SECOND-GENERATION ANTIPSYCHOTIC

Brexpiprazole

Rexulti

D2 partial agonist with less akathisia than aripiprazole, and the only agent approved for agitation in Alzheimer's dementia.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
2-4 mg/day PO	91 h (86 h metabolite)	CYP3A4, CYP2D6	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; brexpiprazole is not approved for dementia-related psychosis without agitation due to Alzheimer's disease. Antidepressants increased suicidal thoughts and behaviors in pediatric and young adult patients; monitor closely.

INDICATIONS

- Adjunctive treatment of major depressive disorder in adults with inadequate response to an antidepressant, at a usual dose of **2 mg/day**.
- Schizophrenia in adults and in pediatric patients ages 13 and older, for acute treatment and for maintenance therapy.
- Agitation associated with dementia due to Alzheimer's disease, the first and so far only antipsychotic approved for this indication.
- The label explicitly states it is not indicated for as-needed treatment of agitation in Alzheimer's dementia, only scheduled dosing.
- Off-label use includes anxious depression and patients who responded to aripiprazole but could not tolerate its akathisia.

DOSING & TITRATION

- Major depressive disorder adjunct: start **0.5-1 mg/day PO**, increase weekly to 1 mg then to the target **2 mg/day**, maximum 3 mg/day.
- Schizophrenia in adults: **1 mg/day** on days 1-4, 2 mg/day on days 5-7, then 4 mg/day on day 8, targeting 2-4 mg/day with a **4 mg/day** maximum.
- Agitation in Alzheimer's dementia: **0.5 mg/day** for 7 days, 1 mg/day for 7 days, then 2 mg/day, with a maximum of **3 mg/day**.
- Halve the dose with a strong CYP2D6 or strong CYP3A4 inhibitor, and reduce to a quarter when both are used together.
- With a strong CYP3A4 inducer such as carbamazepine, double the dose over 1-2 weeks and reverse the change when the inducer stops.
- Cap the dose at **2 mg/day** for depression and 3 mg/day for schizophrenia in moderate to severe hepatic or renal impairment.

MECHANISM OF ACTION

- Partial agonist at dopamine **D2** and **D3** receptors with lower intrinsic activity than aripiprazole, which reduces activation and akathisia.
- Potent partial agonism at serotonin **5-HT1A** and strong antagonism at **5-HT2A** support antidepressant and antipsychotic effects.
- High alpha-1B and alpha-2C adrenergic antagonism distinguishes it from aripiprazole and may add antidepressant activity.
- Low histamine H1 and negligible muscarinic affinity keep sedation and anticholinergic effects modest.
- Partial rather than full D2 blockade means prolactin generally falls or stays flat rather than rising.

PHARMACOKINETICS

- Oral bioavailability is about 95 percent and absorption is unaffected by food, so it may be taken at any time of day.
- Metabolized by **CYP3A4** and **CYP2D6** to DM-3411, a metabolite not considered to contribute meaningfully to clinical effect.
- Terminal half-life is about **91 hours**, so steady state takes 10-14 days and dose changes cannot be judged sooner.
- CYP2D6 poor metabolizers have roughly double the exposure and require half the usual dose, as do patients on strong 2D6 inhibitors.
- Exposure rises with moderate to severe hepatic impairment and with creatinine clearance below **60 mL/min**, both of which cap the dose.

ADVERSE EFFECTS

- Weight gain averages **1.5-3 kg** and increased appetite is common, placing brexpiprazole above aripiprazole but below olanzapine.
- Akathisia occurs in roughly **5-10 percent**, distinctly less than with aripiprazole, and remains dose related.
- Somnolence, headache, fatigue, and restlessness are the other common effects, mostly early and often self-limited.
- Impulse control problems including gambling, compulsive shopping, binge eating, and hypersexuality are labeled and reversible on stopping.
- Serious risks include neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension, and rare leukopenia or neutropenia.
- In elderly patients with dementia, cerebrovascular events and increased mortality remain the dominant safety concern.

MONITORING

- Weight, BMI, blood pressure, fasting glucose or A1c, and lipids at baseline, at 12 weeks, and annually thereafter.
- Assess akathisia and restlessness at each early visit, since patients often describe it as anxiety or as the depression worsening.
- Ask directly about new gambling, spending, eating, or sexual urges at every follow-up, because patients rarely report them unprompted.
- Check renal and hepatic function at baseline to determine whether the reduced dose ceilings apply.
- In Alzheimer's agitation, reassess benefit at least every 3 months and document the rationale for continuing an antipsychotic.

INTERACTIONS & CAUTIONS

- Strong **CYP2D6** inhibitors such as fluoxetine, paroxetine, and quinidine double exposure and require halving the dose.
- Strong **CYP3A4** inhibitors including ketoconazole, itraconazole, and clarithromycin also call for a 50 percent dose reduction.
- Combined strong CYP2D6 and CYP3A4 inhibition requires reducing to **one quarter** of the usual dose.
- Strong inducers such as rifampin and carbamazepine roughly halve exposure and require doubling the dose over 1-2 weeks.
- Additive sedation with opioids, benzodiazepines, and alcohol; intrinsic QT liability is low.

SPECIAL POPULATIONS

- Third-trimester exposure carries the class risk of neonatal extrapyramidal and withdrawal signs; human pregnancy data remain limited.
- Lactation data are lacking, so monitor breastfed infants for sedation and feeding difficulty or choose a better-characterized agent.
- Approved from age 13 for schizophrenia; safety and effectiveness in pediatric major depressive disorder have not been established.
- In older adults with Alzheimer's agitation, weigh the modest benefit against the boxed mortality and cerebrovascular risk in every case.
- Dose ceilings of 2-3 mg/day apply when creatinine clearance is under 60 mL/min or hepatic impairment is Child-Pugh class B or C.

PRESCRIBING PEARLS

- Less akathisia than aripiprazole, more weight gain; that trade-off drives most switches between them.
- A 91-hour half-life means waiting two weeks before calling a dose change ineffective.
- For Alzheimer's agitation, the approved dose is 2-3 mg/day scheduled, never as needed.

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.