WAKEFULNESS-PROMOTING AGENT | C-IV

Modafinil

Provigil

Non-amphetamine wakefulness agent for narcolepsy, sleep apnea, and shift work disorder, with lower abuse liability than stimulants.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
200 mg/day PO; max 400 mg	~15 h (R-isomer driven)	Amidase, CYP3A4; 3A4 inducer	1-2 h; peak 2-4 h

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved in adults to improve wakefulness in excessive daytime sleepiness from narcolepsy, including type 1 and type 2 presentations.
- FDA-approved as an adjunct for residual sleepiness in obstructive sleep apnea, only alongside continued positive airway pressure therapy.
- FDA-approved for excessive sleepiness associated with shift work disorder, dosed one hour before the start of the work shift.
- Used off-label for fatigue and sleepiness in multiple sclerosis, Parkinson disease, and traumatic brain injury when sleep disorders are excluded.
- Used off-label to augment antidepressants for residual fatigue, hypersomnia, and low energy in major depressive and bipolar depression.
- Used off-label for ADHD in adults, though it is not FDA-approved for ADHD and a pediatric application was rejected over serious rash risk.

DOSING & TITRATION

- Narcolepsy and obstructive sleep apnea: **200 mg** PO once daily in the morning, taken with or without food.
- Shift work disorder: **200 mg** PO taken approximately 1 hour before the start of the work shift rather than on a fixed clock time.
- Doses up to **400 mg/day** have been used and are tolerated, but controlled trials show no consistent added benefit over 200 mg.
- Severe hepatic impairment: reduce to **100 mg/day**; no adjustment is required for renal impairment, though data in severe disease are sparse.
- In older adults consider starting at 100 mg daily because clearance falls with age and psychiatric side effects are more common.
- No taper is required and physiologic withdrawal is not seen, though sleepiness returns promptly when the drug is stopped.

MECHANISM OF ACTION

- Binds the dopamine transporter with weak affinity and blocks reuptake, raising extracellular dopamine in striatum and nucleus accumbens.
- Unlike amphetamines it does not reverse transporter flux, and the slow rise in dopamine is thought to explain its lower abuse potential.
- Increases hypothalamic orexin and histamine signaling and activates tuberomammillary wake-promoting nuclei, supporting cortical arousal.
- Raises glutamate and reduces GABA tone in cortex and hypothalamus, and elevates norepinephrine in wake-regulating regions.
- The wakefulness effect is relatively selective, producing less peripheral sympathetic activation and less rebound hypersomnia than stimulants.

PHARMACOKINETICS

- Absorbed with Tmax at 2-4 hours; food delays absorption by about an hour but does not reduce total bioavailability.
- Racemic, with the R-enantiomer half-life near 15 hours and the S-enantiomer near 4 hours, giving an effective half-life of about 15 hours.
- Cleared mainly by hepatic amidase hydrolysis to inactive modafinil acid, with a smaller CYP3A4 pathway and under 10 percent renal excretion.
- Moderately induces CYP3A4 and CYP1A2 while inhibiting CYP2C19, the combination that drives most of its clinically relevant interactions.
- Severe hepatic impairment roughly doubles exposure and requires halving the dose; renal impairment does not require adjustment.

ADVERSE EFFECTS

- Headache in about 34 percent, nausea in 11 percent, nervousness, anxiety, insomnia, dry mouth, and diarrhea are the common complaints.
- Serious rash including Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS has been reported; stop the drug at the first rash.
- Angioedema and anaphylactoid reactions, along with multi-organ hypersensitivity, are labeled warnings requiring immediate discontinuation.
- Psychiatric effects include anxiety, agitation, insomnia, and rarely mania, psychosis, or suicidal ideation, particularly in bipolar disorder.
- Small mean rises in blood pressure and heart rate can require antihypertensive adjustment, especially in patients with sleep apnea.
- Abuse potential is low but real, and euphoria and psychoactive effects consistent with other schedule IV stimulants have been documented.

MONITORING

- Confirm the sleep diagnosis before starting, including polysomnography and adherence to positive airway pressure in obstructive sleep apnea.
- Baseline and periodic blood pressure and heart rate, since small pressor effects can matter in patients with cardiovascular disease.
- Ask about rash, mucosal lesions, fever, or facial swelling at every visit during the first several months and instruct patients to stop and call.
- Track daytime sleepiness with the Epworth Sleepiness Scale or maintenance of wakefulness testing rather than by report of energy alone.
- Screen for emergent anxiety, insomnia, mania, and suicidal ideation, especially in patients with bipolar or psychotic disorders.

INTERACTIONS & CAUTIONS

- Induces CYP3A4 and lowers ethinyl estradiol exposure, reducing effectiveness of oral, patch, ring, and implant contraceptives; use an additional nonhormonal method.
- Contraceptive failure risk persists for one month after modafinil is stopped, so backup contraception must continue past the last dose.
- Inhibits CYP2C19, raising levels of phenytoin, diazepam, omeprazole, propranolol, and clomipramine; monitor and reduce doses as needed.
- CYP3A4 induction lowers concentrations of cyclosporine, midazolam, triazolam, and some direct oral anticoagulants and protease inhibitors.
- Strong CYP3A4 inducers such as carbamazepine and rifampin lower modafinil levels, while inhibitors such as ketoconazole raise them modestly.

SPECIAL POPULATIONS

- Pregnancy: registry data suggest an increased rate of major congenital malformations, so avoid unless there is no reasonable alternative.
- Lactation: limited data on transfer into human milk; if used, monitor the infant for agitation, poor feeding, and disrupted sleep.
- Pediatric: not approved at any age, and a pediatric ADHD application was not approved because of serious rash including Stevens-Johnson syndrome.
- Geriatric: clearance is reduced, so consider starting at 100 mg/day and watch for agitation, insomnia, and blood pressure elevation.
- Severe hepatic impairment requires halving the dose; no renal adjustment is defined, but modafinil acid accumulates in severe renal failure.

PRESCRIBING PEARLS

- Modafinil makes hormonal contraception fail; document a backup method and continue it a month after stopping.
- Any rash on modafinil is a stop-the-drug event until Stevens-Johnson syndrome is confidently excluded.
- In sleep apnea it treats residual sleepiness only, never as a substitute for positive airway pressure.

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.