# Clinical Policy: Cariprazine (Vraylar)

Reference Number: CP.PMN.91
Effective Date: 11.16.16
Last Review Date: 08.23
Line of Business: Commercial, HIM, Medicaid Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Cariprazine (Vraylar®) is an atypical antipsychotic.

## FDA Approved Indication(s)

Vraylar is indicated for:

- Treatment of schizophrenia in adults
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults
- Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that Vraylar is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Bipolar Disorder and Schizophrenia** (must meet all)**:**

1. Diagnosis of bipolar disorder or schizophrenia;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of two preferred atypical antipsychotics (e.g., aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine) at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated;
4. Dose does not exceed any of the following (a or b):
   a. Schizophrenia or manic or mixed episodes of bipolar I disorder (i and ii):
      i. 6 mg per day;
      ii. 1 capsule per day;
   b. Depressive episodes of bipolar I disorder (i and ii):
      i. 3 mg per day;
      ii. 1 capsule per day.

**Approval duration:**
**Medicaid/HIM –** 12 months
**Commercial –** 12 months or duration of request, whichever is less

**B. Major Depressive Disorder** (must meet all)**:**
1. Diagnosis of MDD;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of THREE antidepressants from at least TWO different classes (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) at up to maximally indicated doses, each used for ≥ 4 weeks, unless member is unable to satisfy this requirement due to clinically significant adverse effects experienced, member's age ≥ 65 years, or contraindication(s) to multiple antidepressants;
4. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of a ≥ 4-week trial of aripiprazole at up to maximally indicated doses, used concurrently with an antidepressant, unless contraindicated or clinically significant adverse effects are experienced;
5. Vraylar is prescribed concurrently with an antidepressant;
6. Dose does not exceed both of the following (a and b):
   a. 3 mg per day;
   b. 1 capsule per day.

**Approval duration:**
**Medicaid/HIM –** 12 months
**Commercial –** 12 months or duration of request, whichever is less

**C. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. All Indications in Section I** (must meet all)**:**

1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication via Centene benefit, or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Vraylar for bipolar disorder or schizophrenia and has received this medication for at least 30 days;
   c. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed any of the following (a or b):
   a. Schizophrenia or manic or mixed episodes of bipolar I disorder (I and ii):
      i. 6 mg per day;
      ii. 1 capsule per day;
   b. Depressive episodes of bipolar I disorder or MDD (i and ii):
      i. 3 mg per day;
      ii. 1 capsule per day.

**Approval duration:**
**Medicaid/HIM –** 12 months
**Commercial –** 12 months or duration of request, whichever is less

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace,and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;

