CHOLINESTERASE INHIBITOR

Donepezil

Aricept, Aricept ODT, Adlarity (transdermal)

First-line cholinesterase inhibitor for Alzheimer disease at every severity; it slows symptom decline but does not alter the disease.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
5-10 mg/day PO at bedtime	~70 h; steady state 2-3 wks	CYP2D6, CYP3A4	Benefit judged at 3-6 months

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for dementia of the Alzheimer type across mild, moderate, and severe stages, making it the broadest cholinesterase inhibitor label.
- The 23 mg tablet is approved only for moderate to severe disease after at least 3 months on 10 mg daily, with more gastrointestinal adverse effects.
- Adlarity transdermal system delivers 5 or 10 mg daily through a weekly patch for patients who cannot reliably swallow tablets.
- Used off-label for dementia with Lewy bodies and Parkinson disease dementia, where cholinergic deficits are prominent and often responsive.
- Used off-label for vascular and mixed dementia, where the effect size is smaller and guidelines do not routinely recommend it.
- Expected benefit is stabilization or modest improvement in cognition and function for months, not reversal or prevention of progression.

DOSING & TITRATION

- Start **5 mg** PO once daily at bedtime and hold that dose for at least 4 to 6 weeks before considering an increase.
- Increase to **10 mg** PO daily, the usual maintenance dose for all severities and the best balance of benefit and tolerability.
- Consider **23 mg** daily only in moderate to severe disease after 3 months at 10 mg, accepting substantially more nausea and vomiting.
- If nausea or vivid dreams interfere, move dosing to morning with food or use the weekly transdermal patch instead of oral tablets.
- After an interruption of more than several days, restart at 5 mg and retitrate to avoid a recurrence of gastrointestinal effects.
- No renal or hepatic dose adjustment is specified, but titrate more slowly in frail patients and those with low body weight.

MECHANISM OF ACTION

- Reversibly and noncompetitively inhibits acetylcholinesterase, raising synaptic acetylcholine in cortex and hippocampus.
- It is relatively selective for acetylcholinesterase over butyrylcholinesterase, which differs from rivastigmine and may affect tolerability.
- Increased cholinergic tone partly compensates for the loss of basal forebrain cholinergic neurons that occurs early in Alzheimer disease.
- The effect is symptomatic and neurochemical, with no impact on amyloid, tau, or the underlying rate of neurodegeneration.
- Peripheral cholinergic stimulation from the same mechanism causes nausea, diarrhea, bradycardia, and increased gastric acid secretion.

PHARMACOKINETICS

- Well absorbed with a Tmax of 3-4 hours and bioavailability near 100 percent; food does not meaningfully change absorption.
- Elimination half-life is about 70 hours, so steady state takes 2-3 weeks and a missed dose rarely causes abrupt worsening.
- Metabolized by CYP2D6 and CYP3A4 with subsequent glucuronidation, and roughly 17 percent is excreted unchanged in urine.
- Protein binding is about 96 percent, mainly to albumin, and the drug distributes widely including into the central nervous system.
- No dose adjustment is required for mild to moderate renal or hepatic impairment, though severe impairment has not been well studied.

ADVERSE EFFECTS

- Nausea, diarrhea, vomiting, anorexia, and weight loss are the dominant effects and are dose dependent, especially at 23 mg.
- Insomnia, vivid or disturbing dreams, and muscle cramps are common; switching to morning dosing usually resolves sleep complaints.
- Bradycardia, heart block, and syncope occur through vagotonic effects and matter most in patients with sick sinus syndrome or on rate-control drugs.
- Increased gastric acid secretion raises ulcer and gastrointestinal bleeding risk, particularly with concurrent NSAIDs or anticoagulants.
- Urinary incontinence, worsening bladder outlet symptoms, and increased bronchial secretions in asthma or COPD can emerge with treatment.
- Rare reports include seizures, rhabdomyolysis, and neuroleptic malignant syndrome, chiefly after rapid dose escalation.

MONITORING

- Baseline pulse and an ECG when there is syncope, bradycardia, conduction disease, or concurrent rate-slowing medication.
- Track weight at each visit, since anorexia and weight loss are common and consequential in older adults with dementia.
- Measure cognition and function with MMSE or MoCA plus a functional scale at baseline and about every 6 months.
- Reassess benefit deliberately at 3 to 6 months and discuss discontinuation when there is clear ongoing decline without functional benefit.
- Ask about falls, dizziness, gastrointestinal symptoms, and sleep disruption, the effects most likely to reduce quality of life.

INTERACTIONS & CAUTIONS

- Anticholinergic drugs such as oxybutynin, diphenhydramine, and tricyclic antidepressants directly oppose the mechanism and should be deprescribed.
- Beta-blockers, digoxin, diltiazem, verapamil, and amiodarone add to bradycardia and increase the risk of syncope and falls.
- CYP2D6 and CYP3A4 inhibitors such as paroxetine, fluoxetine, and ketoconazole raise donepezil levels and worsen cholinergic effects.
- Enzyme inducers including carbamazepine, phenytoin, rifampin, and dexamethasone can lower donepezil concentrations and reduce efficacy.
- Cholinesterase inhibition exaggerates succinylcholine-type neuromuscular blockade, so anesthesia teams should be told the patient takes it.

SPECIAL POPULATIONS

- Geriatric: this is the primary population, and the key concerns are bradycardia, falls, weight loss, and anticholinergic co-prescribing.
- Pregnancy and lactation: essentially no relevant human data, and the indication rarely arises in patients of reproductive age.
- Pediatric: safety and effectiveness have not been established, and use for autism or ADHD is not supported by evidence.
- Renal or hepatic impairment: no formal adjustment is required, but clearance is slower in cirrhosis and titration should be cautious.
- Low body weight, typically under 55 kg, predicts more nausea, vomiting, and weight loss and argues for staying at 5-10 mg.

PRESCRIBING PEARLS

- Do not stop and restart casually; after several missed days retitrate from 5 mg to avoid vomiting.
- Vivid nightmares at bedtime dosing usually disappear when the dose is moved to the morning.
- The 23 mg tablet buys little and costs a lot in nausea; most patients belong at 10 mg.

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.