Drug Monograph

Drug/Drug Class: **Vraylar® (cariprazine) capsule / Atypical Antipsychotics**

Prepared for: MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Vraylar® is available in a capsule that contains 1.5 mg, 3 mg, 4.5 mg, or 6 mg cariprazine respectively. It is also available in a starter pack that contains 1 capsule of 1.5 mg and 6 capsules of 3 mg cariprazine. Manufacturer: Actavis Pharma, Inc., Parsippany, NJ 07054
Summary of Findings:	The effect of Vraylar® was evaluated in 3 randomized, double-blind, placebo-controlled, 6-week clinical trials in schizophrenia and 3 placebo-controlled 3-week trials in mixed or manic episodes associated with bipolar I disorder. It effectively reduced schizophrenic symptoms as measured by Positive and Negative Syndrome Scale scores and effectively reduce symptoms of bipolar disorder as measured by Young Mania Rating Scale scores. In both schizophrenia and bipolar disorder, there was an increase in adverse reactions at dosages above 6 mg without additional benefit.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Schizophrenia is a serious mental illness that interferes with a person's ability to think clearly, manage emotions, make decisions and relate to others. It is a complex, long-term medical illness, affecting about 1% of Americans. Symptoms that occur with schizophrenia include delusions, hallucinations, disorganized speech, disorganize or catonic behavior, and negative symptoms. Unfortunately, there is not a cure for schizophrenia, but it can be treated and managed with antipsychotic medications, psychotherapy, and self-management strategies and education.

Bipolar I disorder is a mental health disorder where a person has at least 1 week of a manic episode which caused significant distress or disability. A person may have had a major depressive or hypomanic episode before or after this manic episode. This was not due to a medical or substance use disorder. Bipolar I disorder causes significant impairment in academic, occupational and social functioning. It can also cause irresponsibility and physical violence. Bipolar disorder accounts for 7% of the disability caused by mental illness worldwide.

Dosage Form(s) [1]

Vraylar® is available in a capsule that contains 1.5 mg, 3 mg, 4.5 mg, or 6 mg cariprazine respectively. It is also available in a starter pack that contains 1 capsule of 1.5 mg and 6 capsules of 3 mg cariprazine.

Manufacturer [1]

Actavis Pharma, Inc., Parsippany, NJ 07054

Indication(s) [1]

Vraylar® is indicated for the treatment of schizophrenia or acute treatment of manic or mixed episodes associated with bipolar I disorder.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Vraylar® is an atypical antipsychotic. The mechanism of action 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.

Pharmacokinetics:

	Cariprazine
Metabolism	Liver, via CYP3A4 (major) and CYP2D6 (minor) to DCAR and DDCAR, both equipotent to cariprazine; DCAR via CYP3A4 and 2D6 to DDCAR

Half-life	2 to 4 days, cariprazine 1 to 3 weeks, DDCAR
Protein binding	91% to 97%
Volume of distribution	Not specified
Excretion	Urine, 21% (1.2%, unchanged)

Schizophrenia

Treatment of cariprazine at dosages of 1.5 to 9 mg daily was effective compared with placebo in patients with schizophrenia, but dosages above 6 mg daily resulted in more adverse events without additional efficacy.

STUDY DESIGN	Three randomized, double-blind, placebo-controlled, 6-week studies (study 1, N=711; study 2, N=604; study 3, N=439).
INCLUSION CRITERIA	Adults (18 to 60 years) with schizophrenia.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive cariprazine at dosages ranging from 1.5 to 9 mg daily or placebo.
RESULTS	At week 6, all dosage groups of cariprazine significantly improved the least-squares mean change from baseline PANSS scores compared with placebo: study 1, -22.3 to -19.4 vs -11.8; study 2, -23 to -20.2 vs -14.3; study 3, -25.9 to -22.8 vs -16, respectively.
SAFETY	Increases in adverse reactions at dosages above 6 mg once daily were noted without additional benefit.

Bipolar I Disorder

Treatment with cariprazine at dosages of 3 to 12 mg daily was effective compared with placebo in patients with bipolar I disorder with mixed or manic episodes, but dosages above 6 mg daily resulted in more adverse events without additional efficacy.

STUDY DESIGN	Three placebo-controlled, 3-week studies (study 1, N=492; study 2, N=235; study 3, N=310).
INCLUSION CRITERIA	Adults (18 to 65 years of age) with bipolar I disorder with manic or mixed episodes with or without psychotic features.

EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive cariprazine at dosages ranging from 3 to 12 mg daily or placebo.
RESULTS	At week 3, all dosage groups of cariprazine significantly improved the least-squares mean change from baseline YMRS scores compared with placebo: study 1, -18.6 to -18.5 vs -12.5; study 2, -15 vs -8.9; study 3, -19.6 vs -15.3, respectively.
SAFETY	Increases in adverse reactions at dosages above 6 mg once daily were noted without additional benefit.

