	30 mg (beads, extended-release 15 mg with 15 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	40 mg (beads, extended-release 28 mg with 12 mg immediate-release)	**Metadate® CD** (C-II), UCB
	40 mg (beads, extended-release 20 mg with 20 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	50 mg (beads, extended-release 35 mg with 15 mg immediate-release)	**Metadate® CD** (C-II), UCB
	60 mg (beads, extended-release 42 mg with 18 mg immediate-release)	**Metadate® CD** (C-II), UCB
Solution	5 mg/5 mL	**Methylin® Oral Solution** (C-II), Sciele
	10 mg/5 mL	**Methylin® Oral Solution** (C-II), Sciele
Tablets	5 mg*	**Methylin®** (C-II), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II), Novartis
	10 mg*	**Methylin®** (C-II; scored), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II; scored), Novartis
	20 mg*	**Methylin®** (C-II; scored), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II; scored), Novartis
Tablets, chewable	2.5 mg	**Methylin®** (C-II), Sciele
	5 mg	**Methylin®** (C-II), Sciele
	10 mg	**Methylin®** (C-II; scored), Sciele
Tablets, extended-release	10 mg	**Metadate® ER** (C-II), UCB
		Methylin® ER (C-II), Mallinckrodt
	20 mg*	**Metadate® ER** (C-II), UCB
		Methylin® ER (C-II), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin-SR® (C-II), Novartis
Tablets, extended-release core	18 mg (core 14 mg with 4 mg immediate-release)	**Concerta®** (C-II), McNeil
	27 mg (core 21 mg with 6 mg immediate-release)	**Concerta®** (C-II), McNeil
	36 mg (core 28 mg with 8 mg immediate-release)	**Concerta®** (C-II), McNeil
	54 mg (core 42 mg with 12 mg immediate-release)	**Concerta®** (C-II), McNeil

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Modafinil

■ Modafinil is a CNS stimulant that is structurally and pharmacologically distinct from other currently available CNS stimulants.

Uses

Modafinil is used to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). Careful attention to the diagnosis and treatment of the underlying sleep disorder is essential whenever modafinil is used in patients with these conditions. (See Diagnosis of Sleep Disorders under Warnings/Precautions: General Precautions, in Cautions.)

■ **Narcolepsy** Modafinil is used in the symptomatic treatment of narcolepsy to improve wakefulness in adults with excessive daytime sleepiness (EDS). Narcolepsy is a CNS disorder characterized by somnolence, often accompanied by sudden attacks of weakness (cataplexy) while awake and disrupted nocturnal sleep, and occasionally by hypnagogic hallucinations and/or sleep paralysis before falling asleep or awakening. The disorder involves dysregulation of wakefulness and sleep.

Efficacy of modafinil has been established in the US in 2 double-blind, multicenter, placebo-controlled clinical trials of 9 weeks' duration. In these and other clinical studies, modafinil 200 or 400 mg daily increased daytime wakefulness and alertness and decreased the number of daytime sleep episodes as determined by several objective (e.g., the Multiple Sleep Latency Test [MSLT], the Maintenance of Wakefulness Test [MWT], the Steer Clear Performance Test [SCPT]) and subjective (e.g., the Epworth Sleepiness Scale [ESS]) measures of sleepiness. Patients showed an enhanced ability to remain awake with both dosages relative to placebo at 3, 6, and 9 weeks, and at study end point (last post-basline assessment while the patient was in the study) and also greater global improvement in overall disease status (measured by the Clinical Global Impression of Change [CGI-C]). However, despite the clinical improvement, mean objective and subjective measures of sleepiness did not completely normalize with modafinil therapy, with a degree of clinically important physiologic sleepiness persisting despite therapy. The percentage of patients exhibiting any degree of improvement in overall disease status on the CGI-C in the two 9-week studies establishing efficacy in the US was 60–72, 58–64, or 37–38% for the 400-mg regimen, 200-mg regimen, or placebo, respectively. The efficacy of the 2 modafinil dosage regimens was not shown to differ significantly in these studies.

Although the long-term efficacy of modafinil has not been established systematically beyond 9 weeks, improvements in overall disease status on the CGI-C and in subjective measures of sleepiness on the ESS were maintained in a 40-week open-label extension of one of the trials. In this open-label extension, the percentage of patients exhibiting improvement on the CGI-C ranged from 84% after 2 weeks of extension therapy to 91% after 40 weeks. The drug also was well tolerated for up to 40 weeks of therapy, with 11% of patients discontinuing modafinil because of adverse effects and 14% because of inadequate therapeutic effect. Although most patients enrolled in the 2 clinical trials establishing efficacy in the US had histories of cataplexy, those requiring anticataplectic therapy generally were excluded from enrollment. Therefore, current evidence of efficacy for modafinil is limited principally to effects on excessive daytime sleepiness. In one study in a limited number of patients, cataplexy was not affected by modafinil therapy.

Modafinil did not affect the initiation, maintenance, quality, or quantity of nighttime sleep and did not affect the ability to voluntarily sleep (nap) during the daytime. Like other CNS stimulants modafinil can alter mood, perception, thinking, and feelings and can cause psychoactive and euphoric effects. However, in clinical trials, there was no clinically important association between modafanil and the incidence of agitation in patients. In animals, modafinil is reinforcing; however, the somatic effects of the drug were comparable to those of caffeine and differed from those of amphetamine. Although there currently does not appear to be evidence of problems with modafinil abuse, caution is recommended in patients with a history of drug or stimulant abuse. Withdrawal of modafinil has not been associated with any manifestations of dependency.

