Preemptive policy: This is a P&T approved policy and can be used after the drug is FDA approved until it is superseded by an updated policy

CENTENE® Corporation

Clinical Policy: Psilocybin (COMP360)

Reference Number: CP.PHAR.817
Effective Date: FDA Approval Date
Last Review Date: 11.26
Line of Business: Commercial, HIM/ICHRA, Medicaid

Revision Log

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

Description

Psilocybin (COMP360) is a serotonin 5-hydroxytryptamine 2A (5-HT2A) receptor agonist.

FDA Approved Indication(s) [Pending]

COMP360 is indicated in adults for the treatment of treatment-resistant depression (TRD).

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 COMP360 is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria*

**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

A. Treatment-Resistant Depression (must meet all)**:**

1. Diagnosis of TRD;*
2. Prescribed by or in consultation with a psychiatrist;
3. Age ≥ 18 years;*
4. Member meets one of the following (a, b, or c):
   a. Montgomery-Åsberg Depression Rating Scale (MADRS) score is ≥ 20 (moderate depression) (*see Appendix D*);
   b. Hamilton Rating Scale for Depression (HAM-D) score is ≥ 17 (moderate depression) (*see Appendix D*);
   c. Patient Health Questionnaire (PHQ-9) score is ≥ 15 (moderately severe depression) (*see Appendix D*);
5. 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 F*);
   b. For all other requests, both of the following (i and ii):
      i. Failure of TWO antidepressants from at least two different classes at up to maximally indicated doses but no less than the commonly recognized minimum therapeutic doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine

reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine);
   ii. Failure of ONE of the following antidepressant augmentation therapies, used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: second-generation antipsychotic, lithium, thyroid hormone, buspirone;
6. COMP360 is not prescribed concurrently with Spravato™;
7. Member meets one of the following (a or b):
   a. No prior history of treatment with COMP360;
   b. Documentation of a prior positive response to COMP360 as documented by a history of ≥ 50% reduction in MADRS, HAM-D, or PHQ-9 score;
8. Dose does not exceed both of the following (a and b):*
   a. 25 mg per dose;
   b. A total of 2 doses, given at least 3 weeks apart.

Approval duration: 6 months (up to 2 doses)

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/ICHRA) 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/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) 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/ICHRA, 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/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy*

**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

A. Treatment-Resistant Depression (must meet all)**:**
1. Currently receiving medication via Centene benefit or documentation supports that member is currently receiving COMP360 for a covered indication and has previously received this medication via a healthcare insurer;
2. Member is responding positively to therapy as evidenced by at least a 50% reduction in MADRS, HAM-D, or PHQ-9 score compared to baseline (*see Appendix D*);
3. COMP360 is not prescribed concurrently with Spravato;
4. Dose does not exceed both of the following (a and b):*
   a. 25 mg per dose;
   b. 4 doses per 12 months.

INTERIM POLICY AND INFORMATION SUBJECT TO CHANGE

Approval duration: 12 months

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/ICHRA) 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/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) 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/ICHRA, 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/ICHRA, 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/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

5-HT2A: serotonin 5-hydroxytryptamine 2A
FDA: Food and Drug Administration
HAM-D: Hamilton Rating Scale for Depression
MADRS: Montgomery-Åsberg Depression Rating Scale
PHQ-9: patient health questionnaire
SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
TRD: treatment-resistant depression

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
SSRIs		
citalopram (Celexa®)	20 mg PO QD; may increase to 40 mg PO QD after one week	40 mg/day (≤ 60 years) 20 mg/day (> 60 years)

INTERIM, N.A. INFORMATION IS SUBJECT

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
escitalopram (Lexapro®)	10 mg PO QD; may increase to 20 mg PO QD after 1 week	20 mg/day
fluoxetine (Prozac®, Prozac Weekly®)	Prozac: 20 mg PO QD; may increase by 10-20 mg after several weeks Prozac Weekly: 90 mg PO q week beginning 7 days after the last daily dose	Prozac: 80 mg/day Prozac Weekly: 90 mg/week
paroxetine (Paxil®, Paxil CR®, Pexeva®)	Paxil, Pexeva: 20 mg PO QD; may increase by 10 mg every week as needed Paxil CR: 25 mg PO QD; may increase by 12.5 mg every week as needed	Paxil, Pexeva: 50 mg/day Paxil CR: 62.5 mg/day
sertraline (Zoloft®)	50 mg PO QD; may increase every week as needed	200 mg/day
vilazodone (Viibryd®)	20-40 mg PO QD	40 mg/day
Trintellix® (vortioxetine)	10-20 mg PO QD	20 mg/day
SNRIs		
duloxetine (Cymbalta®)	20 mg PO BID or 30 mg PO BID or 60 mg PO QD	120 mg/day
venlafaxine (Effexor®, Effexor XR®)	Effexor: 75 mg/day PO in 2-3 divided doses; may increase by 75 mg every 4 days as needed Effexor XR: 75 mg PO QD; may increase by 75 mg every 4 days as needed	Effexor: 225 mg/day (outpatient) or 375 mg/day (inpatient) Effexor XR: 225 mg/day
desvenlafaxine (Pristiq®, Khedezla®)	50 mg PO QD	400 mg/day
Fetzima® (levomilnacipran)	20 mg PO QD for 2 days, then 40 mg PO QD; may increase by 40 mg every 2 days	120 mg/day
TCAs		
amitriptyline (Elavil®)	50 to 100 mg/day PO QD or divided doses	150 mg/day
amoxapine	25 to 300 mg/day PO in divided doses	400 mg/day (300 mg/day if geriatric)
clomipramine* (Anafranil®)	12.5 to 150 mg/day PO QD	250 mg/day (200 mg/day if pediatric)
desipramine (Norpramin®)	25 to 300 mg/day PO QD	300 mg/day (100 mg/day if pediatric)
doxepin	25 to 300 mg/day PO QD	300 mg/day
imipramine HCl	25 to 200 mg/day PO QD or divided doses	200 mg/day (150 mg/day if geriatric or pediatric)

