Armodafinil

**Therapeutics**

**Brands**  
- Nuvigil  
*see index for additional brand names*

**Generic?**  
Yes

**Class**
- Neuroscience-based Nomenclature: dopamine reuptake inhibitor (D-RI)
- Wake-promoting

**Commonly Prescribed for**  
(bold for FDA approved)
- Reducing excessive sleepiness in patients with narcolepsy and shift work sleep disorder
- Reducing excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) (adjunct to standard treatment for underlying airway obstruction)
- Attention deficit hyperactivity disorder (ADHD)
- Fatigue and sleepiness in depression
- Fatigue in multiple sclerosis
- Bipolar depression

**How the Drug Works**
- Unknown, but clearly different from classical stimulants such as methylphenidate and amphetamine
- Binds to and requires the presence of the dopamine transporter; also requires the presence of alpha adrenergic receptors
- Hypothetically acts as an inhibitor of the dopamine transporter
- Increases neuronal activity selectively in the hypothalamus
  * Presumably enhances activity in hypothalamic wakefulness center (TMN, tuberomammillary nucleus) within the hypothalamic sleep-wake switch by an unknown mechanism
  * activates tuberomammillary nucleus neurons that release histamine
  * activates other hypothalamic neurons that release orexin/hypocretin

**How Long Until It Works**
- Can immediately reduce daytime sleepiness and improve cognitive task performance within 2 hours of first dosing
- Can take several days to optimize dosing and clinical improvement

**If It Works**
- ✴ Improves daytime sleepiness and may improve attention as well as fatigue
- ✴ Does not generally prevent one from falling asleep when needed
- • May not completely normalize wakefulness
- • Treat until improvement stabilizes and then continue treatment indefinitely as long as improvement persists (studies support at least 12 weeks of treatment)

**If It Doesn’t Work**
- ✴ Change dose; some patients may do better with an increased dose but some may actually do better with a decreased dose
- • Augment or consider an alternative treatment for daytime sleepiness, fatigue, or ADHD

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- ✴ Armodafinil is itself an adjunct to standard treatments for OSAHS; if continuous positive airway pressure (CPAP) is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating armodafinil and CPAP should be continued after initiation of armodafinil
- ✴ Armodafinil is itself an augmenting therapy to antidepressants for residual sleepiness and fatigue in major depressive disorder
- ✴ Armodafinil is itself an augmenting therapy to mood stabilizers for bipolar depression
- • Best to attempt another monotherapy prior to augmenting with other drugs in the treatment of sleepiness associated with sleep disorders or problems concentrating in ADHD
- • Combination of armodafinil with stimulants such as methylphenidate or amphetamine or with atomoxetine for ADHD has not been systematically studied
- • However, such combinations may be useful options for experts, with close monitoring, when numerous monotherapies for sleepiness or ADHD have failed
ARMODAFINIL (continued)

Tests
- None for healthy individuals

Best Augmenting Agents for Side Effects
- Many side effects cannot be improved with an augmenting agent

SIDE EFFECTS

How Drug Causes Side Effects
- Unknown
- CNS side effects presumably due to excessive CNS actions on various neurotransmitter systems

Notable Side Effects
- Headache
- Anxiety, dizziness, insomnia
- Dry mouth, diarrhea, nausea

Life-Threatening or Dangerous Side Effects
- Transient EKG ischemic changes in patients with mitral valve prolapse or left ventricular hypertrophy have been reported (rare)
- Rare activation of (hypo)mania, anxiety, hallucinations, or suicidal ideation
- Rare severe dermatologic reactions (Stevens-Johnson syndrome and others)
- Angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions have been reported

Weight Gain
- Reported but not expected

Sedation
- Reported but not expected
- Patients are usually awakened and some may be activated

What to Do About Side Effects
- Wait
- Lower the dose
- For activation or insomnia, do not give in the evening
- If unacceptable side effects persist, discontinue use
- For life-threatening or dangerous side effects, discontinue immediately (e.g., at first sign of a drug-related rash)

DOsing AND USE

Usual Dosage Range
- 150–250 mg/day

Dosage Forms
- Tablet 50 mg, 150 mg, 250 mg

How to Dose
- Titration up or down only necessary if not optimally efficacious at the standard starting dose of 150 mg once a day
- For OSA and narcolepsy, give as a single dose in the morning
- For shift work sleep disorder, give as a single dose 1 hour prior to the start of the work shift

Dosing Tips
- For sleepiness, more may be more: higher doses may be better than lower doses in patients with daytime sleepiness in sleep disorders
- For problems concentrating and fatigue, less may be more: lower doses may be paradoxically better than higher in some patients
- At high doses, may slightly induce its own metabolism, possibly by actions of inducing CYP450 3A4
- Dose may creep upward in some patients with long-term treatment due to autoinduction; drug holiday may restore efficacy at original dose
- Pharmacokinetics and clinical experience suggest armodafinil has longer duration of action than racemic modafinil, generally requiring only once daily administration