■ **Obstructive Sleep Apnea/Hypopnea Syndrome** Modafinil is used in the symptomatic treatment of OSAHS to improve wakefulness in adults with excessive sleepiness. The drug should be used as an adjunct to standard treatment(s) for the underlying obstruction (e.g., nasal continuous positive airway pressure [CPAP]). If CPAP is considered the treatment of choice for a patient with OSAHS, every effort should be made to optimize CPAP treatment for an adequate period of time prior to initiating modafinil therapy. When modafinil is used adjunctively with CPAP treatment, the encouragement of and periodic assessment of CPAP compliance is necessary.

Efficacy of modafinil in reducing excessive daytime sleepiness in patients with OSAHS was established principally in 2 multicenter, placebo-controlled clinical trials. In both of these studies, enrolled patients met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS, which also are consistent with DSM-IV criteria. These criteria include either excessive sleepiness or insomnia with frequent episodes of impaired breathing during sleep and associated features (e.g., loud snoring, morning headaches, dry mouth upon awakening) or polysomnography demonstrating more than 5 obstructive apneas (each greater than 10 seconds in duration) per hour of sleep and one or more of the following: frequent arousals from sleep associated with the apneas; bradytachycardia; and arterial oxygen desaturation in association with the apneas. In addition, all patients enrolled in these studies had excessive daytime sleepiness as demonstrated by a score of 10 or higher on the Epworth Sleepiness Scale (ESS) despite treatment with CPAP. Evidence that CPAP was effective in reducing the episodes of apnea/hypopnea also was required along with documentation of CPAP use.

In the first multicenter, placebo-controlled study, which was of 12 weeks' duration, patients were randomized to receive modafinil 200 mg daily, modafinil 400 mg daily, or placebo. The majority of patients (80%) in this study were fully compliant with CPAP (defined as CPAP use for more than 4 hours per night on more than 70% of nights); the remainder of patients were partially CPAP compliant (defined as CPAP use for less than 4 hours per night on more than 30% of nights). Efficacy of modafinil was principally evaluated by measurement of sleep latency as assessed by the Maintenance of Wakefulness Test (MWT) and change in the patient's overall disease status as measured by the Clinical Global Impression of Change (CGI-C) at week 12 or at the final visit. The modafinil-treated patients demonstrated a significant improvement in their ability to remain awake as measured by the MWT at the study end point and in their clinical condition as measured by the CGI-C compared with those receiving placebo. The 200- and 400-mg daily doses produced similar clinical efficacy in this study.

In the second multicenter, placebo-controlled study, which was of 4 weeks' duration, patients were randomized to receive either modafinil 400 mg daily or placebo. Documentation of regular CPAP use (for at least 4 hours each night on 70% of nights) was required for all patients. Efficacy in reducing daytime sleepiness was principally assessed by the change from baseline on the ESS at week 4 or the final visit. Patients who received modafinil demonstrated a significant reduction in their ESS score from baseline (mean scores reduced by 4.6) compared with patients receiving placebo (mean scores reduced by 2). In addition, the percentage of patients with normalized daytime sleepiness (ESS score less than 10) was significantly higher for the modafinil group than for those receiving placebo (51 and 27%, respectively). Nighttime sleep as measured by polysomnography was not affected by modafinil administration in these 2 studies.

The manufacturer states that the long-term efficacy (e.g., longer than 12 weeks) of modafinil in OSAHS has not been systematically evaluated in placebo-controlled studies to date. However, a 12-month, noncomparative extension phase of the 12-week, placebo-controlled trial in which patients received modafinil 200, 300, or 400 mg daily demonstrated substantial reductions in ESS scores compared with baseline following 3, 6, 9, and 12 months of therapy. When modafinil is used for extended periods, the need for continued therapy should be reassessed periodically.

■ **Shift Work Sleep Disorder** Modafinil is used in the symptomatic treatment of SWSD to improve wakefulness in adults with excessive sleepiness. Criteria of the International Classification of Sleep Disorders (ICSD-10) for chronic SWSD (which are consistent with DSM-IV criteria for circadian rhythm sleep disorder; shift work type) require a primary complaint of excessive sleepiness or insomnia that is temporally associated with a work period (usually night work) that occurs during the habitual sleep phase or loss of a normal sleep-wake pattern (i.e., disturbed chronobiological rhythmicity) as demonstrated on polysomnography and the Multiple Sleep Latency Test (MSLT) and that the manifestations are not accounted for by another medical or mental disorder and do not meet criteria for any other sleep disorder that produces insomnia or excessive sleepiness (e.g., time zone change [jet lag] syndrome).

Efficacy of modafinil for excessive sleepiness associated with SWSD was demonstrated in a 12-week, placebo-controlled trial in patients with chronic SWSD who were randomized to receive either modafinil 200 mg daily or placebo. Not all patients engaged in shift work who complain of sleepiness meet the criteria for the diagnosis of SWSD; only patients who were symptomatic for at least 3 months were enrolled in the trial. Patients enrolled in this trial also were required to work a minimum of 5 night shifts per month, have excessive sleepiness at the time of their night shifts (MSLT score of less than 6 minutes), and have daytime insomnia documented by a daytime polysomnogram. Patients who were treated with modafinil demonstrated a significant prolongation of the time to sleep onset compared with those receiving placebo as assessed by the nighttime MSLT; significant improvement in the Clinical Global Impression of Change (CGI-C) also was demonstrated in the modafinil group. Despite these improvements, patients receiving the drug in this study continued to have residual sleepiness and impaired performance at night. (See Somnolence under Warnings/Precautions: Warnings, in Cautions.) Daytime sleep measured by polysomnography was not affected by modafinil administration.

