Clinical Policy: Lumateperone (Caplyta)

Reference Number: CP.PMN.232
Effective Date: 03.01.20
Last Review Date: 08.25
Line of Business: Commercial, HIM, Medicaid Revision Log

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

Description

Lumateperone (Caplyta®) is an atypical antipsychotic.

FDA Approved Indication(s)

Caplyta is indicated for the treatment of:

- Schizophrenia in adults
- Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate
- Adjunctive therapy with 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 Caplyta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Schizophrenia (must meet all)**:**

1. Diagnosis of schizophrenia;
2. Age ≥ 18 years;
3. Member meets one of the following (a, b, or c):*
   ** For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
   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 one of the following generic atypical antipsychotics at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: risperidone, quetiapine, olanzapine, ziprasidone;
   c. Member has diabetes mellitus or body mass index (BMI) > 30;
4. Member meets one of the following (a or b):*
   ** For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
   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, unless contraindicated or clinically significant adverse effects are experienced;

5. Dose does not exceed both of the following (a and b):
   a. 42 mg per day;
   b. 1 capsule per day.

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

B. Bipolar Disorder (must meet all)**:**

1. Diagnosis of bipolar disorder;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):*
   * *For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
   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, or 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 both of the following (a and b):
   a. 42 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. Major Depressive Disorder (must meet all)**:**

1. Diagnosis of MDD;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):*
   * *For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
   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):*
   * *For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
   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. Caplyta is prescribed concurrently with an antidepressant;
6. Dose does not exceed both of the following (a and b):
   a. 42 mg per day;
   b. 1 capsule per day.

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

D. 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. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Caplyta for schizophrenia, bipolar disorder, or MDD and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For MDD: Caplyta is prescribed concurrently with an antidepressant;
4. If request is for a dose increase, new dose does not exceed both of the following (a and b):
   a. 42 mg per day;
   b. 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

BMI: body mass index
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** Adults: 10 to 15 mg PO QD	30 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	MDD 2 to 15 mg PO QD as an adjunct to previously established antidepressant treatment	
olanzapine (Zyprexa®)	**Schizophrenia** Initial: 5 to 10 mg PO QD; target: 10 mg PO QD **Bipolar Disorder** Monotherapy: 10 to 15 mg PO QD; adjunct to lithium or valproate: 10 mg PO QD	20 mg/day
quetiapine (Seroquel®)	**Schizophrenia** Initial: 25 mg PO BID; target: 400 to 800 mg/day **Bipolar Disorder** Initial: 50 mg PO BID; target: 400 to 800 mg/day	800 mg/day
risperidone (Risperdal®)	**Schizophrenia** Initial: 1 mg PO BID or 2 mg PO QD; target: 4 to 8 mg PO QD **Bipolar Disorder** 2 to 3 mg PO QD	Schizophrenia: 16 mg/day Bipolar Disorder: 6 mg/day
ziprasidone (Geodon®)	**Schizophrenia** 20 mg PO BID **Bipolar Disorder** Initial: 40 mg PO BID; target: 40 to 80 mg PO BID	160 mg/day
Selective Serotonin Reuptake Inhibitors (SSRIs)		
citalopram (Celexa®)	**MDD** Refer to prescribing information	40 mg/day
escitalopram (Lexapro®)		20 mg/day
fluoxetine (Prozac®)		Immediate-release: 80 mg/day (20 mg/day if pediatric) Delayed-release: 90 mg/week
fluvoxamine* (immediate-release) (Luvox®)		150 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
paroxetine (Paxil®, Paxil CR®, Pexeva®)		Immediate-release: 50 mg/day (40 mg/day if geriatric) 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®)	**MDD** 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®)	**MDD** 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)
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)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Monoamine Oxidase Inhibitors		
isocarboxazid (Marplan®)	**MDD** 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®)	**MDD** 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
trazodone (Desyrel®, Oleptro®)		Immediate-release: 400 mg/day 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 lumateperone or any components of Caplyta
- Boxed warning(s): increased mortality in elderly patients with dementia-related psychosis; suicidal thoughts and behaviors

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

State	Step Therapy Prohibited?	Notes
AR	Yes	For the treatment of psychosis and serious mental illness through antipsychotic prescription drugs, no step therapies allowed.
NV	No	**Applies to Medicaid requests only** • **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. • **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** • **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. • **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, bipolar disorder, MDD	42 mg PO QD Moderate or severe hepatic impairment: 21 mg PO QD	42 mg/day

VI. Product Availability

Capsule: 42 mg, 21 mg, 10.5 mg

VII. References

1. Caplyta Prescribing Information. New York, NY: Intra-Cellular Therapies, Inc.; November 2025. Available at: www.caplyta.com. Accessed November 14, 2025.
2. 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.
3. 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 April 23, 2025.
4. Kadakia A, Dembek C, Heller V, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. BMC Psychiatry. May 2021;21:249..
5. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20:97–170.
6. Clinical Pharmacology [database online]. Philadelphia, PA: Elsevier. Updated periodically. Available at: http://www.clinicalkey.com/pharmacology. Accessed November 14, 2025.
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 November 14, 2025.
8. Qaseem 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 2022 annual review: no significant changes; revised Commercial auth limit from Length of Benefit to 12 months or duration of request whichever is less; RT4: added criteria for the recently FDA-approved indication of bipolar depression; references reviewed and updated.	11.13.21	02.22
RT4: new strengths [10.5 mg, 21 mg] added.	05.06.22	
Template changes applied to other diagnoses/indications.	10.06.22	
1Q 2023 annual review: no significant changes; added dementia-related psychosis to section III; references reviewed and updated.	11.03.22	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	
Added Texas to Appendix D with requirements for single drug redirection for HIM requests.	07.19.23	
Added Nevada to Appendix D with requirements for single drug redirection for Medicaid requests.	08.31.23	
1Q 2024 annual review: no significant changes; references reviewed and updated.	10.13.23	02.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2024 annual review: for Schizophrenia, changed to "failure of one of the following generic atypical antipsychotics…" (previously was failure of two) to align with other atypical antipsychotics; references reviewed and updated.	06.07.24	08.24
3Q 2025 annual review: added step therapy bypass for IL HIM per IL HB 5395; references reviewed and updated.	06.27.25	08.25
RT4: added new indication for use as adjunctive treatment in MDD.	11.14.25	
Removed "applies to HIM request only" from Appendix D for Arkansas per AR HB 1276.	02.13.26	

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.

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.