**B.** Dementia-related psychosis.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

FDA: Food and Drug Administration
MDD: major depressive disorder
SNRI: serotonin/norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| ***Antipsychotics*** | | |
| aripiprazole (Abilify®) | **Bipolar Disorder and Schizophrenia**<br>Adults: 10 to 15 mg PO QD | 30 mg/day |
| olanzapine (Zyprexa®) | **Schizophrenia**<br>Initial: 5 to 10 mg PO QD; target: 10 mg PO QD<br><br>**Bipolar Disorder**<br>Monotherapy: 10 to 15 mg PO QD; adjunct to lithium or valproate: 10 mg PO QD | 20 mg/day |
| quetiapine (Seroquel®) | **Schizophrenia**<br>Initial: 25 mg PO BID; target: 400 to 800 mg/day<br><br>**Bipolar Disorder**<br>Initial: 50 mg PO BID; target: 400 to 800 mg/day | 800 mg/day |
| risperidone (Risperdal®) | **Schizophrenia**<br>Initial: 1 mg PO BID or 2 mg PO QD; target: 4 to 8 mg PO QD<br><br>**Bipolar Disorder**<br>2 to 3 mg PO QD | Schizophrenia: 16 mg/day<br><br>Bipolar Disorder: 6 mg/day |
| ziprasidone (Geodon®) | **Schizophrenia**<br>20 mg PO BID | 160 mg/day |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| | **Bipolar Disorder**<br>Initial: 40 mg PO BID; target: 40 to 80 mg PO BID | |
| ***Selective Serotonin Reuptake Inhibitors (SSRIs)*** | | |
| citalopram (Celexa®) | **Major Depressive Disorder**<br>Refer to prescribing information | 40 mg/day |
| escitalopram (Lexapro®) | | 20 mg/day |
| fluoxetine (Prozac®) | | Immediate-release: 80 mg/day (20 mg/day if pediatric)<br>Delayed-release: 90 mg/week |
| fluvoxamine* (immediate-release) (Luvox®) | | 150 mg/day |
| paroxetine (Paxil®, Paxil CR®, Pexeva®) | | Immediate-release: 50 mg/day (40 mg/day if geriatric)<br>Extended-release: 62.5 mg/day (50 mg/day if geriatric) |
| sertraline (Zoloft®) | | 200 mg/day (20 mg/day if age 6-11 years) |
| ***Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)*** | | |
| desvenlafaxine (Pristiq®) | **Major Depressive Disorder**<br>Refer to prescribing information | 400 mg/day |
| duloxetine (Cymbalta®) | | 120 mg/day |
| Fetzima® (levomilnacipran) | | 120 mg/day |
| venlafaxine (Effexor®, Effexor XR®) | | Extended-release: 225 mg/day |
| ***Tricyclic Antidepressant (TCAs)*** | | |
| amitriptyline (Elavil®) | **Major Depressive Disorder**<br>Refer to prescribing information | 150 mg/day |
| amoxapine | | 400 mg/day (300 mg/day if geriatric) |
| clomipramine* (Anafranil®) | | 250 mg/day (200 mg/day if pediatric) |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| desipramine (Norpramin®) | | 300 mg/day (100 mg/day if pediatric) |
| doxepin (Sinequan®) | | 300 mg/day |
| imipramine HCl (Tofranil®) | | 200 mg/day (150 mg/day if geriatric or pediatric) |
| imipramine pamoate (Tofranil PM®) | | 200 mg/day (100 mg/day if geriatric or pediatric) |
| nortriptyline (Pamelor®) | | 150 mg/day |
| protriptyline (Vivactil®) | | 60 mg/day (30 mg/day if geriatric or pediatric) |
| trimipramine (Surmontil®) | | 200 mg/day (100 mg/day if geriatric or pediatric) |
| ***Monoamine Oxidase Inhibitors*** | | |
| isocarboxazid (Marplan®) | **Major Depressive Disorder** Refer to prescribing information | 60 mg/day |
| phenelzine (Nardil®) | | 90 mg/day |
| selegiline (EMSAM® transdermal; Eldepryl®, Zelapar®, Carbex®) | | Transdermal: 12 mg/24 hr Oral: 30 mg/day |
| tranylcypromine (Parnate®) | | 60 mg/day |
| ***Other Antidepressants*** | | |
| bupropion (Aplenzin®, Budeprion SR® , Budeprion XL®, Forfivo XL®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®) | **Major Depressive Disorder** Refer to prescribing information | Immediate-release: 450 mg/day (300 mg/day if pediatric) Sustained-release: 400 mg/day Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day |
| mirtazapine (Remeron®) | | 45 mg/day |
| perphenazine/ amitriptyline (Triavil®) | | 16 mg/day perphenazine and 200 mg/day amitriptyline |
| maprotiline (Ludiomil®) | | 150 mg/day |
| nefazodone (Serzone®) | | 600 mg/day |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| trazodone (Desyrel®, Oleptro®) | | Immediate-release: 400 mg/day<br>Extended-release: 375 mg/day |
| vortioxetine (Trintellix®) | | 20 mg/day |
| vilazodone (Viibryd®) | | 40 mg/day |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): known hypersensitivity to Vraylar
- Boxed warning(s): Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Vraylar is not approved for the treatment of patients with dementia-related psychosis. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Safety and effectiveness of Vraylar have not been established in pediatric patients.

