SECOND-GENERATION ANTIPSYCHOTIC

Ziprasidone

Geodon

Metabolically clean antipsychotic whose two catches are QT prolongation and an absolute requirement to dose with food.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
40-80 mg PO BID with food	7 h oral; 2-5 h IM	Aldehyde oxidase, CYP3A4	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

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

INDICATIONS

- Schizophrenia in adults, for acute treatment and for maintenance, with efficacy comparable to other second-generation agents when dosed adequately.
- Acute manic or mixed episodes associated with bipolar I disorder in adults, with or without psychotic features.
- Maintenance treatment of bipolar I disorder in adults as an adjunct to lithium or valproate after an acute episode has responded.
- Intramuscular ziprasidone is approved for acute agitation in adults with schizophrenia when rapid control is needed.
- Off-label use includes treatment of psychosis in patients where weight and metabolic risk dominate the choice, and adjunctive use in bipolar depression.

DOSING & TITRATION

- Schizophrenia: start **20 mg twice daily with food**, then titrate at intervals of at least 2 days to a usual **40-80 mg twice daily**.
- Bipolar mania: start **40 mg twice daily with food**, increase to 60-80 mg twice daily on day 2, then adjust within 40-80 mg twice daily.
- The labeled maximum is **100 mg twice daily**, or 200 mg/day, and doses at the low end are commonly subtherapeutic in practice.
- Intramuscular dosing is **10 mg every 2 hours** or 20 mg every 4 hours, up to 40 mg/day, and for no more than 3 consecutive days.
- No adjustment is needed for renal or hepatic impairment, but avoid the intramuscular form in significant renal impairment.
- Taper over one to two weeks when discontinuing, since the short half-life makes abrupt stopping prone to rebound symptoms.

MECHANISM OF ACTION

- Antagonist at dopamine **D2** and potent antagonist at serotonin **5-HT2A**, with one of the highest 5-HT2A to D2 affinity ratios in the class.
- Partial agonism at **5-HT1A** and antagonism at 5-HT2C add antidepressant and anxiolytic properties beyond dopamine blockade.
- Moderate inhibition of serotonin and norepinephrine reuptake distinguishes it pharmacologically and may support mood benefit.
- Very low histamine H1 and muscarinic affinity accounts for minimal weight gain, little sedation, and no anticholinergic burden.
- Blockade of the cardiac potassium channel underlies the dose-related QTc prolongation that limits its use in cardiac disease.

PHARMACOKINETICS

- Absorption is the critical issue: bioavailability roughly doubles when taken with a meal of at least **500 kcal**, so fasting doses fail.
- About two thirds of clearance is by **aldehyde oxidase**, a pathway with few clinically relevant inhibitors, and one third by **CYP3A4**.
- Oral half-life is about **7 hours**, which mandates twice-daily dosing, while the intramuscular half-life is 2-5 hours.
- Ziprasidone is not a meaningful CYP inhibitor or inducer, so it adds little to a complicated medication list.
- Less than 1 percent is excreted unchanged in urine and renal impairment needs no adjustment, though the IM cyclodextrin vehicle is renally cleared.

ADVERSE EFFECTS

- Somnolence, dizziness, akathisia, and nausea are the most common effects and are largely dose related and worse with rapid titration.
- QTc prolongation averages **10-20 ms**, more than most second-generation agents, and is the reason for its cardiac contraindications.
- Weight and metabolic effects are among the lowest of the class, alongside lurasidone and aripiprazole, with essentially neutral lipids.
- Extrapyramidal symptoms and modest prolactin elevation occur, generally less than with risperidone but more than with quetiapine.
- Rare but serious events include neuroleptic malignant syndrome, drug reaction with eosinophilia and systemic symptoms, and priapism.

MONITORING

- Baseline potassium and magnesium, correcting deficits before starting, since hypokalemia and hypomagnesemia amplify QT risk.
- Baseline ECG in patients with cardiac disease, on other QT-prolonging drugs, or with a family history of sudden death or long QT.
- Discontinue if QTc exceeds **500 ms** on treatment, and reassess any concurrent QT-prolonging medication before restarting.
- Standard metabolic panel of weight, blood pressure, fasting glucose or A1c, and lipids at baseline, 12 weeks, and annually.
- Confirm at every visit that the patient is actually taking doses with a substantial meal, because absorption is the usual reason for failure.

INTERACTIONS & CAUTIONS

- Contraindicated with known QT prolongation, recent myocardial infarction, uncompensated heart failure, and other QT-prolonging drugs.
- Avoid combining with dofetilide, sotalol, Class IA and III antiarrhythmics, methadone, moxifloxacin, and pentamidine.
- Strong **CYP3A4** inducers such as carbamazepine reduce exposure by about 35 percent, and ketoconazole increases it by about 35 percent.
- Additive sedation with opioids, benzodiazepines, and alcohol, and additive hypotension with antihypertensive agents.
- Diuretic-induced electrolyte loss is the most common practical route to dangerous QT interaction, so review the diuretic list.

SPECIAL POPULATIONS

- Pregnancy data are more limited than for olanzapine or quetiapine; third-trimester exposure risks neonatal extrapyramidal and withdrawal symptoms.
- Limited lactation data, but the low reported milk concentrations suggest breastfeeding is likely compatible with infant monitoring.
- Not approved in pediatric patients, and adolescent trials in bipolar disorder and schizophrenia failed to establish efficacy.
- In older adults consider a baseline ECG, start at the low end, and remember the dementia-related mortality warning.
- No dose adjustment for renal or hepatic impairment, though the intramuscular vehicle accumulates in renal failure.

PRESCRIBING PEARLS

- A 500 kcal meal is part of the prescription; taken fasting, absorption falls by about half.
- Best metabolic choice when weight matters, provided the ECG and electrolytes are clean.
- Starting at 20 mg twice daily and stopping there is a common cause of apparent nonresponse.

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.