The long-term efficacy (e.g., longer than 12 weeks) of modafinil in SWSD has not been systematically evaluated in placebo-controlled studies to date. When modafinil is used for extended periods, the need for continued therapy should be reassessed periodically.

Dosage and Administration

■ **Administration** In patients with narcolepsy and obstructive sleep apnea/hypopnea syndrome (OSAHS), modafinil usually is administered orally once daily in the morning. The drug also has been administered in 2 divided doses daily for narcolepsy, in the morning and at noon†. In patients with shift work sleep disorder (SWSD), modafinil should be taken approximately 1 hour prior to the start of their work shift.

Although administration with food can delay GI absorption of modafinil by approximately 30 minutes, food does not affect the extent of absorption and the drug can be administered without regard to meals.

■ **Dosage** The usual recommended dosage of modafinil to improve wakefulness in adults and adolescents 16 years of age and older with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, or shift work sleep disorder is 200 mg daily. Although a dosage of 400 mg daily has been well tolerated, there is no consistent evidence indicating that this dosage provides additional clinical benefit beyond that provided by the 200-mg daily dosage.

■ **Special Populations** Hepatic impairment may result in decreased clearance of modafinil. The clearance of modafinil was decreased by 60% and the steady-state concentrations were doubled in patients with severe hepatic impairment and cirrhosis (Child stage B, B+, C, or C+); clinically, all had ascites and almost all were icteric. Therefore, modafinil dosage should be reduced to 100 mg daily (i.e., one-half the usual recommended dosage) in patients with severe hepatic impairment.

Current information is inadequate to make specific modafinil dosage recommendations for patients with severe renal impairment. In such patients (mean creatinine clearance of 16.6 mL/minute), a single 200-mg dose did not result in increased exposure to unchanged modafinil but did result in much higher exposure to modafinil acid, an inactive metabolite. While this metabolite does not appear to contribute to the CNS stimulant effects of modafinil, there is little information on the safety of increased concentrations of modafinil acid.

Because elimination of modafinil and its metabolites may be reduced with age in geriatric patients, consideration should be given to using lower than the usual recommended dosage in this age group. In addition, that possibility that geriatric patients may have decreased renal and/or hepatic function should be considered.

Cautions

■ **Contraindications** Known hypersensitivity to modafinil, armodafinil (the *R*-enantiomer of modafinil), or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Serious Dermatologic Reactions.** Serious rash (including Stevens-Johnson syndrome) and hypersensitivity reactions requiring hospitalization and drug discontinuance have been reported in adult and pediatric patients receiving modafinil. The manufacturer states that modafinil is *not* approved for use in pediatric patients for any indication. (See Cautions: Pediatric Use.)

Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have been reported during pediatric clinical trials and during postmarketing experience with modafinil in adults and pediatric patients worldwide; serious rashes were not reported during clinical trials in adults. No known risk factors predict the occurrence or the severity of rash. The majority of cases occurred within 1–5 weeks after initiation of therapy; however, isolated cases also have been reported after prolonged treatment (e.g., 3 months). Accordingly, duration of therapy cannot be used to predict the potential risk associated with the first appearance of a rash. Although benign rashes also occur with modafinil, it is not possible to predict which rashes will prove to be serious; therefore, the drug should ordinarily be discontinued at the first sign of rash unless the rash is clearly not drug related. (See Advice to Patients.) Treatment discontinuance may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

Angioedema and Anaphylactoid Reactions. Angioedema has been reported during postmarketing experience with modafinil. One serious case of angioedema and 1 case of hypersensitivity (with rash, dysphagia, and bronchospasm) were reported among 1,595 patients treated with armodafinil (the *R*-enantiomer of modafinil). No such cases were observed during clinical trials with modafinil. The manufacturer states that patients should be advised to discontinue therapy and immediately report to their clinician any signs or symptoms suggestive of angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty swallowing or breathing; hoarseness). (See Advice to Patients.)

Multiorgan Hypersensitivity Reactions. Multiorgan hypersensitivity reactions, including at least one fatality, have been reported during postmarketing experience with modafinil. These reactions occurred in close temporal association (median time to detection: 13 days; range: 4–33 days) to initiation of modafinil therapy. Although reported in a limited number of patients, multiorgan hypersensitivity reactions may result in hospitalization or be life-threatening. There are no known factors to predict the risk of occurrence or severity of such reactions to modafinil. Signs and symptoms in the cases reported to date were diverse; however, patients typically presented with fever and rash associated with other organ system involvement. Other reported manifestations included myocarditis, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. However, the manufacturer states that multiorgan hypersensitivity reactions are variable in their clinical presentation and that other organ system signs and symptoms may occur. If a multiorgan hypersensitivity reaction is suspected, modafinil should be discontinued. The manufacturer states that although there are no case reports indicating cross-sensitivity with other drugs that produce this syndrome, experience with other drugs associated with multiorgan hypersensitivity suggests that cross-sensitivity is a possibility.

