

New Drug Bulletin: Armodafinil (Nuvigil™ - Cephalon, Inc)

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Armodafinil (Nuvigil™) was approved by the FDA in June 2007 for use in improving wakefulness in adults with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS), narcolepsy, and shift work sleep disorder (SWSD). Armodafinil is considered an adjunct therapy to continuous positive airway pressure (CPAP) in patients with OSAHS and should only be added after maximal effort to treat with CPAP alone. It is the longer-lived R-enantiomer component of the R- and S-enantiomer mixture contained in modafinil (Provigil™).

Armodafinil's exact mechanism(s) for promoting wakefulness is unknown. At therapeutic concentrations, armodafinil does not bind to or inhibit receptors known to be involved in sleep/wake regulation (dopamine, serotonin, melatonin, GABA, benzodiazepine, etc.). While the alpha1-adrenergic receptor antagonist, prazosin, attenuates the wake-promoting effect of modafinil, other in vitro assays failed to show agonistic activity on alpha-adrenergic receptors. Both modafinil and armodafinil block dopamine reuptake by binding to the dopamine transporter and increase dopamine concentrations in certain regions of the brain. However, unlike amphetamine, dopamine receptor antagonists (ie, haloperidol) and dopamine synthesis inhibitors (alpha-methyl-p-tyrosine) do not affect modafinil's drug-induced wakefulness.

When administered orally in the fasting state, peak plasma concentrations of armodafinil are achieved at approximately 2 hours. While oral bioavailability is not altered significantly by food, time to peak is delayed by 2-4 hours, which can alter time to onset and duration of pharmacological action. Armodafinil exhibits linear, time-independent kinetics with a half-life of 15 hours, which may be prolonged in the elderly. Less than 10% of the drug is eliminated in the urine as unchanged drug. The two major metabolites of armodafinil result from amide hydrolysis (R-modafinil acid) and cytochrome P-450 (CYP) 3A4/5 mediated sulfone formation (modafinil sulfone). Renal failure patients (creatinine clearance \leq 20 mL/min) experience a 9-fold increase in modafinil acid exposure.

The ability of armodafinil to improve wakefulness has been established in patients with OSAHS, narcolepsy, or SWSD in double-blind, placebo-controlled trials. Efficacy was determined by measuring sleep latency using the Maintenance of Wakefulness Test or the Multiple Sleep Latency Test, and change in the patient's overall disease status. Armodafinil 150 mg and 250 mg were superior to placebo for both outcomes in all three sleep disorders.

The most common adverse effects of armodafinil were headache (17%), nausea (7%), dizziness (5%), insomnia (5%), dry mouth (4%), diarrhea (4%), and anxiety (4%). Multiple cases of serious rash requiring hospitalization and multi-organ hypersensitivity reactions have been reported with modafinil. Similar to other CNS stimulants (eg, methylphenidate), armodafinil produces psychoactive and euphoric effects, as well as alterations in mood, perception, thinking, and feelings.

Metabolism of armodafinil may be altered by potent inducers (eg, carbamazepine, phenobarbital, rifampin) or inhibitors (eg, ketoconazole, erythromycin) of CYP3A4/5. Armodafinil reversibly inhibits CYP2C19 and drugs that are substrates of this enzyme (eg, omeprazole, diazepam, phenytoin, and propranolol) may require dosage reductions. Armodafinil weakly induces CYP1A2 and CYP3A4/5. Pharmacokinetic analysis of caffeine, a CYP1A2 substrate, showed no metabolic change when armodafinil was administered concomitantly. However, serum concentrations of cyclosporine, ethinyl estradiol, midazolam, and triazolam (all CYP3A4/5 substrates) had reduced serum concentrations with concomitant use of modafinil. Dosage adjustments may be needed for these agents.

The approved dose of armodafinil for patients with OSAHS or narcolepsy is 150 mg or 250 mg once daily in the morning. For patients experiencing SWSD, the approved dose is 150 mg taken once 1 hour prior to the beginning of a work shift. Dosage reduction is recommended in patients with severe liver dysfunction although no specific recommendation is available. It is unknown whether dosage reduction is necessary in severe renal dysfunction; use caution in patients with creatinine clearance less than 20 mL/min.

Armodafinil is not yet available for purchase. The manufacturer has set 2010 as an estimated marketing date. Pricing information will not be available until then.

In summary, armodafinil is one of two enantiomers found in modafinil and exhibits similar pharmacologic action to that of the racemic mixture. Efficacy and safety have not been compared for the two agents in a head-to-head clinical trial.

References:

1. Nuvigil® (armodafinil) package insert. Frazer, PA: Cephalon, Inc.; June 2007.

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