PDL DRUG REVIEW

Proprietary Name: Vraylar®
Common Name: cariprazine
PDL Category: Antipsychotics, Atypicals

Comparable Products	Preferred Drug List Status
Abilify	Preferred Step 2
Olanzapine	Preferred
Risperidone	Preferred

Summary

Pharmacology/Usage: Cariprazine, the active ingredient of Vraylar®, is an atypical antipsychotic. The exact mechanism of action is not known; however, it is thought it could be mediated through a combination of partial agonist activity at central dopamine D2 and serotonin 5-HT1a receptors and antagonist activity at serotonin 5-HT2A receptors. Desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), two active metabolites, have *in vitro* receptor binding similar to the parent drug.

Indications: For the treatment of schizophrenia AND for the acute treatment of manic or mixed episodes associated with bipolar I disorder.

There is no pregnancy category with this product; however, the risk summary indicates that neonates exposed to antipsychotic drugs during the 3rd trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no data on use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. Based on animal data, Vraylar® may cause fetal harm. It is recommended to advise pregnant women of the potential risk to a fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Capsules: 1.5mg, 3mg, 4.5mg, 6mg; this product is also available in a therapy pack of 1.5mg and 3mg capsules

Recommended Dosage: *Schizophrenia:* 1.5-6mg QD, starting at 1.5mg QD and titrating as needed depending on clinical response and tolerability. *Manic/Mixed Episodes with bipolar I disorder:* 3-6mg QD, starting at 1.5mg QD and titrating dependent on clinical response and tolerability. The maximum recommended dose is 6mg daily.

As cariprazine has a long half-life (2-4 days), as well as its active metabolites (1-3 weeks), a change in dose will not be fully reflected in plasma for several weeks. It is recommended to monitor for adverse reactions and treatment response for several weeks after starting therapy and after each dose change.

Dose adjustments are not required in patients with mild or moderate renal or hepatic impairment; however, use is not recommended in patients with severe renal impairment (CrCl <30ml/minute) or severe hepatic impairment as use has not been studied in this population.

Drug Interactions: It is recommended to reduce the Vraylar® dose if it is used concomitantly with a strong CYP3A inhibitor (such as itraconazole, ketoconazole). The concomitant use of Vraylar® with a CYP3A4 inducer (such as rifampin, carbamazepine) is not recommended.

Common Adverse Drug Reactions: *The listed % incidence for adverse drug reactions= reported % incidence for drug (Vraylar® 4.5-6mg/day in schizophrenia trials) minus placebo.* The most frequently reported adverse events included tachycardia (1%), abdominal pain (0%), constipation (2%), diarrhea (1%), dry mouth (0%), dyspepsia (1%), nausea (2%), vomiting (2%), toothache (0%), fatigue (2%), nasopharyngitis (0%), blood creatine phosphokinase increased (1%), weight increased (1%), decreased appetite (1%), arthralgia (0%), back pain (1%), pain in extremity (0%), akathisia (9%), extrapyramidal symptoms (11%), headache (0%), somnolence (3%), dizziness (3%), agitation (1%), insomnia (2%), restlessness (3%), cough (0%), rash (0%), and hypertension (2%).

As do all antipsychotics, Vraylar® has a box warning regarding the increased risk of mortality in elderly patients with dementia-related psychosis. Vraylar® is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic malignant syndrome (NMS) and tardive dyskinesia have been reported with antipsychotic drugs, including Vraylar®. If signs and symptoms are seen, treatment should be discontinued.

Metabolic changes, including hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain have been reported with antipsychotics. The proportion of patients with shifts in lipid profiles and with shifts in fasting glucose were similar between the Vraylar® treated group and placebo. Weight gain was reported with Vraylar®; thus, it is recommended to monitor weight at baseline and frequently thereafter.

There have been reports of leukopenia and neutropenia during treatment with antipsychotics, including Vraylar®. Agranulocytosis has been reported with other agents in the class. It is recommended to perform a complete blood count frequently during the first few months of treatment in patients with a pre-existing low white blood count or absolute neutrophil count (ANC). It is also recommended to monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection. Discontinue Vryalyar® in patients with ANC <1000/mm^3.

Contraindications: In patients with history of hypersensitivity to cariprazine

Manufacturer: Actavis Pharma

Analysis: The efficacy of Vraylar® was assessed in three 6-week, randomized, double-blind, placebo-controlled studies that included adult patients diagnosed with schizophrenia. An active control arm (risperidone or aripiprazole) was included in two trials to assess assay sensitivity. The primary outcome for all three studies was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at the end of week 6, while a secondary outcome was the change in the Clinical Global Impressions-Severity (CGI-S) rating scale.

Study information can be found in the table below.

Study	N	Comparators	Results
1	711	Vraylar® 1.5mg, 3mg, or 4.5mg QD ***Vs*** placebo ***Vs*** risperidone (active control)	All Vraylar® doses & active control superior to placebo for PANSS & CGI-S
2	604	Vraylar® 3mg or 6mg QD ***Vs*** placebo ***Vs*** aripiprazole (active control)	Vraylar® doses & active control superior to placebo on PANSS & CGI-S
3	439	Vraylar® 3mg to 6mg QD (or 6mg to 9mg QD) ***Vs*** placebo	Vraylar® doses superior to placebo on PANSS & CGI-S

Specific results for the primary outcome of the PANSS total score can be found in the table below, which were obtained from the prescribing information.