Somnolence. Modafinil is used in patients who have abnormal levels of sleepiness. In such patients, the drug has been shown to improve, but *not* to eliminate, this abnormal tendency to fall asleep. (See Advice to Patients.) All patients with excessive sleepiness, including those receiving modafinil, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Clinicians also should be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

Psychiatric Effects. Adverse psychiatric effects have been reported in patients receiving modafinil. Postmarketing adverse psychiatric effects associated with the drug include mania, delusions, hallucinations, and suicidal ideation and have resulted in hospitalization in some cases. In many, but not all, cases, patients had a prior psychiatric history. However, one healthy male developed ideas of reference, paranoid delusions, and auditory hallucinations in association with modafinil and sleep deprivation; there was no evidence of psychosis 36 hours after drug discontinuance. In controlled clinical trials in adults, psychiatric symptoms leading to drug discontinuance in at least 0.3% of patients

and reported more frequently in modafinil-treated patients than placebo recipients included anxiety, nervousness, insomnia, confusion, agitation, and depression. The manufacturer states that modafinil should be used with caution in patients with a history of psychosis, depression, or mania. The manufacturer also states that the possible emergence or exacerbation of psychiatric symptoms in patients treated with the drug should be considered. If adverse psychiatric effects develop in modafinil-treated patients, discontinuance of the drug should be considered. (See Advice to Patients.)

General Precautions **Diagnosis of Sleep Disorders.** The manufacturer states that modafinil should be used only in patients who have had a complete evaluation of their excessive sleepiness and in whom a diagnosis of narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), or shift work sleep disorder (SWSD) has been made in accordance with the International Classification of Sleep Disorders (ICSD) or DSM-IV criteria. Such an evaluation usually consists of a complete history and physical examination, which may be supplemented with testing in a laboratory setting (e.g., polysomnography). Clinicians should be aware that some patients may have more than one sleep disorder contributing to their daytime sleepiness (e.g., OSAHS and SWSD concurrently in the same patient).

Cognitive/Mental Impairment. Although modafinil has not been shown to cause functional impairment, the possibility that the drug, like any other drug affecting the CNS, may alter judgment, thinking, or motor skills should be considered. Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that modafinil does not adversely affect their ability to engage in such activities.

Cardiovascular Effects. The manufacturer recommends that modafinil *not* be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia, or other clinically important manifestation of mitral valve prolapse associated with CNS stimulant use. In clinical studies with modafinil, a few patients have exhibited manifestations such as chest pain, palpitations, dyspnea, and transient ischemic T-wave changes in association with mitral valve prolapse or left ventricular hypertrophy. If new onset of any of these cardiovascular symptoms occurs during modafinil therapy, the manufacturer states that a cardiac evaluation should be considered.

Modafinil should be used with caution in patients with a recent history of myocardial infarction or unstable angina since the drug has not been evaluated or used to any appreciable extent in such patients.

Periodic monitoring of blood pressure may be appropriate during modafinil therapy. No clinically important changes in mean systolic or diastolic blood pressure were observed in patients receiving modafinil in short-term (i.e., less than 3 months) clinical trials. However, retrospective analysis indicated that new or increased use of hypotensive agents was required among a greater proportion of patients receiving modafinil (2.4%) than among those receiving placebo (0.7%) in these studies. When studies of patients with OSAHS were considered separately, the difference was increased, with 3.4 or 1.1% of patients receiving modafinil or placebo, respectively, requiring new or altered therapy with hypotensive agents.

Abuse and Misuse Potential. Patients should be followed closely during modafinil use for possible signs of misuse or abuse (e.g., incrementation of doses, drug-seeking behavior), especially those with a history of drug or stimulant abuse (e.g., amphetamine, cocaine, methylphenidate). Although modafinil can produce psychoactive and euphoric effects and feelings consistent with other CNS stimulants (e.g., methylphenidate), current evidence indicates that the risk of abuse or misuse of modafinil is lower than that associated with such CNS stimulants that are subject to control as schedule II drugs (e.g., amphetamine, methylphenidate). Therefore, modafinil is only subject to control as a schedule IV drug.

Contraceptive Precautions. Because efficacy of hormonal contraceptives may be reduced during and for 1 month after modafinil therapy, patients using such contraceptives should be advised to use alternative or concomitant nonhormonal contraceptive methods during these periods. (See Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.) Women of childbearing potential should be advised of possible hormonal contraceptive failure (i.e., increased risk of pregnancy) during and for 1 month after modafinil use. (See Drug Interactions.)

Lactation. It is not known whether modafinil or its metabolites are distributed into milk. Caution should be exercised when modafinil is used in nursing women.

Pediatric Use. Modafinil is not approved for use in pediatric patients for *any* indication. The manufacturer states that safety and efficacy of the drug have not been established in children younger than 16 years of age.

In a controlled study of 6 weeks' duration, 165 pediatric patients (5–17 years of age) with narcolepsy were treated with modafinil or placebo. The results did not demonstate a statistically significant difference favoring modafinil over placebo in prolonging sleep latency (as measured by the Multiple Sleep Latency Test [MSLT]) or in perceptions of sleepiness (as determined by the Clinical Global Impression of Change [CGI-C] score).

Serious rashes, including erythema multiforme major and Stevens-Johnson syndrome, have been associated with modafinil use in pediatric patients. In clinical trials in pediatric patients younger than 17 years of age, the incidence of rash resulting in drug discontinuance was 0.8% (13 cases out of 1,585); these cases included 1 case of possible Stevens-Johnson syndrome and 1 case of apparent multiorgan hypersensitivity reaction. Several cases were associated with fever and other abnormalities (e.g., vomiting, leukopenia). The median time to rash that resulted in drug discontinuance was 13 days. No such cases were observed among placebo recipients. (See Warnings/Precautions: Warnings, under Cautions.)

In controlled and open-label clinical trials, adverse CNS effects reported in modafinil-treated pediatric patients included Tourette's syndrome, insomnia, hostility, increased cataplexy, increased hypnagogic hallucinations, and suicidal ideation. Transient leukopenia, which resolved without medical intervention, also occurred. In the controlled clinical trial, dysmenorrhea occurred in 3 out of 38 girls 12 years of age or younger treated with modafinil compared with 0 out of 10 girls receiving placebo.

