

Buspirone

BuSpar (US brand discontinued), available as generic

5-HT_{1A} partial agonist anxiolytic with no sedation, no dependence, and no withdrawal, but it takes weeks to work and is never a PRN.

USUAL ADULT RANGE

20-30 mg/day PO divided

HALF-LIFE

2-3 h; active 1-PP metabolite

METABOLISM

CYP3A4 (extensive first pass)

ONSET

2-4 wks; never used as PRN

✔ **No FDA boxed warning** on the current US label.

INDICATIONS

- FDA-approved for the management of anxiety disorders and for the short-term relief of anxiety symptoms in adults.
- Best supported in generalized anxiety disorder, where it is a reasonable option for patients in whom benzodiazepines are undesirable.
- Off-label as an augmenting agent for major depressive disorder after inadequate SSRI response, as tested in the STAR-D program.
- Off-label for antidepressant-induced sexual dysfunction, where the 5-HT_{1A} action may partially reverse serotonergic blunting.
- Off-label for aggression and agitation in dementia or traumatic brain injury, and for sleep-related bruxism.
- Safety and effectiveness in patients under 18 years have not been established, and pediatric trials did not demonstrate efficacy.

DOSING & TITRATION

- Start **7.5 mg PO twice daily** or 5 mg three times daily, then increase by **5 mg/day** every 2 to 3 days as tolerated.
- The usual effective range is **20-30 mg/day** in divided doses; the maximum recommended dose is **60 mg/day**.
- Underdosing is the most common reason for apparent failure, since many patients are left at 15 mg/day indefinitely.
- Supplied as 5, 7.5, 10, 15, and 30 mg tablets, with the 15 and 30 mg tablets scored for flexible divided dosing.
- Reduce the dose to **2.5 mg twice daily** when a strong CYP3A4 inhibitor such as itraconazole cannot be avoided.
- Not recommended in severe hepatic or severe renal impairment; no taper is needed because withdrawal does not occur.

MECHANISM OF ACTION

- Partial agonist at presynaptic and postsynaptic serotonin 5-HT_{1A} receptors, modulating serotonergic tone rather than blocking reuptake.
- Presynaptic autoreceptor agonism initially reduces serotonin firing, and receptor desensitization over weeks yields the anxiolytic effect.
- It has no activity at the benzodiazepine site or at GABA-A receptors, which is why it produces neither sedation nor dependence.
- Moderate dopamine D₂ receptor affinity explains occasional restlessness or akathisia-like symptoms in a minority of patients.
- Because it does not act on GABA, it neither treats benzodiazepine withdrawal nor provides any acute relief of panic.

PHARMACOKINETICS

- Rapidly absorbed but subject to very extensive first-pass metabolism, giving an oral bioavailability of only about 4 percent.
- Food slows absorption yet increases overall bioavailability, so patients should take doses consistently with or without food.
- Elimination half-life is only 2 to 3 hours, which is why divided daily dosing is required for a stable clinical effect.
- Metabolized by CYP3A4 to 1-pyrimidinylpiperazine, an active metabolite with alpha-2 adrenergic antagonist properties.
- Grapefruit juice and strong CYP3A4 inhibitors raise plasma concentrations several-fold and can cause dizziness and sedation.

ADVERSE EFFECTS

- Dizziness affects roughly 12 percent of patients and is the most common reason for early discontinuation of the drug.
- Nausea occurs in about 8 percent and headache in about 6 percent, with lightheadedness and nervousness also frequent.
- Restlessness, and occasionally akathisia-like symptoms, arise from dopamine D₂ affinity and can be mistaken for worsening anxiety.
- It causes no meaningful sedation, no psychomotor impairment, and no respiratory depression, so driving is generally unaffected.
- There is no physical dependence, no withdrawal syndrome, and no established abuse liability with this agent.
- Serotonin syndrome has been reported rarely when buspirone is combined with other serotonergic drugs or an MAO inhibitor.

MONITORING

- No routine laboratory monitoring is required, which is a practical advantage over many alternative anxiolytic strategies.
- Reassess anxiety severity at 4 weeks with a standardized scale, since response is gradual and easily missed by impression alone.
- Verify the total daily dose at each visit, because failure is far more often from underdosing than from true nonresponse.
- Screen for hepatic and renal impairment before starting, as severe impairment of either organ makes the drug inappropriate.
- Ask about grapefruit juice intake and about new CYP3A4 inhibitors whenever dizziness or lightheadedness emerges.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and within 14 days of stopping one because of hypertensive reactions.
- Strong CYP3A4 inhibitors such as itraconazole, clarithromycin, ritonavir, and nefazodone sharply raise levels and require dose reduction.
- CYP3A4 inducers including rifampin, carbamazepine, and phenytoin lower concentrations enough to abolish the clinical effect.
- Grapefruit juice raises exposure substantially and should be avoided or kept consistent during buspirone treatment.
- Additive serotonergic risk exists with SSRIs, SNRIs, triptans, and linezolid, though clinically significant events are uncommon.

SPECIAL POPULATIONS

- Human pregnancy data are limited but reassuring in the small studies available, and animal reproduction studies show no clear harm.
- Lactation data are sparse; the very low bioavailability suggests limited infant exposure, but monitoring the infant is prudent.
- Not approved under 18 years, and controlled pediatric trials in generalized anxiety disorder failed to separate from placebo.
- A reasonable anxiolytic in older adults because it avoids the falls, sedation, and cognitive impairment of benzodiazepines.
- Avoid in severe hepatic impairment and in severe renal impairment, since clearance falls and metabolite exposure rises.

PRESCRIBING PEARLS

- No boxed warning, no dependence, no withdrawal, and no sedation, but also no acute relief.
- Most failures are underdosing; push toward **30 mg/day** divided before abandoning it.
- Useless for benzodiazepine withdrawal because it has no activity at the GABA-A receptor.

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.