Treatment group	Mean baseline PANSS total score	LS Mean Change from baseline	Placebo-subtracted difference
Study 1			
Vraylar® 1.5mg	97.1	-19.4	-7.6
Vraylar® 3mg	97.2	-20.7	-8.8
Vraylar® 4.5mg	96.7	-22.3	-10.4
Placebo	97.3	-11.8	
Study 2			
Vraylar® 3mg	96.1	-20.2	-6.0
Vraylar® 6mg	95.7	-23.0	-8.8
Placebo	96.5	-14.3	
Study 3			
Vraylar® 3-6mg	96.3	-22.8	-6.8
Vraylar® 6-9mg	96.3	-25.9	-9.9
Placebo	96.6	-16.0	

Specific data was not included for active comparators in the prescribing information. However, in the published study by Durgam et al[2], statistically significant differences from placebo were seen with aripiprazole in study 2 on the PANSS total score (LS mean change -7.0; p=0.0008) and on the CGI-S (LS mean change -0.4; p=0.0001).

There were three 3-week placebo-controlled studies to assess the safety and efficacy of Vraylar® when used for the treatment of bipolar mania. These studies included adults with bipolar I disorder with manic or mixed episodes with or without psychotic features. The Young Mania Rating Scale (YMRS) total score was the primary outcome assessed, while the Clinical Global Impressions-Severity (CGI-S) scale was a secondary outcome assessed.

Study information can be found in the table below.

Study	N	Comparators	Results
1	492	Vraylar® 3 to 6mg or 6 to 12mg QD ***Vs*** placebo	Vraylar® doses superior to placebo on YMRS & CGI-S (6-12mg/day showed no additional advantage)
2	235	Vraylar® 3 to 12mg ***Vs*** placebo	Vraylar® superior to placebo on YMRS & CGI-S
3	310	Vraylar® 3mg to 12mg QD ***Vs*** placebo	Vraylar® superior to placebo on YMRS & CGI-S

Specific results for the primary endpoint of the YMRS total can be found in the table below, which was obtained from the prescribing information. Doses >6mg/day did not appear to have additional benefit over lower doses.

Treatment group	Mean baseline YMRS total score	LS Mean Change from baseline	Placebo-subtracted difference
Study 1			
Vraylar® 3-6mg	33.2	-18.6	-6.1
Vraylar® 6-12mg	32.9	-18.5	-5.9
Placebo	32.6	-12.5	
Study 2			
Vraylar® 3-12mg	30.6	-15	-6.1
Placebo	30.2	-8.9	

Treatment group	Mean baseline YMRS total score	LS Mean Change from baseline	Placebo-subtracted difference
Study 3			
Vraylar® 3-12mg	32.3	-19.6	-4.3
Placebo	32.1	-15.3	

Place in Therapy: Vraylar® is a new antipsychotic indicated for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. There are numerous treatment options available for these indications.

A 2015 network meta-analysis by Yildiz et al[262] included 57 randomized controlled trials (N=14256) to assess the efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. The primary outcome was improvement in manic symptoms as assessed by the Young Mania Rating Scale (YMRS). Results suggested that there was superior improvement in manic symptoms over placebo for 13 drugs, including aripiprazole (standardized mean difference [SMD] 0.37), asenapine (SMD 0.36), carbamazepine (SMD 0.44), cariprazine (SMD 0.47), haloperidol (SMD 0.54), lithium (SMD 0.45), olanzapine (SMD 0.48), paliperidone (SMD 0.37), quetiapine (SMD 0.35), risperidone (SMD 0.65), tamoxifen (SMD 2.92), valproate (SMD 0.32), and ziprasidone (SMD 0.33). There was no superiority of one agent over another, except for risperidone as compared with aripiprazole (SMD 0.27) and compared with valproate (SMD 0.33), both significantly favoring risperidone. Aripiprazole (odds ratio [OR] 0.68), olanzapine (OR 0.47), quetiapine (OR 0.63), risperidone (OR 0.60), and valproate (OR 0.67) had significantly less all-cause, short-term discontinuation as compared to placebo. Furthermore, olanzapine was associated with significantly lower discontinuation rates than haloperidol (OR 0.63), asenapine (OR 0.53), carbamazepine (OR 0.53), lithium (OR 0.49), and cariprazine (OR 0.45).

There is no evidence at this time to support that Vraylar® is safer or more effective than the currently available, more cost effective medications. It is therefore recommended that Vraylar® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or have failed on any preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred Step 3**

References

[1] Vraylar [package insert]. Parsippany, NJ: Actavis Pharma, Inc; 2015.

[2] Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbations of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015; 76(12): e1574-82.

[3] Yildiz A, Nikodem M, Vieta E, et al. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. *Psychol Med*. 2015; 45(2): 299-317.