Geriatric Use. Safety and efficacy of modafinil have not been established in geriatric patients 65 years of age and older, although experience in a limited number of patients in this age group showed an adverse effect profile similar to that in younger patients. Reduced dosage should be considered. (See Dosage and Administration: Special Populations.)

Renal Impairment. Caution is advised if modafinil is used in patients with severe renal impairment. (See Dosage and Administration: Special Populations.)

Hepatic Impairment. Reduced dosage of modafinil is recommended if the drug is used in patients with severe hepatic impairment, with or without cirrhosis, because clearance of the drug is reduced in such patients. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Common adverse effects occurring in 5% or more of patients receiving modafinil and more frequently than with placebo include headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. In placebo-controlled, phase III clinical trials, although adverse effects generally were mild to moderate and well tolerated, 8% of patients discontinued modafinil because of adverse effects, principally because of headache, nausea, anxiety, dizziness, insomnia, chest pain, and nervousness. In a Canadian trial, a 35-year old obese narcoleptic male with a history of syncopal episodes experienced a 9-second episode of asystole after 27 days of modafinil 300 mg daily in divided doses.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Potent inducers (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors (e.g., ketoconazole, itraconazole) of the cytochrome P-450 (CYP) isoenzyme 3A4 could alter the elimination of modafinil because of the partial involvement of this isoenzyme in modafinil's metabolism.

The possibility that modafinil might also induce its own metabolism (e.g., with chronic administration of relatively high [400 mg daily] dosages) also should be considered.

Modafinil has been shown to slightly induce CYP isoenzymes 1A2, 2B6, and 3A4 in a concentration-dependent manner. Although induction results from in vitro studies are not necessarily predictive of response in vivo, caution should be exercised if modafinil is administered in patients receiving drugs that are metabolized by these isoenzymes. The possibility of an interaction with the clearance (increased) of cyclosporine, hormonal contraceptives, and, to a lesser degree, theophylline should be considered.

In vitro studies have shown that modafinil has little or no capacity to inhibit major CYP isoenzymes except 2C19, which is reversibly inhibited at pharmacologically relevant concentrations. Therefore, the possibility of prolonged elimination of drugs that are largely eliminated via the CYP2C19 isoenzyme (e.g., diazepam, propranolol, phenytoin, *S*-mephenytoin) should be considered when modafinil is used concomitantly.

Clozapine Elevated serum clozapine concentrations and resulting clozapine toxicity occurred in a patient receiving modafinil for clozapine-associated sedation. Although the precise mechanism is unclear, this interaction was thought to be caused by decreased clearance of clozapine (a CYP2C19 substrate). Pending further evaluation of this potential interaction, caution should be used whenever modafinil and clozapine are given concurrently; close monitoring of serum clozapine concentrations also is recommended.

Cyclosporine In at least one patient, blood cyclosporine concentrations were decreased by 50% after 1 month of therapy with modafinil 200 mg daily. This interaction was thought to be caused by increased metabolism of cyclosporine (a CYP3A4 substrate) since no other factor expected to affect the disposition of the drug had changed. Monitoring of cyclosporine concentrations and appropriate dosage adjustment should be considered when these drugs are used concomitantly.

Hormonal Contraceptives In female volunteers receiving long-term ethinyl estradiol therapy, administration of modafinil 200 mg daily for 7 days followed by 400 mg daily for an additional 21 days resulted in mean decreases of 11 and 18% in the peak concentrations and area under the plasma concentration-time curve (AUC), respectively, of ethinyl estradiol. No change in the elimination rate of ethinyl estradiol was observed in this study. The possibility of hormonal contraceptive failure secondary to induction of metabolism of the hormones by modafinil should be considered, and women of childbearing potential should be advised to use an alternative or concomitant nonhormonal contraceptive during and for 1 month after modafinil therapy.

Phenytoin Because phenytoin is a substrate for the CYP2C9 isoenzyme, patients receiving the anticonvulsant concomitantly with modafinil should be monitored for signs of phenytoin toxicity.

Triazolam Administration of a single dose of triazolam (0.125 mg) in female volunteers receiving modafinil 200 mg daily for 7 days followed by 400 mg daily for an additional 21 days resulted in mean decreases of 42 and 59% in the peak plasma concentrations and AUC, respectively, of triazolam and a decrease in its elimination half-life of approximately 1 hour. Dosage adjustment of triazolam may be necessary when these drugs are used concomitantly.

Tricyclic Antidepressants CYP2C19 provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine, desipramine) that are principally metabolized via the CYP2D6 isoenzyme. In patients treated with such tricyclics who are CYP2D6 deficient (i.e., those who are poor metabolizers of debrisoquin; 7–10% of the Caucasian population, similar or lower percentages of other populations), the dependency on CYP2C19 metabolism may be increased and concomitant modafinil therapy could increase serum concentrations of drugs metabolized by this isoenzyme. Therefore, clinicians should be aware that a reduction of tricyclic antidepressant dosage may be necessary during modafinil therapy.

Although concomitant administration of a single 50-mg clomipramine dose on the first of 3 days of modafinil 200 mg daily in healthy individuals did not appear to alter the pharmacokinetics of either drug, at least one patient with narcolepsy developed a dose-dependent and reversible increase in plasma concentrations of clomipramine and its active desmethyl metabolite following initiation of modafinil therapy. The patient was a phenotypic CYP2D6 poor metabolizer. Because clomipramine may be considered for concomitant therapy to manage manifestations of cataplexy in narcoleptic patients, the possibility of this metabolic interaction should be considered.

