NON-BENZODIAZEPINE ANXIOLYTIC

Hydroxyzine

Vistaril, Atarax (brand discontinued in the US)

Sedating first-generation antihistamine used as a non-addictive as-needed anxiolytic when a benzodiazepine is unwise.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
25-50 mg PO 3-4 times daily	~20 h (29 h in elderly)	ADH to cetirizine; CYP3A4/5	15-30 min; peak ~2 h

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease with anxiety.
- FDA-approved for pruritus due to allergic conditions including chronic urticaria and atopic or contact dermatoses.
- FDA-approved as a sedative for premedication before and following general anesthesia, and the intramuscular form as an antiemetic.
- The intramuscular hydrochloride salt is labeled as adjunctive therapy in acute alcoholism with delirium tremens or hallucinosis.
- Off-label but widely used as a scheduled or as-needed anxiolytic in patients with substance use disorder, since it is not controlled.
- Off-label for insomnia; a Cochrane review found modest short-term anxiolytic benefit in generalized anxiety but no long-term data.

DOSING & TITRATION

- Anxiety in practice: **25-50 mg PO three or four times daily** or as needed; the older label lists 50-100 mg four times daily, which is rarely used.
- European regulators cap total daily dosing at **100 mg/day in adults** and 50 mg/day in older adults because of QT prolongation risk.
- Pruritus: 25 mg PO three or four times daily; premedication before anesthesia 50-100 mg PO or 25-100 mg intramuscularly.
- Children under 6 years: 50 mg/day in divided doses; children over 6 years: 50-100 mg/day in divided doses for anxiety or pruritus.
- The intramuscular route only; hydroxyzine must never be given intravenously, subcutaneously or intra-arterially because of tissue necrosis and hemolysis.
- No taper is required on discontinuation, and there is no withdrawal syndrome, which is a major practical advantage over benzodiazepines.

MECHANISM OF ACTION

- Potent inverse agonist at the histamine H1 receptor, and central H1 blockade is the source of both sedation and anxiolysis.
- Blocks 5-HT2A and dopamine D2 receptors weakly, and has modest anticholinergic activity that contributes to dry mouth and confusion.
- It has no activity at GABA-A receptors, which is why it produces no tolerance, no physical dependence and no withdrawal syndrome.
- Blocks the cardiac hERG potassium channel at higher concentrations, the mechanism behind QT prolongation and rare torsades de pointes.
- Its active metabolite cetirizine is a peripherally selective H1 antagonist that carries the antihistaminic but not the sedating effect.

PHARMACOKINETICS

- Rapidly absorbed with clinical effect within 15-30 minutes and peak plasma concentrations at about 2 hours after an oral dose.
- Elimination half-life is roughly **20 hours** in healthy adults, lengthening to about 29 hours in older patients.
- Metabolized principally by alcohol dehydrogenase to **cetirizine**, an active metabolite, with additional CYP3A4 and CYP3A5 oxidation.
- Half-life extends to about 37 hours in primary biliary cirrhosis, so dose reduction is appropriate in significant hepatic impairment.
- Cetirizine is renally cleared, so accumulation and prolonged antihistaminic effects occur in advanced renal impairment.

ADVERSE EFFECTS

- Sedation is the most common effect and is dose-related, along with dry mouth, dizziness, blurred vision and constipation.
- Anticholinergic burden causing urinary retention, confusion and worsened cognition, which is the main limit in older adults.
- QT prolongation and rare torsades de pointes, more likely at higher doses, with hypokalemia, or alongside other QT-prolonging drugs.
- Rare acute generalized exanthematous pustulosis and fixed drug eruption, and hypersensitivity in patients allergic to cetirizine.
- Paradoxical CNS stimulation, tremor and rarely seizures, described more often in children and at higher doses.
- Intramuscular injection can cause marked local pain, sterile abscess and tissue necrosis if given by any other route.

MONITORING

- Obtain a baseline ECG when the dose exceeds 50 mg/day, in older adults, or when other QT-prolonging medications are in use.
- Check potassium and magnesium in patients on diuretics or with vomiting or diarrhea, since hypokalemia amplifies torsades risk.
- Assess daytime sedation, cognition, falls and anticholinergic symptoms at follow-up, particularly in patients over 65.
- Reassess whether as-needed dosing is actually reducing anxiety, since tolerance to sedation can be mistaken for loss of anxiolysis.
- No routine laboratory monitoring is otherwise required and no controlled substance monitoring applies, since it is not scheduled.

INTERACTIONS & CAUTIONS

- Contraindicated with other QT-prolonging drugs where possible, including citalopram at higher doses, methadone, ondansetron and antipsychotics.
- Additive sedation and psychomotor impairment with opioids, alcohol, benzodiazepines, gabapentinoids and other CNS depressants.
- Additive anticholinergic burden with tricyclic antidepressants, oxybutynin, benztropine, paroxetine and low-potency antipsychotics.
- Contraindicated in known hypersensitivity to hydroxyzine, cetirizine or levocetirizine, and in patients with congenital long QT syndrome.
- The label contraindicates use in early pregnancy, and it may mask the cutaneous response in allergy skin testing for several days.

SPECIAL POPULATIONS

- Pregnancy: contraindicated in early pregnancy per the label; later use is sometimes accepted for nausea but should be individualized.
- Lactation: hydroxyzine and cetirizine pass into breast milk and infant sedation is possible; monitor feeding and alertness.
- Pediatrics: dosing is established from infancy for pruritus and anxiety, though paradoxical stimulation is more common in children.
- Older adults: the AGS Beers Criteria advise avoiding first-generation antihistamines including hydroxyzine due to anticholinergic effects and delirium.
- Hepatic and renal impairment: reduce the dose in cirrhosis given the prolonged half-life, and in renal impairment where cetirizine accumulates.

PRESCRIBING PEARLS

- Not scheduled and not habit forming, so it is a first choice when a benzodiazepine is unwise.
- Get an ECG above 50 mg/day or in older adults; hERG blockade prolongs QT dose-dependently.
- Give intramuscularly or orally only; intravenous or subcutaneous routes cause tissue necrosis.

References

American Geriatrics Society Beers Criteria Update Expert Panel. (2023). American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society, 71*(7), 2052-2081. https://doi.org/10.1111/jgs.18372

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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.