 on the MADRS. Cariprazine 1.5 mg/day had an average decrease of 15.1, while 3.0 mg/day had an average decrease of 13.7 on the MADRS. The only serious adverse events considered related to study drug were depression and hypomania.

Limitations: Interpretation of these results is limited by the lack of an active comparator and short treatment duration. Since only patients with bipolar I disorder without serious psychiatric comorbidities were enrolled, the generalizability of findings to patients with psychiatric comorbidities or bipolar II disorder is unclear. The study was not powered to detect a potential dose response, so it is unknown whether there is a relationship between cariprazine dosage and therapeutic effect. The study included a one week drug wash out period, which might not have been long enough in patients previously on an antipsychotic drug. The study was supported by Forest Laboratories, an Allergan affiliate, and Gedeon Richter.

Conclusion: Cariprazine at 1.5 mg/day demonstrated the most efficacy and safety when used for the treatment of bipolar I depression. Given the limited number of positive studies for atypical antipsychotics in bipolar I depression, future studies are needed to further use.

Contraindications[1,2,3,4,5]:

Black box 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. Although causes of death were varied, most of them appeared to be either cardiovascular or infectious in nature. Cariprazine is not approved for the treatment of patients with dementia-related psychosis.

Hypersensitivity to cariprazine or any component of the formulation. Cariprazine is contraindicated in patients with history of a hypersensitivity reaction to cariprazine. Reactions reported include rash, pruritus, urticarial, and events suggestive of angioedema.

Precautions:

Blood dyscrasias: Leukopenia, neutropenia, and agranulocytosis have been reported in clinical trials and postmarking reports with antipsychotic use. Presence of risk factors should prompt periodic blood count assessments. Discontinue therapy if absolute neutrophil count less than 1,000/mm^3, or at first signs of blood dyscrasias.

CNS depression: May cause, which can impair physical or mental abilities. Caution patients about performing tasks that require mental alertness.

Dyslipidemia: Reported with atypical antipsychotics. In clinical trials, lipid changes observed with cariprazine monotherapy were similar to placebo.

Esophsageal dysmotility/aspiration: Has been associated with antipsychotic use. Use with caution in patients at risk for aspiration pneumonia.

Extrapyramidal symptoms: May be caused by antipsychotics. Symptoms include pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia. Risk of dystonia may be greater with increased doses, use of conventional antipsychotics, males, and younger patients. Factors associated with greater vulnerability to tardive dyskinesia include older in age, female combinded with postmenopausal status, Parkinson disease, pseudoparkinsonism symptoms, affective disorders, and concurrent medical diseases such as diabetes, previous brain damage, alcoholism, poor treatment response, and use of high doses of antipsychotics. Consider therapy discontinuation with signs/symptoms of tardive dyskinesia.

Hyperglycemia: Development has been associated with use of atypical antipsychotics, in some cases may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Monitor patients for symptoms of hyperglycemia: polydipsia, polyuria, polyphagia, and weakness. Use caution in patients with diabetes, monitor for worsening of glucose control.

Neuroleptic malignant syndrome: May be associated with use. Monitor for mental status changes, fever, muscle rigidity, autonomic instability, increased creatine phosphokinase, rhabdomyolysis, and/or acute renal failure. If suspected, discontinue immediately, provide symptomatic treatment, and monitor patient. Neuroleptic malignant syndrome can recur. Carefully consider reintroduction of drug therapy.

Orthostatic hypotension: Risk is increased at initial dose titration and when increasing the dose. Use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes. Consider using lower starting dosages and slower titrations in these patients.

Parkinson disease: Use antipsychotics with caution, may aggravate motor disturbances.

Seizures: Use with caution in patients at risk of seizures or with conditions that potentially lower the seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication with anticholinergic effects.

Weight gain: Significant weight gain (>7%) has been observed with antipsychotic therapy. Monitor waist circumference and BMI.

Adverse effects[2]:

Occurring in >10% of patients

Central Nervous System

Drug-induced extrapyramidal reaction (excluding akathisia and restlessness: 15% to 26%)
Parkinsonian-like syndrome (13% to 21%)
Akathisia (9% to 20%)
Headache (14%)
Insomnia (9% to 13%)

Gastrointestinal

Nausea (7% to 13%)

Occurring in >1% to <10% of patients

Cardiovascular

Hypertension (2% to 5%)
Tachycardia (2%)

Central Nervous System

Drowsiness (7% to 8%)
Restlessness (4% to 7%)
Dizziness (3% to 7%)
Anxiety (5% to 6%)
Agitation (5%)
Dystonia (2% to 5%)
Fatigue (3% to 4%)

Dermatologic

Skin rash (2%)

Endocrine & Metabolic

Weight gain (2% to 3%)

Gastrointestinal

Vomiting (4% to 10%)
Dyspepsia (5% to 7%)
Abdominal pain (6%)
Constipation (6%)
Diarrhea (4%)
Toothache (4%)
Decreased appetite (3%)
Xerostomia (3%)

Hepatic

Increased liver enzymes (1%)

Neuromuscular & Skeletal

Leg pain (4%)
Back pain (3%)
Musculoskeletal stiffness (2% to 3%)
Arthralgia (2%)
Increased creatine phosphokinase (2%)

Ophthalmic

Blurred vision (4%)

Drug Interactions[2,4]:

Acetylcholinesterase inhibitors

May enhance the neurotoxic effect of antipsychotic agents. Severe extrapyramidal symptoms have occurred in some patients

Antidiabetic agents

Hyperglycemia associated agents may diminish the therapeutic effect of antidiabetic agents

Blood pressure lowering agents

May enhance the hypotensive effect of atypical antipsychotic agents

CNS Depressants

May enhance the adverse/toxic effect of other CNS depressants, such as cariprazine. Exception of nasal levocabastine.

