NMDA RECEPTOR ANTAGONIST

Memantine

Namenda, Namenda XR, Namzaric (with donepezil)

Uncompetitive NMDA antagonist for moderate to severe Alzheimer disease; well tolerated, modest benefit, no disease modification.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
10 mg PO BID; XR 28 mg/day	60-80 h	Minimal hepatic; renal excretion	Assess benefit at 3-6 months

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for moderate to severe dementia of the Alzheimer type, as immediate-release tablets, oral solution, or extended-release capsules.
- Namzaric, a fixed combination of memantine extended-release with donepezil 10 mg, is approved for patients already stabilized on both drugs.
- It is not approved for mild Alzheimer disease, and trials in mild disease and in mild cognitive impairment have been negative.
- Commonly added to a cholinesterase inhibitor in moderate to severe disease, a combination supported by modest but consistent trial data.
- Used off-label for vascular dementia and for agitation in dementia, where evidence is weak and antipsychotic-sparing benefit is unproven.
- Used off-label as an augmentation strategy in obsessive-compulsive disorder, supported only by small randomized trials.

DOSING & TITRATION

- Immediate-release: start **5 mg** PO once daily and increase by **5 mg** weekly to a target of **10 mg twice daily**.
- Extended-release: start **7 mg** PO once daily and increase by 7 mg weekly to a target of **28 mg once daily** as tolerated.
- Severe renal impairment with creatinine clearance 5-29 mL/min: maximum **5 mg twice daily** immediate-release or **14 mg/day** extended-release.
- Switching from immediate-release 10 mg twice daily to extended-release 28 mg daily is done the day after the last immediate-release dose.
- Extended-release capsules may be opened and sprinkled on applesauce and swallowed without chewing for patients with swallowing difficulty.
- No hepatic adjustment is required in mild to moderate impairment; severe hepatic impairment has not been studied.

MECHANISM OF ACTION

- Uncompetitive, low-affinity, voltage-dependent antagonist at the NMDA glutamate receptor channel with rapid unblocking kinetics.
- It blocks pathologic tonic glutamate signaling while still permitting the phasic bursts required for learning and memory.
- Reducing excessive calcium influx is thought to limit excitotoxic injury, though no clinical trial has shown a disease-modifying effect.
- The low affinity and fast off-rate explain why it lacks the psychotomimetic effects of high-affinity NMDA antagonists such as ketamine.
- It also has weak antagonist activity at 5-HT3 and nicotinic receptors and agonist activity at dopamine D2 receptors.

PHARMACOKINETICS

- Well absorbed with Tmax of 3-7 hours and bioavailability near 100 percent; food has no clinically relevant effect on absorption.
- Half-life is 60-80 hours, so steady state takes several weeks and the drug can be dosed once daily in the extended-release form.
- Undergoes minimal hepatic metabolism to inactive metabolites and is excreted 57-82 percent unchanged in urine.
- Renal elimination uses cationic transport, so alkaline urine from carbonic anhydrase inhibitors or bicarbonate reduces clearance and raises levels.
- Because clearance is renal, dose adjustment depends on creatinine clearance rather than on liver function.

ADVERSE EFFECTS

- Dizziness in about 7 percent, headache, confusion, and constipation are the most common effects and are usually mild.
- Somnolence, fatigue, and agitation occur less often, and overall tolerability is better than with cholinesterase inhibitors.
- Blood pressure elevation and, rarely, hypertension have been reported and warrant periodic vital sign checks.
- Confusion or worsening agitation early in titration usually reflects too-rapid escalation and improves with slower titration.
- Rare hallucinations, gait disturbance, and falls occur, particularly when renal function declines and levels rise.
- It does not cause the nausea, diarrhea, bradycardia, or weight loss that limit cholinesterase inhibitor therapy.

MONITORING

- Check creatinine clearance before starting and periodically thereafter, since dosing depends on renal function rather than age alone.
- Measure blood pressure at routine visits, since hypertension has been reported during memantine treatment.
- Track cognition and function with MMSE or MoCA plus a caregiver-reported functional scale about every 6 months.
- Reassess benefit at 3 to 6 months and discuss stopping when decline continues without meaningful functional or behavioral benefit.
- Review urinary alkalinizing drugs and any new renal impairment, both of which raise memantine levels and can cause confusion.

INTERACTIONS & CAUTIONS

- Drugs that alkalinize urine, including sodium bicarbonate and carbonic anhydrase inhibitors such as acetazolamide, reduce clearance and raise levels.
- Other NMDA antagonists including amantadine, ketamine, and dextromethorphan should generally be avoided because effects are additive.
- Cimetidine, ranitidine, quinidine, nicotine, and hydrochlorothiazide share the renal cationic transport system and may alter concentrations.
- Memantine does not meaningfully inhibit or induce CYP enzymes, so it is straightforward to combine with most psychotropics.
- It can be combined safely with donepezil, and the fixed-dose combination product exists specifically for that pairing.

SPECIAL POPULATIONS

- Geriatric: this is the target population, and renal function rather than chronological age determines the correct maximum dose.
- Renal impairment: reduce the dose when creatinine clearance falls below 30 mL/min; no data exist for dialysis patients.
- Hepatic impairment: no adjustment for mild or moderate disease, and severe impairment has not been studied.
- Pregnancy and lactation: human data are essentially absent, and the indication rarely applies in patients of reproductive age.
- Pediatric: not approved at any age, and trials in autism and ADHD have not demonstrated meaningful benefit.

PRESCRIBING PEARLS

- It is for moderate to severe disease; adding it in mild Alzheimer disease has repeatedly failed in trials.
- Dose by creatinine clearance, not by age; confusion often means renal decline, not disease progression.
- Tolerability is its strength, so it suits patients who cannot manage cholinesterase inhibitor nausea.

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.