GLUTAMATERGIC ANTIDEPRESSANT

Dextromethorphan-Bupropion

Auvelity

First oral NMDA antagonist antidepressant, pairing dextromethorphan with bupropion as a CYP2D6 inhibitor to make oral dosing viable.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
45/105 mg PO twice daily	DXM 22 h; bupropion 15 h	CYP2D6 (DXM), CYP2B6 (bup)	1-2 wks; 6 wks full effect

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders. Closely monitor all patients for clinical worsening and emergence of suicidality, especially early in treatment and after dose changes.

INDICATIONS

- FDA-approved in August 2022 for the treatment of major depressive disorder in adults, as a fixed-dose oral combination tablet.
- Positioned as an alternative to standard monoamine antidepressants when a faster onset or a nonserotonergic mechanism is desired.
- Registration trials showed separation from placebo as early as week 1, faster than typical for SSRI or SNRI therapy.
- Off-label interest exists for treatment-resistant depression, but the drug was studied and approved in general adult MDD populations.
- Not approved for smoking cessation, seasonal affective disorder, or agitation in dementia despite the bupropion component.
- Safety and effectiveness in pediatric patients have not been established and use under 18 years is not recommended.

DOSING & TITRATION

- Start **one tablet (45 mg/105 mg) PO once daily in the morning** for 3 days, then increase to one tablet twice daily.
- Separate the two daily doses by at least 8 hours; the maximum dose is **two tablets (90 mg/210 mg) per day**.
- Swallow tablets whole and do not crush, chew, or split them, since the extended-release matrix controls bupropion exposure.
- In moderate renal impairment with eGFR **30-59 mL/min/1.73 m2**, limit to one tablet once daily; avoid if eGFR is below 30.
- In moderate hepatic impairment give one tablet once daily, and avoid the product entirely in severe hepatic impairment.
- Taper is not formally required, but gradual reduction is prudent given the serotonergic and noradrenergic components.

MECHANISM OF ACTION

- Dextromethorphan is an uncompetitive NMDA receptor antagonist, producing rapid glutamatergic modulation analogous to ketamine.
- It is also a sigma-1 receptor agonist and inhibits serotonin and norepinephrine reuptake, adding monoaminergic and neuroplastic effects.
- Bupropion is a norepinephrine and dopamine reuptake inhibitor that contributes independent antidepressant activity to the combination.
- Bupropion is a strong CYP2D6 inhibitor, and this is the pharmacokinetic reason it is present: it blocks first-pass clearance of dextromethorphan.
- Without bupropion, oral dextromethorphan is metabolized so rapidly that plasma concentrations never reach the therapeutic range.

PHARMACOKINETICS

- Dextromethorphan peak concentrations occur about 3 hours after dosing, with bupropion peaking around 3 hours as well.
- CYP2D6 inhibition by bupropion raises the dextromethorphan half-life to roughly 22 hours, compared with about 4 hours when given alone.
- Bupropion has a half-life near 15 hours and is metabolized by CYP2B6 to hydroxybupropion, an active metabolite with a longer half-life.
- Steady state for both components is reached in approximately 8 days of twice-daily dosing with the extended-release tablet.
- In known CYP2D6 poor metabolizers dextromethorphan exposure rises substantially, so the maximum is one tablet once daily.

ADVERSE EFFECTS

- Dizziness affects roughly 16 percent of patients, headache about 8 percent, and diarrhea and somnolence about 7 percent each.
- Dry mouth, hyperhidrosis, and sexual dysfunction occur but are less frequent than with serotonergic antidepressants.
- Seizure risk is dose dependent from the bupropion component, which is why the product is contraindicated in seizure disorders.
- Blood pressure and heart rate can rise, so hypertension should be controlled before starting and monitored during treatment.
- Activation, insomnia, anxiety, and manic switch in undiagnosed bipolar disorder are all recognized with this combination.
- Angle-closure glaucoma, hepatotoxicity, and rare serious hypersensitivity reactions are described in the product labeling.

MONITORING

- Check blood pressure and heart rate at baseline and periodically thereafter, since bupropion raises both in some patients.
- Screen every patient for a personal or family history of seizures, eating disorders, and bipolar disorder before the first dose.
- Monitor for emergent suicidality, agitation, and behavioral activation during the first weeks and after any dose change.
- Verify renal and hepatic function before starting, since both moderate impairments require reduction to once-daily dosing.
- Ask about concurrent CYP2D6 substrates at each visit, because bupropion can raise their levels substantially and unexpectedly.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and within 14 days of stopping one because of hypertensive reactions and serotonin syndrome.
- Contraindicated in seizure disorder, current or prior bulimia or anorexia nervosa, and abrupt withdrawal from alcohol or sedatives.
- Do not combine with other bupropion-containing products or with additional dextromethorphan-containing cough preparations.
- As a strong CYP2D6 inhibitor it raises levels of tricyclics, risperidone, metoprolol, and tamoxifen, reducing tamoxifen efficacy.
- CYP2B6 inducers such as carbamazepine, phenytoin, ritonavir, and efavirenz can lower bupropion exposure and blunt response.

SPECIAL POPULATIONS

- Pregnancy data are limited; bupropion exposure registries have not shown a consistent teratogenic signal but data remain sparse.
- Both components enter breast milk, and seizures have been reported in a breastfed infant exposed to bupropion, so caution applies.
- Not approved under 18 years, and adolescents carry the class suicidality warning if the drug is prescribed off-label.
- In older adults use standard dosing but monitor blood pressure closely and consider reduced renal clearance of bupropion metabolites.
- Limit to one tablet daily in moderate renal or hepatic impairment, and avoid entirely with severe impairment of either organ.

PRESCRIBING PEARLS

- Bupropion is here as a CYP2D6 inhibitor; without it oral dextromethorphan never reaches useful levels.
- Never add another bupropion product; the seizure risk is additive and dose dependent.
- CYP2D6 poor metabolizers should receive no more than one tablet daily.

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.