Warfarin In vitro evidence suggested that modafinil can suppress the expression of CYP2C9 activity in a concentration-dependent manner. In a subsequent clinical study performed in healthy individuals, chronic modafinil administration did not substantially alter the single-dose pharmacokinetics of warfarin when compared with placebo. However, pending further evaluation of this potential interaction, the manufacturer recommends more frequent monitoring of prothrombin time and/or international normalized ratio (INR) whenever modafinil and warfarin are given concurrently.

■ **Amphetamines** In a single-dose study in healthy individuals, concomitant administration of a single 200-mg modafinil dose and a 10-mg dextroamphetamine dose did not produce a clinically important pharmacokinetic interaction with either drug. However, the absorption of modafinil was delayed by approximately 1 hour when these drugs were given concurrently in this study. In a subsequent study in healthy individuals, the steady-state pharmacokinetics of modafinil (200 mg daily for 7 days followed by 400 mg daily for 21 days) were not significantly affected by chronic administration of a 20-mg dose of dextroamphetamine given in the afternoon; the adverse event profile of these drugs administered concurrently was similar to that of modafinil alone.

■ **Methylphenidate** In a single-dose study in healthy individuals, concomitant administration of a single 200-mg dose of modafinil and 40-mg dose of methylphenidate did not significantly alter the pharmacokinetics of either drug. GI absorption of modafinil was delayed by approximately 1 hour; however, the extent of absorption was not affected. In a multiple-dose study in healthy individuals, concomitant administration of methylphenidate 20 mg daily and modafinil (200 mg daily for 7 days followed by 400 mg daily for 21 days) did not significantly alter the pharmacokinetics of modafinil. Therefore, a clinically important pharmacokinetic interaction between these drugs seems unlikely.

■ **Monoamine Oxidase Inhibitors** Because drug interaction studies have not been performed with monoamine oxidase (MAO) inhibitors, caution is advised during concomitant modafinil therapy.

Description

Modafinil, a benzhydryl sulfinylacetamide derivative, is a CNS stimulant that is structurally and pharmacologically distinct from other currently available CNS stimulants (e.g., amphetamines, caffeine, cocaine, methylphenidate). Modafinil promotes vigilance and wakefulness and decreases the number of daytime sleep episodes associated with narcolepsy and obstructive sleep apnea/hypopnea syndrome and reduces the excessive sleepiness associated with shift work sleep disorder. Although the wakefulness-promoting effects of modafinil are comparable to those exhibited by amphetamines or methylphenidate, modafinil alters metabolic activity and increases neuronal activity in specific areas of the brain that control sleep/wakefulness and the biologic clock while amphetamines increase neuronal activity more widely throughout the brain, suggesting distinct mechanisms for modafinil and relatively high selectivity.

The exact mechanism(s) of action of modafinil is unknown, but animal studies have shown that the drug inhibits the release of γ-aminobutyric acid (GABA) and increases the release of glutamate from the cerebral cortex, hippocampus, nucleus acumbens, medial preoptic area, and posterior hypothalamus. GABA is an inhibitory neurotransmitter that acts as a CNS depressant while glutamate is an excitatory neurotransmitter. Modafinil does not appear to be an indirect- or direct-acting dopamine-receptor agonist nor to act as a sympathomimetic agent. Haloperidol, a dopamine-receptor antagonist, inhibits the wake-promoting activity of amphetamine but not the wake-promoting activity of modafinil.

The manufacturer states that modafinil does not appear to be a direct or indirect α_1-adrenergic agonist, as evidenced by lack of activity in assay systems known to be responsive to such agonists. However, the drug's stimulant effects (e.g., on wakefulness, locomotion, and the EEG) are antagonized by α_1-antagonists (e.g., prazosin, phenoxybenzamine), thus indicating that an intact central α_1-adrenergic system is necessary for modafanil's CNS activity. In addition, it has been suggested that the drug itself may stimulate central α_1-adrenergic activity (e.g., at the postsynaptic level). Modafinil does not appear to exhibit clinically important peripheral adrenergic activity, even at high doses. In animals, modafinil increased locomotor activity but did not increase dopamine activity; however, in vitro studies showed that modafinil binds to dopamine reuptake sites and increases extracellular dopamine concentrations.

At usual pharmacologic concentrations, modafinil does not bind to certain norepinephrine, serotonin, dopamine, GABA, adenosine, histamine H_3, melatonin, or benzodiazepine receptors that regulate sleep and wakefulness. The drug also does not inhibit type B monoamine oxidase (MAO-B) or phosphodiesterase and does not alter plasma melatonin or cortisol hormone profiles, which may limit short-term adverse effects.

Although the effects, if any, of modafinil on blood pressure during long-term therapy remain to be elucidated, 300 mg (200 mg before breakfast and 100 mg before lunch) given on a single day in normotensive patients with obstructive sleep apnea did not appear to substantially affect blood pressure, although increases were noted relative to placebo under mental and physical stress tests.

Like other CNS stimulants, modafinil is reinforcing in animals and produces psychoactive (e.g., alterations in mood and thinking), euphoric, and subjective effects typical of classic psychomotor stimulants (e.g., amphetamines) in humans. Despite this pharmacologic similarity to such stimulants, the chemical properties of modafinil (e.g., not water soluble, decomposes in heat) may limit its abuse potential. In addition, there are substantial relative potency differences between modafinil and CNS stimulants that are subject to control under the Federal Controlled Substances Act as schedule II drugs. These differences reduce the likelihood that modafinil could be abused by the parenteral, intranasal, or inhalation route, as are cocaine, methylphenidate, and amphetamine; therefore, modafinil is subject to control as a schedule IV rather than II drug.

