MODAFINIL (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾CN809

Note: Controlled substance classification¾Note: Controlled substance in the U.S.
U.S.¾Schedule IV
Commonly used brand name(s):Provigil.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Central nervous system (CNS) stimulant.

Indications

Accepted

Narcolepsy (treatment)¾Modafinil is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy 1.

Continuing efficacy beyond 9 weeks has not been evaluated in placebo-controlled trials 1.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾273.36 2

Solubility¾Practically insoluble in water 1.

Mechanism of action/Effect:

The mechanism of action of modafinil is uncertain 1.

The pharmacological profile of modafinil differs from that of sympathomimetic amines 1.

The CNS-activating actions of modafinil, methylphenidate, and amphetamine were studied in cats given doses of each medication that produced equivalent wakefulness 1.

CNS-activation with methylphenidate and with amphetamine was widespread; however, CNS-activation with modafinil occurred in discrete brain regions 1 , suggesting a more specific wakefulness-promoting effect with modafinil 1.

Modafinil does not show alpha-adrenergic agonist activity in vitro or in animal studies; however, the wakefulness induced by modafinil can be attenuated by prazosin, an alpha 1-adrenergic antagonist 1.

Modafinil does not bind to norepinephrine, serotonin, dopamine, gamma-aminobutyric acid (GABA), adenosine, histamine H 3, melatonin, or benzodiazepine receptors, nor does it inhibit monoamine oxidase (MAO)-B or phosphodiesterases II through V 1.

Modafinil is a racemic compound 1.

Animal studies showed no pharmacological differences between the two enantiomers; human studies have not been conducted 1.

Other actions/effects:

Modafinil produces alterations in mood, perception, thinking, and feelings that are typical of other CNS stimulants and is reinforcing in primate self-administration tests of abuse potential 1.

Also, modafinil blocks dopamine reuptake in vitro1.

There is in vitro evidence that modafinil induces cytochrome P450 1A2 (CYP1A2), CYP2B6, and CYP3A4 to a small degree and in a concentration-dependent manner 1.

However, in vivo evidence of enzyme induction by modafinil exists only for CYP3A4 1.

Modafinil is a reversible inhibitor of CYP2C19 in humans and shows CYP2C9-inhibiting activity in in vitro studies 1.

Absorption:

Rapid 1.

Absolute bioavailability is unknown 1.

Food may delay absorption but does not affect bioavailability 1.

Distribution:

Vol D¾Large; about 0.9 L per kg of body weight 1.

Protein binding:

Moderate (60%) 1 ; primarily to albumin 1.

Biotransformation:

Hepatic 1.

Modafinil undergoes hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation, forming inactive metabolites 1.

Decreases in plasma trough concentrations of about 20% were seen after 9 weeks of modafinil administration at doses of 400 mg per day in human subjects, indicating some autoinduction of metabolism 1.

The isoenzyme CYP3A4 is involved in modafinil metabolism 1.

In nine patients with cirrhosis of the liver (stages B, B+, C, and C+ by the Child criteria), oral clearance of modafinil was reduced by about 60% and steady-state concentration was doubled compared with values from patients with normal hepatic function 1.

Half-life:

Elimination¾
Effectively, about 15 hours after multiple dosing 1 ; the elimination half-life of the levo-isomer is about three times that of the dextro-isomer 1.

Time to peak plasma concentration

2 to 4 hours 1.

Time to steady-state plasma concentration

2 to 4 days 1.

Peak serum concentration:

At steady-state with a dosage of 400 mg per day, peak serum concentration is 40 micromoles per L 1.

Elimination:

Primarily renal, < 10% as unchanged modafinil 1.

After administration of a radiolabeled dose to human subjects, 80% and 1% of the administered dose were recovered in the urine and the feces, respectively, over 11 days 1.

Severe renal failure (creatinine clearance £ 20 mL per minute) had no effect on the pharmacokinetics of modafinil after administration of a single 200-mg dose; however, exposure to an inactive metabolite (modafinil acid) was increased ninefold 1.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients who have had left ventricular hypertrophy or clinically significant, symptomatic mitral valve prolapse in association with the use of other CNS stimulant medications may experience similar effects with the use of modafinil 1.

Carcinogenicity/Tumorigenicity/Mutagenicity

Modafinil showed no evidence of being carcinogenic, tumorigenic, or mutagenic in rodent studies or in in vitro testing 1.

