WAKEFULNESS-PROMOTING AGENT | C-IV

Armodafinil

Nuvigil

The longer-lived R-enantiomer of modafinil, giving higher late-day concentrations for the same wakefulness indications in adults.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
150-250 mg/day PO each morning	~15 h	Amidase, CYP3A4; 3A4 inducer	1-2 h; peak 2 h

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved in adults to improve wakefulness in excessive sleepiness associated with narcolepsy, at 150 to 250 mg each morning.
- FDA-approved as adjunctive treatment for residual excessive sleepiness in obstructive sleep apnea alongside ongoing positive airway pressure use.
- FDA-approved for excessive sleepiness of shift work disorder, given about one hour before the start of the work shift.
- Used off-label as adjunctive treatment for bipolar I depression, where randomized trials show small and inconsistent benefit over placebo.
- Used off-label for fatigue in multiple sclerosis, Parkinson disease, cancer, and traumatic brain injury after treatable causes are excluded.
- Used off-label for residual sedation and hypersomnia in major depressive disorder, jet lag, and sedating antipsychotic regimens.

DOSING & TITRATION

- Narcolepsy and obstructive sleep apnea: **150-250 mg** PO once daily in the morning; doses above 150 mg add little in sleep apnea.
- Shift work disorder: **150 mg** PO approximately 1 hour before the start of the shift, rather than at a fixed clock time.
- Severe hepatic impairment: reduce the dose by about half and titrate slowly with attention to psychiatric and cardiovascular effects.
- Older adults should generally start at **50-100 mg/day** because clearance declines with age and adverse effects are more frequent.
- Available as 50, 150, 200, and 250 mg tablets, which allows dose splitting for tolerability rather than fixed 150 mg increments.
- No taper is required, and stopping produces return of sleepiness rather than a physiologic withdrawal syndrome.

MECHANISM OF ACTION

- Weakly binds and blocks the dopamine transporter, raising extracellular dopamine without reversing transporter flux as amphetamines do.
- Activates orexin and histaminergic tuberomammillary wake circuits in the hypothalamus, supporting cortical arousal rather than global stimulation.
- Increases cortical glutamate and reduces GABA tone, contributing to sustained alertness with relatively little peripheral sympathetic effect.
- As the pure R-enantiomer it avoids the rapidly cleared S-isomer, so plasma concentrations stay higher 6-14 hours after a morning dose.
- Reinforcing effects exist but are weaker than with stimulants, consistent with schedule IV rather than schedule II placement.

PHARMACOKINETICS

- Tmax is about 2 hours in the fasted state, and food delays the peak by 2-4 hours without changing overall exposure.
- Terminal half-life is roughly 15 hours, and steady state is reached in about 7 days with once-daily dosing.
- Cleared mainly by hepatic amidase hydrolysis to inactive modafinil acid, with a lesser CYP3A4 route and minimal unchanged renal excretion.
- Moderately induces CYP3A4 and inhibits CYP2C19, the two effects behind nearly all of its clinically significant drug interactions.
- Severe hepatic impairment markedly raises exposure and requires dose reduction; renal impairment needs no adjustment but data are limited.

ADVERSE EFFECTS

- Headache in about 17 percent, nausea in 7 percent, insomnia, dizziness, anxiety, and dry mouth are the most common adverse effects.
- Serious rash including Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS has been reported; any new rash should stop the drug.
- Angioedema and anaphylactoid reactions plus multi-organ hypersensitivity reactions are labeled warnings that require permanent discontinuation.
- Psychiatric adverse effects include anxiety, agitation, insomnia, mania, psychosis, and rarely suicidal ideation, especially in bipolar disorder.
- Blood pressure and heart rate can rise slightly, and some patients need antihypertensive adjustment during ongoing therapy.
- Insomnia is more likely than with modafinil when dosed later in the day because of higher afternoon and evening concentrations.

MONITORING

- Confirm the sleep diagnosis and, in obstructive sleep apnea, verify ongoing positive airway pressure adherence before and during treatment.
- Check blood pressure and pulse at baseline and periodically, particularly in patients with hypertension or established cardiac disease.
- Ask about rash, mucosal ulceration, fever, or facial swelling at each visit and instruct the patient to stop the drug and call immediately.
- Measure sleepiness with the Epworth Sleepiness Scale or maintenance of wakefulness testing rather than relying on subjective energy reports.
- Screen for insomnia, anxiety, mood elevation, and suicidal thinking, particularly when used off-label in bipolar depression.

INTERACTIONS & CAUTIONS

- Induces CYP3A4 and reduces ethinyl estradiol exposure, so hormonal contraceptives can fail; add a nonhormonal method during use.
- The contraceptive interaction persists for one month after armodafinil is stopped, so backup contraception must continue beyond the last dose.
- Inhibits CYP2C19, raising concentrations of phenytoin, diazepam, propranolol, omeprazole, and clomipramine, sometimes requiring dose reduction.
- Lowers levels of cyclosporine, midazolam, triazolam, and some antiretrovirals through CYP3A4 induction, which can cause therapeutic failure.
- Strong CYP3A4 inducers such as carbamazepine and rifampin reduce armodafinil exposure, while ketoconazole raises it modestly.

SPECIAL POPULATIONS

- Pregnancy: pregnancy registry data for modafinil and armodafinil suggest increased major congenital malformations, so avoid where alternatives exist.
- Lactation: human milk data are limited; if used, watch the infant for irritability, poor feeding, and disturbed sleep.
- Pediatric: safety and effectiveness have not been established in patients under 17 years, and serious rash risk argues against off-label pediatric use.
- Geriatric: reduced clearance justifies lower starting doses and closer monitoring for insomnia, agitation, and blood pressure changes.
- Severe hepatic impairment requires dose reduction; no renal adjustment is defined although modafinil acid accumulates in severe renal failure.

PRESCRIBING PEARLS

- Same wakefulness effect as modafinil but higher afternoon levels, so evening insomnia is the usual complaint.
- Treat any rash as potential Stevens-Johnson syndrome and stop the drug before investigating.
- It reduces hormonal contraceptive efficacy during use and for a month afterward; document a backup method.

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.