With chronic dosing, modafinil induces its own metabolism via induction of the cytochrome P-450 (CYP) isoenzyme 3A4. Clearance of modafinil may be altered by other inducers (e.g., phenobarbital, carbamazepine, rifampin) or inhibitors (e.g., ketoconazole, itraconazole) of this isoenzyme. (See Drug Interactions.) Inhibition of the CYP isoenzymes 2C9 and 2C19 by modafinil results in several potential drug interactions (e.g., warfarin, phenytoin, diazepam, propranolol, clomipramine, desipramine). (See Drug Interactions.)

Advice to Patients

Importance of reading patient information leaflet provided by the manufacturer.

Importance of advising clinician of existing or contemplated therapy, including prescription and OTC drugs or herbal supplements. Avoidance of alcohol while taking modafinil is prudent since combined use has not been studied.

Risk of pregnancy in women taking hormonal contraceptives. (See Contraceptive Precautions under Warnings/Precautions: General Precautions, in Cautions.) Discuss alternative contraceptive measures; importance of informing clinician if patient is or plans to become pregnant or plans to breast-feed.

Risk of serious rash or serious allergic reaction. Importance of immediately discontinuing modafinil and seeking immediate medical attention if rash or other signs of allergic reaction occur (e.g., hives, mouth sores, blisters, peeling skin, difficulty swallowing or breathing, or a related allergic phenomenon).

Risk of mental (psychiatric) symptoms or heart problems. Importance of discontinuing modafinil and informing clinician if chest pain, depression, anxiety, or signs of psychosis or mania occur.

Advise that modafinil may affect judgment, thinking, or motor skills. Importance of using caution when operating machinery or driving a motor vehicle until effects of the drug are known.

Advise that modafinil may improve but not eliminate the abnormal tendency to fall asleep. Advise against altering previous behavior with regard to potentially dangerous activities (e.g., driving, operating machinery, other activities requiring appropriate levels of wakefulness) until and unless modafinil has been shown to produce levels of wakefulness that permit such activities. Advise that modafinil is *not* a replacement for sleep.

Importance of continuing previously prescribed therapy (e.g., patients with obstructive sleep apnea/hypopnea should continue receiving continuous positive airway pressure).

Importance of informing patient of other important precautionary information. (See Cautions.)

Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on the usual cautions, precautions, and contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Modafinil is subject to control under the Federal Controlled Substances Act of 1970 as a schedule IV (C-IV) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Modafinil

Oral

Tablets	100 mg	**Provigil®** (C-IV), Cephalon
	200 mg	**Provigil®** (C-IV scored), Cephalon

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Phentermine
Phenyl-tertiary-butylamine

Phentermine Hydrochloride

■ Phentermine is an amphetamine congener that is used as an anorexigenic agent.

Uses

Phentermine is used as an adjunct to exercise, behavioral modification, and caloric restriction in the short-term management (a few weeks) of exogenous obesity. Phentermine therapy is indicated for patients with no underlying risk factor but a pretreatment body mass index (BMI) of 30 kg/m^2 or greater and those with an underlying risk factor (e.g., hypertension, diabetes mellitus, hyperlipidemia) and a pretreatment BMI of 27 kg/m^2 or greater. Phentermine is indicated *only* for monotherapy in the management of exogenous obesity; the drug should *not* be used in combination with selective serotonin-reuptake inhibitor antidepressants (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or monoamine oxidase (MAO) inhibitors. To help bring about and maintain loss of weight, the patient must be taught to curtail overeating and to consume a suitable diet. Phentermine also has been used for longer periods† combined with fenfluramine† (no longer commercially available in the US) in selected patients for the management of this condition. Such combined† long-term therapy had been used widely in the 1990s in the management of exogenous obesity. However, because of accumulated data on adverse effects associated with the drugs, fenfluramine hydrochloride (Pondimin®) and its dextrorotatory isomer dexfenfluramine hydrochloride (Redux®) were withdrawn from the US market in 1997. (See Cautions and also see Cautions, in the Amphetamines General Statement 28:20.04.)

Dosage and Administration

■ **Administration** Phentermine is administered orally in the form of the hydrochloride salt or the resin complex.

■ **Dosage** The usual adult dosage of phentermine hydrochloride is 8 mg 3 times daily, given 30 minutes before meals. Alternatively, 15 or 30 mg of phentermine as the resin complex, or 15–37.5 mg of phentermine hydrochloride, may be given as a single daily dose in the morning.

Cautions

■ **Cardiovascular Effects** In 1997, during postmarketing surveillance, abnormal heart valve findings, including echocardiographic features, dyspnea, chest pain, syncope, lower extremity edema, and/or heart murmurs, were reported in some patients who were receiving phentermine in combination with fenfluramine or dexfenfluramine for the management of obesity. Preliminary analysis by the US Food and Drug Administration (FDA) of pooled data from several medical centers revealed abnormal echocardiographic findings in about 32% of 291 evaluated asymptomatic patients receiving fenfluramine or dexfenfluramine for up to 24 months, usually in combination with phentermine. Preliminary data also suggest that the incidence of heart valve abnormalities may be higher in patients exposed to the anorexigenic agents for 6 months or longer when compared with those receiving the drugs for less than 6 months. Since a temporal association between use of fenfluramine and dexfenfluramine and these abnormal heart valve findings (e.g., development of unusual mitral, aortic, tricuspid, and/or pulmonary valvular [usually multivalvular]) and echocardiographic abnormalities (that sometimes occurred concomitantly with pulmonary hypertension, occasionally required open heart surgery, and rarely were fatal) were established, the manufacturer of fenfluramine (Pondimin®) and dexfenfluramine (Redux®) voluntarily withdrew these anorexigenic agents from the US market in 1997. (See Cautions, in the Amphetamines General Statement 28:20.04.)