However, dosage in one rodent study was insufficient to fully evaluate the carcinogenicity of modafinil 1.

Pregnancy/Reproduction

Fertility¾No effect on fertility was seen when male and female rats were administered modafinil in doses of 4.8 times the maximum recommended human dose (MRHD) on a mg per square meter of body surface area (mg/m 2) basis prior to and throughout mating and gestation 1.

However, dosage may have been insufficient and sample size may have been too small to fully evaluate the effect of modafinil on fertility 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Modafinil may decrease the effectiveness of steroidal contraceptives during concurrent use and for 1 month after discontinuation of modafinil, making pregnancy more likely unless alternate forms of contraception are employed 1.

Offspring of rats given modafinil in oral doses of 200 mg per kg per day (10 times the MRHD on a mg/m 2 basis) during fetal organogenesis exhibited hydronephrosis and skeletal variations 1.

Also, the number of resorptions was increased 1.

Maternal toxicity was not seen 1.

No effect was seen in the offspring of rats given an oral dose of 100 mg per kg per day (5 times the MRHD on a mg/m 2 basis) 1.

No embryotoxicity was seen in the offspring of rabbits given modafinil in oral doses of 100 mg per kg per day (10 times the MRHD on a mg/m 2 basis) during fetal organogenesis 1.

However, animal studies were insufficient to ensure a comprehensive evaluation of modafinil's effects in pregnancy 1.

FDA Pregnancy Category C 1.

Labor and delivery¾The effect of modafinil on labor and delivery in humans has not been systematically evaluated 1.

Breast-feeding

It is not known whether modafinil or its metabolites are distributed into human breast milk 1.

Pediatrics

No information is available on the relationship of age to the effects of modafinil in pediatric patients. Safety and efficacy in children younger than 16 years of age have not been established 1.

Geriatrics

Appropriate studies on the relationship of age to the effects of modafinil have not been performed in the geriatric population. Small pharmacokinetic studies indicate that modafinil clearance may be reduced in geriatric patients by about 20% 1.

However, in 15 patients older than 65 years of age who participated in clinical trials, the incidence of adverse effects was similar to that in other age groups 1.

Pharmacogenetics

In patients who are deficient in CYP2D6 activity, plasma concentrations of CYP2D6 substrates that have an ancillary metabolic pathway involving CYP2C19 (e.g., clomipramine, desipramine) may be increased due to CYP2C19 inhibition by modafinil 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Alcohol

(the effects of alcohol use in patients receiving modafinil are unknown; avoiding drinking alcohol is recommended 1)

>> Antidepressants, tricyclic

(although a brief trial in healthy volunteers showed no effect on the pharmacokinetics of either medication, one patient receiving modafinil in a clinical trial had increased plasma concentrations of clomipramine and its active metabolite desmethylclomipramine with concurrent use; the clearance of medications that are metabolized primarily by cytochrome P450 2D6 [CYP2D6] but that have an ancillary metabolic pathway involving CYP2C19, such as some tricyclic antidepressants, including clomipramine and desipramine, may be reduced with concurrent modafinil use in patients who are poor metabolizers of CYP2D6 substrates 1)

>> CNS stimulation-producing medications, other (see Appendix II)

(additive CNS stimulation may occur, causing nervousness, irritability, insomnia, or possibly seizures or cardiac arrhythmias; close observation is recommended during concurrent use with modafinil 3)
(the absorption of modafinil may be delayed by approximately 1 hour when coadministered with methylphenidate, although the extent of absorption and the disposition of both agents are unchanged 1)

Inducers of CYP3A4, such as:
Carbamazepine or
Phenobarbital or
Rifampin

(plasma concentrations of modafinil may be decreased 1)

Inhibitors of CYP3A4, such as:
Itraconazole or
Ketoconazole

(plasma concentrations of modafinil may be increased 1)

>> Monoamine oxidase (MAO) inhibitors, including furazolidone, procarbazine, and selegiline

(studies have not been done; caution is advised during concomitant use of modafinil and an MAO inhibitor 1)

>> Substrates of CYP2C9, such as:
Phenytoin or
Warfarin

(in vitro, modafinil suppresses CYP2C9 activity in human hepatocytes in a concentration-related manner; increased concentrations of these medications may occur; patient monitoring is advised during concomitant use of modafinil and CYP2C9 substrates 1)

