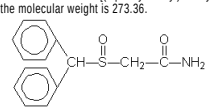
PROVIGIL® (modafinil) Tablets [C IV]

DESCRIPTION

PROVIGIL (modafinil) is a wakefulness-promoting agent for oral administration. Modafinil is a racemic compound. The chemical name for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36.

The chemical structure is:



Modafinil is a white to off-white, crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in methanol and acetone. PROVIGIL tablets contain 100 mg or 200 mg of modafinil and the following inactive ingredients: lactose, corn starch, magnesium silicate, croscarmellose sodium, povidone, magnesium stearate, and talc.

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacology

The precise mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines.

At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V.

Modafinil is not a direct- or indirect-acting dopamine receptor agonist and is inactive in several *in vivo* preclinical models capable of detecting enhanced dopaminergic activity. *In vitro*, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. In a preclinical model, the wakefulness induced by amphetamine, but not modafinil, is antagonized by the dopamine receptor antagonist haloperidol.

Modafinil does not appear to be a direct or indirect α_1-adrenergic agonist. Although modafinil-induced wakefulness can be attenuated by the α_1-adrenergic receptor antagonist, prazosin, in assay systems known to be responsive to α-adrenergic agonists, modafinil has no activity. Modafinil does not display sympathomimetic activity in the rat vas deferens preparations (agonist-stimulated or electrically stimulated) nor does it increase the formation of the adrenergic receptor-mediated second messenger phosphatidyl inositol in *in vitro* models. Unlike sympathomimetic agents, modafinil does not reduce cataplexy in narcoleptic canines and has minimal effects on cardiovascular and hemodynamic parameters.

In the cat, equal wakefulness-promoting doses of methylphenidate and amphetamine increased neuronal activation throughout the brain. Modafinil at an equivalent wakefulness-promoting dose selectively and prominently increased neuronal activation in more discrete regions of the brain. The relationship of this finding in cats to the effects of modafinil in humans is unknown.

In addition to its wakefulness-promoting effects and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.

The optical enantiomers of modafinil have similar pharmacological actions in animals. The enantiomers have not been individually studied in humans. Two major metabolites of modafinil, modafinil acid and modafinil sulfone, do not appear to contribute to the CNS-activating properties of modafinil.

Pharmacokinetics

Modafinil is a racemic compound, whose enantiomers have different pharmacokinetics (e.g., the half-life of the *l*-isomer is approximately three times that of the *d*-isomer in humans). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration (C_{minss}) of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing.

Absorption and Distribution

Absorption of PROVIGIL tablets is rapid, with peak plasma concentrations occurring at 2-4 hours. The bioavailability of PROVIGIL tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined due to the aqueous insolubility (<1 mg/mL) of modafinil, which precluded intravenous administration. Food has no effect on overall PROVIGIL bioavailability; however, its absorption (t_{max}) may be delayed by approximately one hour if taken with food.

Modafinil is well distributed in body tissue with an apparent volume of distribution (~0.9 L/kg) larger than the volume of total body water (0.6 L/kg). In human plasma, *in vitro*, modafinil is moderately bound to plasma protein (~60%, mainly to albumin). At serum concentrations obtained at steady state after doses of 200 mg/day, modafinil exhibits no displacement of protein binding of warfarin, diazepam, or propranolol. Even at much larger concentrations (1000 µM; >25 times the C_{max} of 40 µM at steady state at 400 mg/day), modafinil has no effect on warfarin binding. Modafinil acid at concentrations >500 µM decreases the extent of warfarin binding, but these concentrations are > 35 times those achieved therapeutically.

Metabolism and Elimination

The major route of elimination (~90%) is metabolism, primarily by the liver, with subsequent renal elimination of the metabolites. Urine alkalinization has no effect on the elimination of modafinil.

Metabolism occurs through hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation. Less than 10% of an administered dose is excreted as the parent compound. In a clinical study using radiolabeled modafinil, a total of 81% of the administered radioactivity was recovered in 11 days post-dose, predominantly in the urine (80% vs. 1.0% in the feces). The largest fraction of the drug in urine was modafinil acid, but at least six other metabolites were present in lower concentrations. Only two metabolites reach appreciable concentrations in plasma, i.e., modafinil acid and modafinil sulfone. In preclinical models, modafinil acid, modafinil sulfone, 2-[(diphenylmethyl)sulfonyl]acetic acid and 4-hydroxy modafinil, were inactive or did not appear to mediate the arousal effects of modafinil.

In humans, modafinil shows a possible induction effect on its own metabolism after chronic administration of doses ≥ 400 mg/day. Induction of hepatic metabolizing enzymes, most importantly cytochrome P-450 (CYP) 3A4, has also been observed *in vitro* after incubation of primary cultures of human hepatocytes with modafinil. (For further discussion of the effects of modafinil on CYP enzyme activities see **PRECAUTIONS, Drug Interactions**).

Drug-Drug Interactions: Because modafinil is a reversible inhibitor of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, phenytoin and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6 (i.e., 7-10% of the Caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co-administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications (See **PRECAUTIONS, Drug Interactions**).

Chronic administration of modafinil may also cause modest induction of the metabolizing enzyme CYP3A4, thus reducing the levels of co-administered substrates for that enzyme system, such as steroidal contraceptives, cyclosporine and, to a lesser degree, theophylline. Dose adjustments may be necessary for patients being treated with these and similar medications (See **PRECAUTIONS, Drug Interactions**).

An apparent concentration-related suppression of CYP2C9 activity was observed in human hepatocytes after exposure to modafinil *in vitro*. Although no other indication of CYP2C9 suppression has been observed, the *in vitro* results suggest that there is potential for metabolic interaction between PROVIGIL and CYP2C9 substrates, such as warfarin or phenytoin (See **PRECAUTIONS, Drug Interactions**).