Overdose
- Agitation, insomnia, increase in hemodynamic parameters
- Postmarketing experience includes CNS symptoms, such as restlessness, disorientation, confusion, excitation, and hallucinations; digestive changes, such as
nausea and diarrhea; and cardiovascular changes, such as tachycardia, bradycardia, hypertension, and chest pain

Long-Term Use
• The need for continued treatment should be reevaluated periodically

Habit Forming
• Schedule IV; may have some potential for abuse but unusual in clinical practice

How to Stop
• Taper not necessary; patients may have sleepiness on discontinuation

Pharmacokinetics
• Metabolized by the liver
• Elimination half-life approximately 15 hours
• Inhibits CYP450 2C19
• Induces CYP450 3A4 (and slightly 1A2)

Drug Interactions
• May increase plasma levels of drugs metabolized by CYP450 2C19 (e.g., diazepam, phenytoin, propranolol)
• May decrease plasma levels of CYP450 3A4 substrates such as ethinyl estradiol and triazolam
• Due to induction of CYP450 3A4, effectiveness of steroidal contraceptives may be reduced by armodafinil, including 1 month after discontinuation
• Inducers or inhibitors of CYP450 3A4 may affect levels of armodafinil (e.g., carbamazepine may lower modafinil plasma levels; fluvoxamine and fluoxetine may raise armodafinil plasma levels)
• Armodafinil may slightly reduce its own levels by autoinduction of CYP450 3A4
• Patients on armodafinil and warfarin should have prothrombin times monitored
• Methylphenidate and dextroamphetamine may delay absorption of armodafinil by an hour
★ However, coadministration with methylphenidate or dextroamphetamine does not significantly change the pharmacokinetics of armodafinil or either stimulant
• Interaction studies with MAOIs have not been performed, but MAOIs can be given with armodafinil by experts with cautious monitoring

Other Warnings/Precautions
• Patients with history of drug abuse should be monitored closely
• Armodafinil may cause CNS effects similar to those caused by other CNS agents (e.g., changes in mood and, theoretically, activation of psychosis, mania, or suicidal ideation)
• Armodafinil should be used in patients with sleep disorders that have been completely evaluated for narcolepsy, OSAHS, and shift work sleep disorder
• In OSAHS patients for whom CPAP is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating armodafinil, and then CPAP should be continued after initiating armodafinil
• The effectiveness of steroidal contraceptives may be reduced when used with armodafinil and for 1 month after discontinuation of armodafinil
• Armodafinil is not a replacement for sleep

Do Not Use
• If there is a proven allergy to armodafinil or modafinil

SPECIAL POPULATIONS

Renal Impairment
• Use with caution

Hepatic Impairment
• Reduce dose in severely impaired patients

Cardiac Impairment
• Use with caution
• Not recommended for use in patients with a history of left ventricular hypertrophy, ischemic EKG changes, chest pain, arrhythmias, or recent myocardial infarction

Elderly
• Limited experience in patients over 65
• Clearance of armodafinil may be reduced in elderly patients
ARMODAFINIL (continued)

**Children and Adolescents**
- Safety and efficacy have not been established
- Can be used cautiously by experts for children and adolescents

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLRR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Intrauterine growth restriction and spontaneous abortion have been reported with armodafinil and modafinil
- In animal studies, developmental toxicity was observed at clinically relevant plasma exposures
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- Generally, armodafinil should be discontinued prior to anticipated pregnancies

**Breast Feeding**
- Unknown if armodafinil is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

**Potential Advantages**
- Selective for areas of brain involved in sleep/wake promotion
- Less activating and less abuse potential than stimulants

**Potential Disadvantages**
- May not work as well as stimulants in some patients

**Primary Target Symptoms**
- Sleepiness
- Concentration
- Physical and mental fatigue

**Pearls**
- Armodafinil is the longer-lasting R enantiomer of racemic modafinil
- Armodafinil maintains high plasma concentrations later in the day than does modafinil on a mg-to-mg basis, which could theoretically result in improved wakefulness throughout the day with armodafinil compared to modafinil
- Armodafinil is not a replacement for sleep
- The treatment for sleep deprivation is sleep, not armodafinil
- Controlled studies suggest armodafinil improves attention in OSAHS and shift work sleep disorder, but controlled studies of attention have not been performed in ADHD or major depressive disorder
- Controlled studies of racemic modafinil in ADHD suggest improvement in attention
- May be useful to treat fatigue in patients with depression as well as other disorders, such as multiple sclerosis, myotonic dystrophy, HIV/AIDS
- May be useful in treating sleepiness associated with opioid analgesia, particularly in end-of-life management
- Subjective sensation associated with armodafinil is usually one of normal wakefulness, not of stimulation, although jitteriness can rarely occur
- Compared to traditional stimulants, armodafinil has a novel mechanism of action, novel therapeutic uses, and less abuse potential
- Alpha 1 antagonists such as prazosin may block the therapeutic actions of armodafinil
- Some controlled trials suggest efficacy in bipolar depression as an adjunct to atypical antipsychotics