>> Substrates of CYP2C19, such as:
Diazepam or
Mephenytoin or
Propranolol

(modafinil reversibly inhibits the activity of CYP2C19; metabolism of medications that are largely metabolized by CYP2C19 may be reduced during concurrent modafinil treatment; dosages of these medications may need to be reduced 1)

>> Substrates of CYP3A4, other, such as:
Cyclosporine or
Steroidal contraceptives or
Theophylline

(modafinil modestly induces CYP3A4, which may lead to decreased plasma concentrations of concomitantly administered medications that are metabolized by this isoenzyme 1)
(cyclosporine concentrations were reduced by 50% in a transplant patient after 1 month of concomitant therapy with 200 mg per day of modafinil 1)
(nonsteroidal contraceptive methods should be used during and for 1 month after discontinuation of modafinil use 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Eosinophil counts

(abnormally high eosinophil counts occurred in about 2% of patients during premarketing studies of modafinil; however, elevations were clinically insignificant 1)

Gamma-glutamyltransferase (GGT) plasma concentrations

(increased GGT concentrations occurred in patients receiving modafinil in premarketing studies; elevations were clinically insignificant but were outside of the normal range in about 1% of patients; however, GGT concentrations appeared to increase over time in subjects receiving modafinil in trials that were of 9 weeks duration 1)
(no changes were seen in other measures of hepatic function 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Angina, unstable or

Myocardial infarction, recent history of

(experience with modafinil in patients with these conditions is limited; caution is recommended 1)

>> Clinically significant manifestations of mitral valve prolapse in association with use of other CNS stimulants, history of or

>> Left ventricular hypertrophy in association with use of other CNS stimulants, history of

(the risk of developing similar effects with modafinil use may be increased; use of modafinil is not recommended 1)

>> Hepatic function impairment (severe)

(clearance of modafinil is reduced; dosage reductions of 50% are recommended 1)

Hypertension

(use of modafinil in patients with hypertension has not been systematically evaluated; monitoring of blood pressure is recommended 1)

>> Psychosis, history of

(multiple doses of 600 mg per day of modafinil, in association with sleep deprivation, induced ideas of reference, paranoid delusions, and auditory hallucinations in one healthy male volunteer; modafinil should be used with caution in patients with a history of psychosis 1)

Renal function impairment (severe)

(although exposure to modafinil was unaffected, exposure to modafinil acid, a metabolite of modafinil, was increased ninefold in patients with creatinine clearance £ 20 mL per minute compared with patients with normal renal function; the safety of exposure to high concentrations of modafinil acid is unknown 1)

Sensitivity to modafinil 1

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Assessment of amount and frequency of modafinil use

(studies designed to measure abuse potential indicate that modafinil produces psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants; patients should be monitored at periodic intervals for signs of abuse or misuse of modafinil, such as dosage escalation or drug-seeking behavior 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Ataxia 1 clumsiness or unsteadiness); cardiac arrhythmia, hypotension, or hypertension 1 dizziness or fainting); CNS effects, including amnesia 1 problems with memory); confusion 1; emotional lability 1 rapidly changing moods); or mental depression 1; chills or fever 1; dyskinesia, oro-facial 1 uncontrolled movements of the face, mouth, or tongue); hyperglycemia 1 increased thirst); increased urination); pharyngitis 1 sore throat); shortness of breath 1; urinary retention 1 trouble in

urinating); vision changes; including abnormal vision 1; or amblyopia 1 blurred vision or other changes in vision)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Anxiety 1; headache 1¾may be dose-related; insomnia 1 (trouble in sleeping); nausea 1; nervousness 1
Incidence less frequent

Anorexia 1 (decrease in appetite); diarrhea 1; dizziness 1; dryness of mouth 1; dryness of skin 1; hypertonia 1 (muscle stiffness); increased thirst 1; rhinitis 1 (stuffy or runny nose); paresthesia 1 (tingling, burning, or prickling sensations in the skin); tremor 1 (trembling or shaking); vasodilation 1 (headache; flushing or redness of skin); vomiting 1
Those indicating possible abuse of modafinil and the need for medical attention

Psychosis 1 severe mental illness, similar to schizophrenia)¾after repeated, high-dose use 1

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

Note: Two patients who took modafinil doses of ³ 4000 mg displayed non-life-threatening adverse effects and were fully recovered by the next day 1.

In 151 instances of ingestion of ³ 1000 mg of modafinil, no unexpected effects or specific organ toxicities were seen 1.

