SECOND-GENERATION ANTIPSYCHOTIC

Olanzapine-Samidorphan

Lybalvi

Olanzapine paired with an opioid antagonist to blunt weight gain; absolutely contraindicated in anyone using opioids.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
10/10-20/10 mg/day PO	Olanzapine 35 h; sami 8 h	CYP1A2, UGT; sami CYP3A4	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs; olanzapine and samidorphan is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS

- Schizophrenia in adults, delivering olanzapine efficacy with a fixed 10 mg samidorphan component intended to limit weight gain.
- Acute manic or mixed episodes of bipolar I disorder in adults, as monotherapy or as an adjunct to lithium or valproate.
- Maintenance monotherapy treatment of bipolar I disorder in adults after an acute episode has responded.
- Positioned for patients who need olanzapine-level efficacy but for whom weight gain has ended or would end prior olanzapine trials.
- It is not approved and has no established role in opioid use disorder, alcohol use disorder, or any indication of samidorphan alone.

DOSING & TITRATION

- Schizophrenia: start **5/10 mg or 10/10 mg once daily**, then adjust in 5 mg olanzapine increments weekly to a maximum of **20/10 mg/day**.
- Bipolar I mania as monotherapy: start **10/10 mg or 15/10 mg once daily**, adjusting no more often than every 24 hours in 5 mg steps.
- As adjunct to lithium or valproate, start at **10/10 mg once daily**, with a recommended range of 10/10 to 20/10 mg once daily.
- The samidorphan component is fixed at **10 mg** in every strength, so only the olanzapine dose is actually being titrated.
- Patients using opioids must be opioid free for at least **7 days** after short-acting and **14 days** after long-acting opioids before starting.
- Start at 5/10 mg in those predisposed to hypotension, slower olanzapine metabolism, or heightened pharmacodynamic sensitivity.

MECHANISM OF ACTION

- Olanzapine provides the antipsychotic effect through **D2** and **5-HT2A** antagonism with strong H1 and 5-HT2C blockade.
- Samidorphan is a **mu-opioid receptor antagonist** with partial agonist activity at kappa and delta receptors.
- Opioid receptor blockade is thought to interrupt the reward and appetite signaling that drives olanzapine-associated weight gain.
- The antipsychotic pharmacology is unchanged, so efficacy, sedation, and anticholinergic effects mirror olanzapine alone.
- Because samidorphan blocks mu receptors, it precipitates withdrawal in opioid-dependent patients and blocks opioid analgesia.

PHARMACOKINETICS

- Both components are absorbed independently of food, and the fixed-dose tablet must be swallowed whole without splitting or combining strengths.
- Olanzapine is cleared by **CYP1A2** and **UGT1A4** with a half-life near 35 hours, so smoking status still shifts its levels.
- Samidorphan is metabolized mainly by **CYP3A4** with a half-life of roughly 8 hours and no meaningful effect on olanzapine exposure.
- Mu-opioid receptor blockade persists across the dosing interval, which is why opioid analgesia is unreliable during treatment.
- No dose adjustment is needed for mild to moderate renal or hepatic impairment, but severe impairment warrants caution.

ADVERSE EFFECTS

- Weight gain still occurs and averages roughly 4 percent of body weight over 6 months, less than olanzapine alone but far from neutral.
- Sedation, dry mouth, increased appetite, constipation, and dizziness are common and reflect the olanzapine component.
- Hyperglycemia, dyslipidemia, and new-onset diabetes remain real risks and are not eliminated by the opioid antagonist.
- Precipitated opioid withdrawal can be abrupt and severe in a dependent patient and may require emergency management.
- After stopping, reduced opioid tolerance raises the risk of fatal overdose if a patient resumes their previous opioid dose.
- Neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension, and seizures carry the usual antipsychotic-class risk.

MONITORING

- Take a careful opioid history before starting, including buprenorphine, methadone, and as-needed analgesics, and document the opioid-free interval.
- Weight and BMI at baseline and every visit for the first 3 months, then quarterly, with fasting glucose or A1c and lipids at 12 weeks and annually.
- Counsel and document that opioid analgesia will be blocked, and plan non-opioid strategies for any anticipated surgery or injury.
- Blood pressure and orthostatic vitals during titration, particularly in older adults and patients on antihypertensives.
- AIMS examination at baseline and every 6-12 months, plus attention to smoking changes that alter olanzapine levels.

INTERACTIONS & CAUTIONS

- Contraindicated in patients using **opioids** and in those undergoing acute opioid withdrawal, without exception for analgesic intent.
- **Fluvoxamine** and other CYP1A2 inhibitors raise the olanzapine component, while carbamazepine and cigarette smoke lower it.
- Strong CYP3A4 inducers reduce samidorphan exposure, which could weaken the weight-mitigating effect but not the antipsychotic action.
- Additive sedation and hypotension with benzodiazepines, alcohol, and antihypertensives, as with olanzapine alone.
- Emergency opioid analgesia requires higher doses under continuous monitoring in a setting equipped for respiratory support.

SPECIAL POPULATIONS

- In pregnancy the opioid antagonist adds risk for any patient on opioid agonist therapy, and third-trimester exposure carries neonatal withdrawal risk.
- Lactation data for samidorphan are absent, and olanzapine passes into milk, so monitor breastfed infants for sedation.
- Safety and effectiveness have not been established in pediatric patients, so use is confined to adults.
- In older adults the olanzapine anticholinergic and orthostatic burden applies, along with the boxed dementia mortality warning.
- Use caution in severe hepatic or renal impairment, and avoid entirely in patients who may need opioid analgesia soon.

PRESCRIBING PEARLS

- Contraindicated with any opioid use; it will precipitate withdrawal and block analgesia.
- Weight mitigation is partial, not protective; metabolic monitoring is unchanged from olanzapine.
- After stopping, lost opioid tolerance makes a previously usual dose potentially fatal.

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.