

Lumateperone

Caplyta

Single-dose antipsychotic with unusually clean metabolic and motor profiles, now covering schizophrenia, bipolar depression, and adjunctive MDD.

USUAL ADULT RANGE

42 mg/day PO

HALF-LIFE

About 18 h

METABOLISM

UGT, CYP3A4, AKR

ONSET

1-2 wks; 4-6 wks full

FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; lumateperone is not approved for that use. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients; monitor closely for clinical worsening and emergent suicidality.

INDICATIONS

- Schizophrenia in adults, at a single fixed dose that requires no titration and no dose finding.
- Depressive episodes associated with bipolar I or bipolar II disorder in adults, as monotherapy and as adjunct to lithium or valproate.
- Adjunctive therapy with antidepressants for major depressive disorder in adults, an indication added to the US label in 2025.
- Bipolar II depression coverage is notable, since most approved agents in this space are limited to bipolar I disorder.
- Off-label appeal is greatest in patients where weight gain, akathisia, or prolactin elevation ended prior antipsychotic trials.

DOSING & TITRATION

- The recommended dose is **42 mg once daily** for every approved indication, with no titration and no dose adjustment for response.
- Capsules are available as **42 mg**, 21 mg, and 10.5 mg, with the smaller strengths existing purely for interaction and hepatic adjustments.
- Reduce to **21 mg once daily** with a moderate CYP3A4 inhibitor and to **10.5 mg once daily** with a strong CYP3A4 inhibitor.
- Reduce to **21 mg once daily** in moderate or severe hepatic impairment; mild impairment needs no change.
- Avoid concomitant CYP3A4 inducers, since exposure falls substantially and no compensating dose increase is defined.
- Taper is not formally required, but gradual discontinuation is prudent in patients with a history of rapid relapse.

MECHANISM OF ACTION

- Very potent **5-HT_{2A}** antagonism with roughly 60-fold higher affinity than for D₂, which is the highest ratio among available agents.
- Acts as a presynaptic dopamine **D₂** partial agonist and a postsynaptic D₂ antagonist, giving modulation rather than pure blockade.
- Indirectly modulates glutamate through **D₁**-dependent enhancement of NMDA and AMPA currents in prefrontal cortex.
- Moderate inhibition of the serotonin transporter contributes to antidepressant activity in bipolar and unipolar depression.
- Negligible histamine, muscarinic, and alpha-1 affinity explains minimal weight gain, low anticholinergic load, and little orthostasis.

PHARMACOKINETICS

- Absorbed with or without food, though a high-fat meal lowers peak concentration and delays absorption without changing overall exposure.
- Cleared by multiple **UGT** isoforms, aldoketoreductase, and **CYP3A4**, producing more than fifty metabolites of limited clinical importance.
- Terminal half-life is about **18 hours**, supporting once-daily dosing with steady state reached in roughly 5 days.
- Exposure roughly doubles with moderate to severe hepatic impairment, which is why the dose drops to **21 mg** in Child-Pugh class B or C.
- Strong CYP3A4 inhibition raises exposure severalfold, so the dose falls to **10.5 mg** rather than being simply monitored.

ADVERSE EFFECTS

- Somnolence and sedation are the most common effects, reported by roughly **24 percent** in trials and usually manageable with evening dosing.
- Dry mouth, nausea, dizziness, and elevations in creatine phosphokinase or transaminases are the other frequent findings.
- Weight change is close to placebo in short-term trials, one of the strongest arguments for the drug in metabolically vulnerable patients.
- Extrapyramidal symptoms, akathisia, and prolactin elevation are all low, which distinguishes it from risperidone and aripiprazole.
- Labeled risks include neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension, seizures, and leukopenia or neutropenia.
- Cerebrovascular events and increased mortality are the specific concerns in elderly patients with dementia-related psychosis.

MONITORING

- Weight, BMI, blood pressure, fasting glucose or A1c, and lipids at baseline, at 12 weeks, and annually, despite the favorable profile.
- Complete blood count in patients with pre-existing low white cell count or a history of leukopenia, with discontinuation if ANC falls below 1000/uL.
- Hepatic panel at baseline to establish whether the reduced 21 mg dose applies, and again if transaminases rise on treatment.
- AIMS examination at baseline and every 6-12 months, since low short-term motor risk does not eliminate tardive dyskinesia over years.
- Review the medication list for CYP3A4 inhibitors and inducers at every visit, since dosing hinges entirely on that pathway.

INTERACTIONS & CAUTIONS

- Strong **CYP3A4** inhibitors such as ketoconazole, itraconazole, clarithromycin, and ritonavir require reducing the dose to 10.5 mg daily.
- Moderate **CYP3A4** inhibitors including diltiazem, verapamil, erythromycin, and fluconazole require reducing the dose to 21 mg daily.
- **CYP3A4** inducers such as rifampin, carbamazepine, and St. John's wort should be avoided because exposure falls markedly.
- Additive sedation with opioids, benzodiazepines, and alcohol, which matters given the drug's leading adverse effect is somnolence.
- Contraindicated in patients with a history of hypersensitivity reaction to lumateperone, including rash, pruritus, or urticaria.

SPECIAL POPULATIONS

- Human pregnancy data are limited; third-trimester exposure carries the class risk of neonatal extrapyramidal and withdrawal symptoms.
- Lactation data are absent, so monitor breastfed infants for sedation and feeding difficulty or select a better-characterized agent.
- Safety and effectiveness have not been established in pediatric patients, so use is restricted to adults.
- In older adults the low anticholinergic and orthostatic burden is attractive, but the dementia mortality warning still applies.
- Reduce to 21 mg daily in moderate or severe hepatic impairment; no renal dose adjustment has been specified.

PRESCRIBING PEARLS

- One dose for every indication: 42 mg daily, with no titration and nothing to optimize.
- The 21 mg and 10.5 mg capsules exist only for hepatic impairment and CYP3A4 inhibitors.
- Among the few options approved for bipolar II depression, not just bipolar I.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.