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Acute

Agitation or excitation 1; increased blood pressure 1; increased heart rate 1; insomnia 1 trouble in sleeping)
Treatment of overdose

There is no specific antidote to modafinil 1.

Treatment is primarily symptomatic and supportive 1.

To decrease absorption¾Emesis or gastric lavage may be employed in the absence of contraindications to these measures 1.

Monitoring¾Cardiovascular function should be monitored 1.

Supportive care¾Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Note: There is no evidence that dialysis or manipulation of urinary pH will enhance the elimination of modafinil 1.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Modafinil (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to other CNS stimulants
Pharmacogenetics¾In patients with CYP2D6 deficiency, decreased clearance of CYP2D6 substrates that have ancillary metabolism via CYP2C19
Other medications, especially other CNS stimulation-producing medications; monoamine oxidase inhibitors; or substrates of CYP2C9, CYP2C19, or CYP3A4
Other medical problems, especially severe hepatic function impairment, history of left ventricular hypertrophy or clinically significant manifestations of mitral valve prolapse in association with use of other CNS stimulants, or history of psychosis
Proper use of this medication

>> Taking only as directed by physician because of habit-forming potential

>> Proper dosing
Missed dose: Taking if remembered before 12:00 noon; skipping if remembered later to avoid interference with nighttime sleep; returning to regular dosing schedule; not doubling doses
>> Proper storage
Precautions while using this medication

Regular visits to physician to check progress of therapy

>> Not increasing dose if medication becomes less effective; checking with physician

>> Using alternative to steroidal contraceptives during and for 1 month after discontinuing modafinil therapy because of possible decreased efficacy of steroidal contraceptives

>> Possible impairment of judgment, thinking, motor skills, or vision; not driving, using machines, or engaging in other potentially dangerous activities until effects of medication are known 1

>> Checking with physician if dependence on modafinil is suspected

>> Checking with physician before discontinuing after long-term or high-dose therapy; tapering of dosage may be required

Side/adverse effects

Signs of potential side effects, especially ataxia; cardiac arrhythmia, hypotension, or hypertension; CNS effects, including amnesia, confusion, emotional lability, mental depression; chills or fever; oro-facial dyskinesia; hyperglycemia; pharyngitis; shortness of breath; urinary retention; and vision changes, including abnormal vision or amblyopia

Possible psychosis with modafinil abuse

General Dosing Information

Female patients with child-bearing potential should be advised to use nonsteroidal contraception during and for 1 month following modafinil use 1.

Patients should be advised to notify physician immediately of any signs or symptoms of an allergic reaction, such as skin rash or hives, that develop during modafinil therapy 1.

Placebo-controlled trials to determine the efficacy of modafinil beyond 9 weeks have not been conducted 1.

Patients who receive long-term modafinil therapy should be evaluated periodically to determine the continuing effectiveness of the medication 1.

Prolonged or high-dose use of modafinil may result in psychological or physical dependence 3.

After long-term use, modafinil should be withdrawn gradually to avoid the possibility of withdrawal symptoms 3.

Oral Dosage Forms

MODAFINIL TABLETS

Usual adult dose

Narcolepsy¾
Oral, 200 mg once a day in the morning 1.

Note: Doses of 400 mg once a day are well tolerated, but have not shown greater efficacy than doses of 200 mg once a day 1.

Patients with severe hepatic function impairment should receive one half of the dosage recommended for patients with normal hepatic function 1.

Usual adult prescribing limits

400 mg per day 1.

Usual pediatric dose

Narcolepsy¾
Safety and efficacy in children up to 16 years of age have not been established 1.

Usual geriatric dose

Narcolepsy¾
See Usual adult dose .

Note: Reduced doses should be considered in geriatric patients because of possible reduced elimination of modafinil 1.

Strength(s) usually available

U.S.¾100 mg (Rx)[Provigil (lactose) (corn starch) (magnesium silicate) (croscarmellose sodium) (povidone) (magnesium stearate) (talc) 1]

200 mg (Rx)[Provigil (scored) (lactose) (corn starch) (magnesium silicate) (croscarmellose sodium) (povidone) (magnesium stearate) (talc) 1]

Packaging and storage:

Store between 20 and 25 °C (68 and 77 °F) 1 , unless otherwise specified by manufacturer.

Auxiliary labeling:

· May cause dizziness or blurred vision.
· May interfere with the effectiveness of birth control pills or implants.