SECOND-GENERATION ANTIPSYCHOTIC

Lurasidone

Latuda

Metabolically light agent with strong bipolar depression data; efficacy depends entirely on taking it with a real meal.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
40-160 mg/day PO with food	18 h	CYP3A4 (major substrate)	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; lurasidone 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 and in adolescents ages 13-17, both for acute episodes and for continued maintenance treatment.
- Depressive episodes associated with bipolar I disorder as monotherapy in adults and in pediatric patients ages 10-17.
- Bipolar I depression in adults as adjunctive therapy with lithium or valproate when monotherapy is insufficient.
- Frequently chosen when metabolic risk, obesity, diabetes, or dyslipidemia makes olanzapine or quetiapine unattractive.
- Off-label uses include augmentation in unipolar depression with mixed features and maintenance treatment of bipolar I disorder.

DOSING & TITRATION

- Schizophrenia in adults: start **40 mg once daily with food**, with a usual range of 40-160 mg/day and no initial titration required.
- Bipolar depression in adults: start **20 mg once daily with food** and titrate as needed, with a labeled maximum of **120 mg/day**.
- Adolescents with schizophrenia start at 40 mg/day with a maximum of **80 mg/day**; pediatric bipolar depression starts at 20 mg with the same cap.
- With a moderate CYP3A4 inhibitor such as diltiazem, start at **20 mg/day** and do not exceed **80 mg/day**.
- Renal impairment with clearance under 50 mL/min and moderate hepatic impairment both cap the dose at **80 mg/day**; severe hepatic caps at 40 mg/day.
- Taper gradually when discontinuing, and remember that a switch away from lurasidone often unmasks weight or sedation from the new agent.

MECHANISM OF ACTION

- High-affinity antagonist at dopamine **D2** and serotonin **5-HT2A** receptors, giving antipsychotic efficacy with moderate extrapyramidal liability.
- Potent **5-HT7** antagonism is a distinguishing feature, linked in preclinical work to antidepressant and procognitive effects.
- Partial agonism at **5-HT1A** contributes to mood and anxiety benefit and may soften striatal dopamine blockade.
- Essentially no histamine H1 or muscarinic affinity, which explains minimal weight gain, low sedation, and no anticholinergic burden.
- Modest alpha-2C antagonism may add to antidepressant action, while low alpha-1 affinity limits orthostatic hypotension.

PHARMACOKINETICS

- Bioavailability roughly doubles when taken with a meal of at least **350 calories**, and fasting administration is a common cause of failure.
- Metabolized almost entirely by **CYP3A4**, which makes it contraindicated with strong inhibitors and strong inducers of that enzyme.
- Terminal half-life is about **18 hours**, supporting once-daily dosing with steady state reached in roughly 7 days.
- Two active metabolites contribute modestly to effect, and about 9 percent of the dose is recovered in urine.
- Exposure rises with renal and hepatic impairment, so both carry explicit dose caps rather than simple caution statements.

ADVERSE EFFECTS

- Akathisia and parkinsonism are the leading adverse effects and are clearly dose related, appearing more often above 80 mg/day.
- Somnolence, nausea, and agitation are common early, and taking the dose in the evening with supper mitigates both sedation and nausea.
- Weight and metabolic effects are among the lowest in the class, with mean weight change near **1 kg** and neutral lipid and glucose effects.
- Prolactin elevation is small but real, larger in women and adolescents than in adult men, and occasionally causes menstrual change.
- Serious risks are those of the class: neuroleptic malignant syndrome, tardive dyskinesia, and rare severe cutaneous reactions.

MONITORING

- Weight, BMI, blood pressure, fasting glucose or A1c, and lipids at baseline, at 12 weeks, and then annually, as for any antipsychotic.
- Assess for akathisia and parkinsonism at every early visit, since these are the effects most likely to end treatment.
- Serum creatinine and hepatic panel at baseline to determine whether the 80 mg or 40 mg dose ceiling applies.
- Verify at each visit that doses are taken with a meal of at least 350 calories, and consider this first when response is poor.
- AIMS at baseline and every 6-12 months, plus prolactin testing when menstrual or sexual symptoms emerge.

INTERACTIONS & CAUTIONS

- Contraindicated with strong **CYP3A4** inhibitors including ketoconazole, itraconazole, clarithromycin, ritonavir, and voriconazole.
- Contraindicated with strong **CYP3A4** inducers including rifampin, carbamazepine, phenytoin, and St. John's wort.
- Moderate inhibitors such as diltiazem, verapamil, erythromycin, and fluconazole require the reduced **80 mg/day** ceiling.
- Grapefruit juice should be avoided because it inhibits intestinal CYP3A4 and unpredictably raises exposure.
- Additive sedation with opioids, benzodiazepines, and alcohol, but minimal QT effect compared with ziprasidone or iloperidone.

SPECIAL POPULATIONS

- Third-trimester exposure risks neonatal extrapyramidal and withdrawal symptoms; pregnancy data are more limited than for older agents.
- Lactation data are sparse, so monitor breastfed infants for sedation and poor feeding and consider better-characterized alternatives.
- Approved from age 10 for bipolar depression and 13 for schizophrenia, with a lower maximum dose than adults in both indications.
- Older adults tolerate it relatively well given low anticholinergic and orthostatic effects, but the dementia mortality warning still applies.
- Dose ceilings of 80 mg/day apply in moderate to severe renal impairment and moderate hepatic impairment, and 40 mg/day in severe hepatic disease.

PRESCRIBING PEARLS

- Give it with supper: under 350 calories, exposure falls by half and the drug looks ineffective.
- Strong CYP3A4 inhibitors and inducers are contraindications, not cautions; check the med list first.
- Akathisia at higher doses is the usual failure mode, not weight gain.

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.