CYP3A4 inducers (moderate)

May decrease the serum concentration of cariprazine.

CYP3A4 inducers (strong)

May decrease the serum concentration of cariprazine. Avoid combination

CYP3A4 inhibitors (moderate)

May decrease the metabolism and increase the serum concentration of cariprazine

CYP3A4 inhibitors (strong)

May increase the serum concentration of cariprazine. Management: Cariprazine dose reductions of 50% are required; specific recommended management varies slightly for those stable on cariprazine versus those just starting cariprazine. See Dosing/Administration section below for more information. Consider therapy modification.

Selective serotonin reuptake inhibitors

CNS depressants may enhance the adverse/toxic effect of selective serotonin reuptake inhibitors. Specifically, the risk of psychomotor impairment may be enhanced.

Serotonin modulators

May enhance the adverse/toxic effect of antipsychotic agents. Specifically, serotonin modulators may enhance dopamine blockage, possibly increasing the risk for neuroleptic malignant syndrome. Antipsychotic agents may enhance the serotonergic effect of serotonin modulators, possibly resulting in serotonin syndrome.

Dosing/Administration:

Adult:

Bipolar I disorder:

Initial: 1.5 mg once daily; adjust dose based on response and tolerability to 3 mg on day 2 and make further adjustments in increments of 1.5 or 3 mg.

Recommended dosing range: 3 mg to 6 mg once daily

Maximum dose: 6 mg daily

Schizophrenia:

Initial: 1.5 mg once daily; adjust dose based on response and tolerability to 3 mg on day 2 and make further adjustments in increments of 1.5 or 3 mg

Recommended dosing range: 1.5 mg to 6 mg once daily

Maximum dose: 6 mg daily

Dosage adjustment with concurrent CYP450 inducer or inhibitor

Strong CYP3A4 inhibitor initiated while on stable dose of cariprazine: Reduce the current dose of cariprazine by 50%. For patients taking 4.5 mg daily, reduce the dose to 1.5 mg or 3

mg daily. For patients taking 1.5 mg daily, adjust the dose to every other day. The cariprazine dose may need to be increased if the CYP3A4 inhibitor is withdrawn.
Initiating cariprazine therapy while already on a strong CYP3A4 inhibitor: Administer cariprazine 1.5 mg on day 1 and day 3 (no dose administered on day 2). Administer 1.5 mg daily starting on day 4 and increase to a maximum of 3 mg daily. The cariprazine dose may need to be increased if the CYP3A4 inhibitor is withdrawn.
Concomitant use of cariprazine and CYP3A4 inducers: Use is not recommended

Geriatric

Refer to adult dosing

Pediatric

Safety and effectiveness in pediatric patients have not been established

Renal Impairment

CrCl>30 mL/min: No dosage adjustment necessary
CrCl<30 mL/min: Use not recommended, has not been studied

Hepatic Impairment

Mild to moderate impairment: No dosage adjustment necessary
Severe impairment: use not recommended, has not been studied

Use in special circumstances:

Pregnancy[2]: Antipsychotic use during the third trimester of pregnancy has a risk for abnormal muscle movements and/or withdrawal symptoms in newborns following delivery. Symptoms in the newborn may include agitation, feeding disorder, hypertonia, hypotonia, respiratory distress, somnolence, and tremor; these effects may be self-limiting or require hospitalization.

Lactation[2,5]: 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. The manufacturer recommends the development and health benefits of breast-feeding be considered along with the mother's clinical need for therapy and any potential adverse effects on the breast-fed infant.

Conclusion:

Cariprazine is an effective therapy for treatment of patients with schizophrenia and bipolar I disorder. The studies included in this monograph mostly dealt with bipolar disorder, but there are studies available showing cariprazines effectiveness in schizophrenia. More studies need to be conducted for its use in other psychiatric disorders. Cariprazine does have many drug interactions, which can be problematic if a patient has multiple chronic conditions. Side effects occurring with cariprazine

occur with other atypical antipsychotics. Studies evaluating cariprazine to an active comparison would be needed to help define cariprazine's place in therapy.

Recommended References:

1. Cariprazine. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: http://www.clinicalpharmacology.com Accessed: May 23, 2016.
2. Cariprazine. Lexi-Drugs [database online]. Lexi-Comp, Inc; May 23, 2016.
3. Cariprazine. In: DRUGDEX System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: May 23, 2016.
4. Cariprazine Oral. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: May 23, 2016.
5. Cariprazine [package insert]. Parsippany, NJ: Actavis Pharma, Inc: 2015.
6. Monica Holmberg. Vraylar. [published May 13, 2016]. Pharmacy Times. Available at: http://www.pharmacytimes.com/publications/issue /2016/May2016/Vraylar. Accessed May 31, 2016.

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