Contraindications [(1)]

- History of hypersensitivity reaction to cariprazine

Warnings and Precautions [(1)]

- Increased risk of death among elderly patients with dementia-related psychosis reported (unapproved use).
- Cerebrovascular adverse reactions including stroke, fatal stroke, and transient ischemic attack occurred more frequently in elderly patients with dementia-related psychosis after antipsychotic therapy.
- Neuroleptic malignant syndrome has been reported in association with antipsychotics and may be life-threatening; discontinue immediately if suspected and monitor closely.
- Tardive dyskinesia, potentially irreversible, may occur; increased risk among elderly, especially elderly women; use lowest dose and shortest treatment duration appropriate.
- Late-occurring adverse reactions may occur after several weeks due to drug accumulation; monitoring recommended for several weeks after starting therapy or dosage increases.
- Metabolic changes have been reported with atypical antipsychotic use; monitoring recommended.
- Hyperglycemia has been reported with atypical antipsychotic use; monitoring recommended.
- Leukopenia and neutropenia have been reported; increased risk among patients with a history of drug-induced leukopenia or neutropenia, low WBC, or low absolute neutrophil count.
- Fatal agranulocytosis has been reported with antipsychotic use.
- Orthostatic hypotension and syncope may occur, especially during initial dose titration, dosage increases, and in patients with known cardiovascular disease, cerebrovascular disease, or at risk for hypotension.
- Seizures may occur; use caution in patients with a history of seizures, the elderly, or with conditions that lower seizure threshold.
- Potential cognitive and motor impairment may affect how patients operate machinery or motor vehicles; caution advised until drug effect are known.
- Disruption of body temperature regulation has been reported with atypical antipsychotic

use; caution advised in patients with conditions that may contribute to elevated body temperature.
- Dysphagia has been reported; caution advised in patients at risk for aspiration.
- Aspiration and esophageal dysmotility have been reported with antipsychotic drug use; caution advised in patients at risk for aspiration.
- Hypersensitivity reactions have been reported, including rash, pruritus, urticarial, and events suggestive of angioedema.
- Concomitant use with CYP3A4 inducers is not recommended.
- Concomitant use with strong CYP3A4 inhibitors; dosage adjustment recommended.
- Severe hepatic impairment, use not recommended.
- Severe renal impairment, use not recommended.

Adverse Effects [(1)]

	Schizophrenia		
Most common, ≥ 4%	**Vraylar® 1.5 – 3mg (n=539)**	**Vraylar® 4.5 – 6mg (n=575)**	**Placebo (n=584)**
Extrapyramidal symptoms	15%	19%	8%
Insomnia	12%	13%	11%
Akathisia	9%	13%	4%
Anxiety	6%	5%	4%
Constipation	6%	7%	5%
Somnolence	5%	8%	5%
Nausea	5%	7%	5%
Dyspepsia	4%	5%	4%
Restlessness	4%	6%	3%
Vomiting	4%	5%	3%
Agitation	3%	5%	4%
Dizziness	3%	5%	2%
Diarrhea	1%	4%	3%

Drug Interactions [(1)]

- CYP3A4 inducers: rifampin, carbamazepine
- CYP3A4 inhibitors: ketoconazole, itraconazole

Dosage and Administration [(1)]

Schizophrenia: The starting dose is 1.5 mg with a recommended dose range of 1.5 mg to 6 mg once daily. The dosage can be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments.

Manic or Mixed Episodes Associate with Bipolar I Disorder: The starting dose is 1.5 mg and should be increased to 3 mg on Day 2. The recommended dose range is 3 mg to 6 mg once daily. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST*/ Month
Cariprazine	Vraylar	Actavis	1.5 mg	1 capsule daily	$1,005.90
			3 mg		
			4.5 mg		
			6 mg		
Brexpiprazole	Rexulti	Otsuka	All strengths	1 tablet daily	$865.50

* Wholesale Acquisition Cost

Conclusion

Vraylar® is an oral atypical antipsychotic indicated in adults for treatment of schizophrenia and as acute treatment of manic or mixed episodes associated with bipolar I disorder. In 3 clinical trials, it effectively reduces schizophrenic symptoms at dosages of 1.5 mg to 9 mg per day. However, increased adverse reactions occurred above 6 mg without additional benefit. In these clinical trials, it also reduces symptoms of bipolar disorder at dosages of 3 mg to 12 mg per day. There was also an increase in adverse reactions above 6 mg per day without additional benefit. The cost is similar to other once daily oral atypical antipsychotics. Vraylar® is not indicated for the treatment of elderly patients with dementia-related psychosis because of an increased risk of death. Extrapyramidal symptoms, insomnia, and akathisia are the most common adverse reactions.

Recommendation

The Division recommends adding this drug to the current atypical antipsychotics clinical edit.

References

1. Product Information: Vraylar®. Cariprazine capsules. Actavis Pharma, Inc, Parsippany, NJ, 09/2015.
2. Schizophrenia. Retrieved 5/25/2016 from https://www.nami.org
3. Bipolar I Disorder. Retrieved 5/25/2016 from www.mentalhealth.com

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