*Appendix D: States with Limitations against Redirections in Certain Mental Health Settings*

| State | Step Therapy Prohibited? | Notes |
|---|---|---|
| AR | Yes | **Applies to HIM requests only**<br>For the treatment of psychosis and serious mental illness through antipsychotic prescription drugs, no step therapies allowed. |
| NV | No | **Applies to Medicaid requests only**<br>• **MDD**: Failure of aripiprazole or an antidepressant (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) at up to maximally indicated doses, used for ≥ 4 weeks, unless member is unable to satisfy this requirement due to clinically significant adverse effects experienced, member's age ≥ 65 years, or contraindication(s) to multiple antidepressants.<br>• **Bipolar Disorder** and **Schizophrenia**: Failure of ONE preferred atypical antipsychotic (e.g., aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine) at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated. |
| TX | No | **Applies to HIM requests only**<br>• **MDD**: Failure of aripiprazole or an antidepressant (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) at up to maximally indicated doses, used for ≥ 4 weeks, unless |

| State | Step Therapy Prohibited? | Notes |
|---|---|---|
| | | member is unable to satisfy this requirement due to clinically significant adverse effects experienced, member's age ≥ 65 years, or contraindication(s) to multiple antidepressants.<br>• **Bipolar Disorder** and **Schizophrenia**: Failure of ONE preferred atypical antipsychotic (e.g., aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine) at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated. |

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| Schizophrenia | 1.5 mg to 6 mg PO QD | 6 mg/day |
| Bipolar I disorder | Manic or mixed episodes: 3 mg to 6 mg PO QD<br>Depressive episodes: 1.5 mg or 3 mg PO QD | Manic or mixed episodes: 6 mg/day<br>Depressive episodes: 3 mg/day |
| MDD | As adjunct to antidepressants: 1.5 mg to 3 mg PO QD | 3 mg/day |

## VI. Product Availability

Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg

## VII. References

1. Vraylar Prescribing Information. Irvine, CA: Allergan USA, Inc.; December 2022. Available at: http://www.vraylar.com/. Accessed April 21, 2023.
2. Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder, second edition. Arlington, VA: American Psychiatric Association; April 2002. Available online at http://www.psychiatryonline.org/guidelines. Accessed May 8, 2023.
3. Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 Update. J Clin Psychiatry. 2007; 68:1751-1762.
4. Suppes T, Swann AC, Dennehy EB, et al. Texas medication algorithm project: development and feasibility testing of a treatment algorithm for patients with bipolar disorder. J Clin Psychiatry. 2021;62(2):429-447/
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 8, 2023.
6. Keepers G, Fochtmann L, Anzia J, et al. APA Practice guideline for the treatment of patients with schizophrenia, third edition. Am J Psychiatry. 2020 Sept;177(9):868-872.
7. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder, third edition. Arlington, VA: American Psychiatric Association; May 2010. Available online at http://www.psychiatryonline.org/guidelines. Accessed May 8, 2023.

8. Qaseeem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacological and pharmacologic treatments of adults in the acute phase of major depressive disorder: A living clinical guideline from the American College of Physicians. Annals of Internal Medicine. February 2023; 172(2):239-253.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q 2019 annual review: no significant changes; references reviewed and updated. | 10.30.18 | 02.19 |
| RT4: updated policy to add newly FDA-approved indication for depressive episodes associated with bipolar I disorder; references updated. | 06.14.19 | |
| 1Q 2020 annual review: no significant changes; references reviewed and updated. | 11.30.19 | 02.20 |
| 1Q 2021 annual review: no significant changes; references reviewed and updated. | 11.29.20 | 02.21 |
| 1Q 2022 annual review: no significant changes; revised Commercial auth limit from Length of Benefit to 12 months or duration of request whichever is less; references reviewed and updated. | 11.13.21 | 02.22 |
| Per September SDC added HIM line of business to policy. | 09.26.22 | 11.22 |
| 1Q 2023 annual review: no significant changes; addition of dementia-related psychosis to section III for diagnoses/indications for which coverage is not authorized; references reviewed and updated.<br>RT4: added new indication for use as adjunctive treatment in MDD per PI. Template changes applied to other diagnoses/indications and continued therapy section. | 01.09.23 | 02.23 |
| Added redirection bypass for members in a State with limitations on step therapy in certain mental health settings along with Appendix D, which includes Arkansas. | 07.05.23 | |
| 3Q 2023 annual review: no significant changes; references reviewed and updated. Added Texas to Appendix D with requirements for single drug redirection for HIM requests. | 07.13.23 | 08.23 |
| Added Nevada to Appendix D with requirements for single drug redirection for Medicaid requests. | 08.31.23 | |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in

developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.