Because of the severity of the mentioned cardiac effects, the US Department of Health and Human Services (DHHS) issued in 1997 interim recommendations that were developed by FDA in conjunction with the US Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) (the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases) and in consultation with the American Heart Association (AHA), the American College of Cardiology (ACC), and the American Dental Association (ADA) for individuals who received fenfluramine or dexfenfluramine as monotherapy or in combination with other drugs (e.g., phentermine). These interim recommendations include information concerning detection and immediate management of heart valve disease associated with these anorexigenic agents. (See Cautions, in the Amphetamines General Statement 28:20.04.) However, because of uncertainties about the described heart valve abnormalities (e.g., unknown incidence of substantial heart valve abnormalities; uncertainty about which patients might be at high or low risk for developing such abnormalities and whether such abnormalities would be reversible upon discontinuance of the anorexigenic drugs; uncertainty about the optimal timing of follow-up echocardiograms to determine progression, regression, or stabilization of cardiac valve lesions), the DHHS states that clinicians should exercise their best judgment based on the individual patient's history and clinical and cardiac status to determine the need for additional echocardiographic follow-up. The DHHS anticipates that within 1 year sufficient data will become available to make further recommendations about such acquired cardiac valvular disease. In addition, one manufacturer of phentermine (Ionamin®) states that patients who have received fenfluramine or dexfenfluramine either as monotherapy or in combination with phentermine should undergo cardiac evaluation before initiating any new treatment for exogenous obesity. This manufacturer also states that safety and efficacy of phentermine in patients with existing heart valve abnormalities and/or heart murmur, in whom increased sympathomimetic activity is not desirable, have not been established; therefore, phentermine should not be used in such patients.

As of mid-September 1997, recommendations concerning phentermine monotherapy for obesity were not affected by the recall of fenfluramine and dexfenfluramine and patients were not being advised to necessarily discontinue such therapy if indicated. However, one manufacturer of phentermine (Fastin®) states that heart valve abnormalities have been reported rarely in patients receiving monotherapy with phentermine. The etiology of these valvulopathies has not been elucidated and the course of these heart valve abnormalities in patients who have discontinued the anorexigenic agents also is not known. (See Valvulopathy and Pulmonary Hypertension: Mechanism of Cardiac Abnormalities, under Cautions in the Amphetamines General Statement 28:20.04.) However, the manufacturers state that the drug *only* should be used for short-term management (a few weeks) of exogenous obesity and should *not* be used in combination with selective serotonin-reuptake inhibitor antidepressants (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or monoamine oxidase (MAO) inhibitors.

In addition, abnormal heart valve findings and/or primary pulmonary hypertension have been reported in some patients receiving phendimetrazine tartrate who had a history of receiving at least one other anorexigenic agent. One manufacturer of phendimetrazine tartrate (Plegine®) states that since the withdrawal of fenfluramine and dexfenfluramine from the US market, there have been reports that clinicians started prescribing phendimetrazine in combination with phentermine for the management of exogenous obesity in a limited number of patients. One manufacturer of phendimetrazine tartrate (Plegine®) also states that phendimetrazine should be used *only* for short-term management (a few weeks) of exogenous obesity and should *not* be used in combination with other anorexigenic agents (e.g., phentermine).

Palpitation, tachycardia, and increased blood pressure may occur in patients receiving phentermine.

■ **Nervous System Effects** Adverse nervous system effects of phentermine may include overstimulation, restlessness, insomnia, tremor, dizziness, headache, euphoria, and dysphoria. Rarely, psychotic episodes may occur in patients receiving recommended dosages.

■ **GI Effects** GI effects of phentermine may include dryness of the mouth, unpleasant taste, diarrhea, and vomiting.

■ **Other Adverse Effects** Urticaria, impotence, and changes in libido may occur in patients receiving phentermine.

■ **Precautions and Contraindications** Patients should be warned that phentermine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Phentermine should be used with caution in patients with mild hypertension, and blood pressure should be closely monitored.

Pulmonary hypertension has been reported in patients receiving phentermine in combination with dexfenfluramine (no longer commercially available in the US), fenfluramine (no longer commercially available in the US), and in those with a history of receiving at least one other anorexigenic agent; however, the possibility of an association between pulmonary hypertension and the use of phentermine as monotherapy cannot be ruled out. Primary pulmonary hypertension is a rare, frequently fatal pulmonary disease. The initial symptom of pulmonary hypertension generally is dyspnea. Other initial manifestations include angina pectoris, syncope, or edema of the lower extremities. Phentermine should be discontinued in any patient who develops new, unexplained symptoms of dyspnea, angina, syncope, or edema of the lower extremities. Such patients should be evaluated for the possible presence of pulmonary hypertension. In addition, patients receiving phentermine should be advised to report immediately any deterioration in exercise tolerance.

Phentermine should *not* be used in combination with selective serotonin-reuptake inhibitor antidepressants (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or MAO inhibitors, since severe adverse reactions may occur. In addition, one manufacturer of phendimetrazine tartrate (Plegine®) states that phendimetrazine should *not* be used in combination with other anorexigenic