INTERIM POLICY AND INFORMATION IS SUBJECT TO CHANGE

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
imipramine pamoate (Tofranil PM®)	25 to 200 mg/day PO QD or divided doses	200 mg/day (100 mg/day if geriatric or pediatric)
nortriptyline (Pamelor®)	25 to 150 mg/day PO QD	150 mg/day
protriptyline (Vivactil®)	10 to 60 mg/day PO in divided doses	60 mg/day (30 mg/day if geriatric or pediatric)
trimipramine (Surmontil®)	25 to 200 mg/day PO QD	200 mg/day (100 mg/day if geriatric or pediatric)
Second Generation Antipsychotics		
aripiprazole (Abilify®)	2 to 15 mg PO QD	15 mg/day
Rexulti® (brexpiprazole)	0.5 to 3 mg PO QD	3 mg/day
Vraylar® (cariprazine)*	0.5 to 4.5 mg PO QD	4.5 mg/day
olanzapine (Zyprexa®)*	5 to 20 mg PO QD	20 mg/day
quetiapine (Seroquel®, Seroquel XR®)*	Seroquel: 25 to 400 mg PO QD Seroquel XR: 150 mg to 300 mg PO QD	Seroquel: 400 mg/day Seroquel XR: 300 mg/day
risperidone (Risperdal®)*	0.25 to 3 mg PO QD	3 mg/day
ziprasidone (Geodon®)*	20 to 80 mg PO BID	160 mg/day
Other Antidepressants		
bupropion (Aplenzin®, Budeprion SR®, Budeprion XL®, Forfivo XL®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	Varies	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
buspirone*	15 to 20 mg/day PO in 2 divided doses	60 mg/day
mirtazapine (Remeron®)	15 to 45 mg PO QD	45 mg/day
lithium*	300 mg PO QD or BID; up to 600 to 1,200 mg PO daily in divided doses	1,200 mg/day
thyroid hormone*	25 to 50 mcg/day PO	62.5 mcg/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.
**Off-label*

INTERNAL POLICY AND INFORMATION IS SUBJECT TO CHANGE

Appendix C: Contraindications/Boxed Warnings [Pending]

- Contraindication(s): pending
- Boxed warning(s): pending

Appendix D: PHQ-9, MADRS, and HAM-D Rating Scales

- The PHQ-9 is a 9-item multiple choice questionnaire used for diagnosis, screening, monitoring and measuring the severity of depression.

PHQ-9 Score	Depression Severity
5 – 9	Minimal symptoms
10 – 14	Minor depression Major depression, mild
15 – 19	Major depression, moderately severe
> 20	Major depression, severe

- The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

MADRS Score	Depression Rating
0 – 6	Normal/symptom absent
7 – 19	Mild depression
20 – 34	Moderate depression
> 34	Severe depression

- The HAM-D is a 17-item depression assessment scale to assess severity of, and change in, depressive symptoms.

HAM-D Score	Depression Rating
0 – 7	Normal, absence or remission of depression
8 – 16	Mild depression
17 – 23	Moderate depression
> 24	Severe depression

Appendix E: General Information

- Positive responses to therapy include but are not limited to:
  - Previous demonstrated improvement in depressive symptoms
  - Improvement from baseline in PHQ-9, MADRS, or HAM-D score.

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

State	Step Therapy Prohibited?	Notes
TX	No	Failure of ONE of the following antidepressant augmentation therapies, used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: second-generation antipsychotic, lithium, thyroid hormone, buspirone

INTERNAL POLICY AND INFORMATION IS SUBJECT TO CHANGE

V. Dosage and Administration [Pending]

Indication	Dosing Regimen	Maximum Dose
TRD*	25 mg PO as a single dose under healthcare provider supervision with psychological support. A second 25 mg dose may be given at least 3 weeks after the first dose; retreatment is at the discretion of the treating clinician.*	25 mg per dose*

VI. Product Availability [Pending]

Capsule: 25 mg*

VII. References

1. ClinicalTrials.gov. Efficacy, safety, and tolerability of COMP360 in participants with TRD (COMP005). Available at: https://clinicaltrials.gov/study/NCT05624268. Accessed October 1, 2026.
2. ClinicalTrials.gov. Efficacy, safety, and tolerability of two administrations of COMP360 in participants with TRD (COMP006). Available at: https://clinicaltrials.gov/study/NCT05711940. Accessed October 1, 2026.
3. Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med. 2022;387(18):1637-1648.
4. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. November 2010. Available at: http://psychiatryonline.org/guidelines.aspx.
5. VA/DoD Clinical practice guideline for the management of major depressive disorder, 2022. Available at: https://www.healthquality.va.gov/guidelines/MH/mdd/VADODMDDCPGFinal508.pdf. Accessed October 1, 2026.
6. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613.
7. Montgomery–Åsberg Depression Rating Scale. Available at: https://www.mdcalc.com/calc/4058/montgomery-asberg-depression-rating-scale-madrs#evidence. Accessed October 1, 2026.
8. Sharp, Rachel. The Hamilton rating scale for depression. Occupational Medicine. 2015; 65(4):340.

INTERNAL POLICY AND INFORMATION IS SUBJECT TO CHANGE

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	10.20.26	11.26

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.

INTERIM POLICY AND INFORMATION IS SUBJECT TO CHANGE

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.

©2026 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.

INTERIM POLICY AND INFORMATION IS SUBJECT TO CHANGE