Special Populations

Gender Effect: The pharmacokinetics of modafinil are not affected by gender.

Age Effect: A slight decrease (~20%) in the oral clearance (CL/F) of modafinil was observed in a single dose study at 200 mg in 12 subjects with a mean age of 63 years (range 53 – 72 years), but the change was considered unlikely to be clinically significant. In a multiple dose study (300 mg/day) in 12 patients with a mean age of 82 years (range 67 – 87 years), the mean levels of modafinil in plasma were approximately two times those historically obtained in matched younger subjects. Due to potential effects from the multiple concomitant medications with which most of the patients were being treated, the apparent difference in modafinil pharmacokinetics may not be attributable solely to the effects of aging. However, the results suggest that the clearance of modafinil may be reduced in the elderly (See **DOSAGE AND ADMINISTRATION**).

Race Effect: The influence of race on the pharmacokinetics of modafinil has not been studied.

Renal Impairment: In a single dose 200 mg modafinil study, severe chronic renal failure (creatinine clearance ≤ 20 mL/min) did not significantly influence the pharmacokinetics of modafinil, but exposure to modafinil acid (an inactive metabolite) was increased 9 fold (See **PRECAUTIONS**).

Hepatic Impairment: Pharmacokinetics and metabolism were examined in patients with cirrhosis of the liver (6 M and 3 F). Three patients had stage B or B+ cirrhosis (per the Child criteria) and 6 patients had stage C or C+ cirrhosis. Clinically 8 of 9 patients were icteric and all had ascites. In these patients, the oral clearance of modafinil was decreased by about 60% and the steady state concentration was doubled compared to normal patients. The dose of PROVIGIL should be reduced in patients with severe hepatic impairment (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

The effectiveness of PROVIGIL in reducing the excessive daytime sleepiness (EDS) associated with narcolepsy was established in two US 9-week, multicenter, placebo-controlled, two-dose (200 mg per day and 400 mg per day) parallel-group, double-blind studies of outpatients who met the ICD-9 and American Sleep Disorders Association criteria for narcolepsy (which are also consistent with the American Psychiatric Association DSM-IV criteria). These criteria include either 1) recurrent daytime naps or lapses into sleep that occur almost daily for at least three months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy) or 2) a complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviors, disrupted major sleep episode; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes. In addition, for entry into these studies, all patients were required to have objectively documented excessive daytime sleepiness, a Multiple Sleep Latency Test (MSLT) with two or more sleep onset REM periods, and the absence of any other clinically significant active medical or psychiatric disorder. The MSLT, an objective daytime polysomnographic assessment of the patient's ability to fall asleep in an unstimulating environment, measures latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was told to lie quietly and attempt to sleep. Each test session was terminated after 20 minutes if no sleep occurred or 15 minutes after sleep onset.

In both studies, the primary measures of effectiveness were 1) sleep latency, as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C). For a successful trial, both measures had to show significant improvement.

The MWT measures latency (in minutes) to sleep onset averaged over 4 test sessions at 2 hour intervals following nocturnal polysomnography. For each test session, the subject was asked to attempt to remain awake without using extraordinary measures. Each test session was terminated after 20 minutes if no sleep occurred or 10 minutes after sleep onset. The CGI-C is a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. Patients were rated by evaluators who had no access to any data about the patients other than a measure of their baseline severity. Evaluators were not given any specific guidance about the criteria they were to apply when rating patients.

Other assessments of effect included the Multiple Sleep Latency Test (MSLT), Epworth Sleepiness Scale (ESS; a series of questions designed to assess the degree of sleepiness in everyday situations) the Steer Clear Performance Test (SCPT; a computer-based evaluation of a patient's ability to avoid hitting obstacles in a simulated driving situation), standard nocturnal polysomnography, and patient's daily sleep log. Patients were also assessed with the Quality of Life in Narcolepsy (QOLIN) scale, which contains the validated SF-36 health questionnaire.

Both studies demonstrated improvement in objective and subjective measures of excessive daytime sleepiness for both the 200 mg and 400 mg doses compared to placebo. Patients treated with either dose of PROVIGIL showed a statistically significantly enhanced ability to remain awake on the MWT (all p values <0.001) at weeks 3, 6, 9, and endpoint compared to placebo and a statistically significantly greater global improvement, as rated on the CGI-C scale (all p values <0.05).

The average sleep latencies (in minutes) on the MWT at endpoint in the 2 controlled trials are shown in the table below:

Table 1. MWT Average Sleep Latency at Endpoint

Average Sleep Latency at Endpoint			
		PROVIGIL	
	Placebo	200 mg*	400 mg*
Trial 1	5.07	8.18	8.90
Trial 2	5.35	8.28	7.86

* significantly different from placebo for both trials (p<0.001)

The percentages of patients who showed any degree of improvement on the CGI-C in the two clinical trials are shown in the table below:

Table 2. Clinical Global Impression of Change (CGI-C)

Percent of Patients Who Improved at Endpoint			
		PROVIGIL	
	Placebo	200 mg*	400 mg*
Trial 1	37%	64%	72%
Trial 2	38%	58%	60%

* significantly different from placebo for both trials (Trial 1: p<0.001; Trial 2: p<0.01)

Similar statistically significant treatment-related improvements were seen on other measures of impairment in narcolepsy, including a decrease in the propensity to fall asleep on the MSLT (p<0.001 for each dose in comparison to placebo) and a statistically significant lessening of patient-assessed level of daytime sleepiness on the ESS (p<0.001 for each dose in comparison to placebo).

Although PROVIGIL tended to be numerically superior to placebo on several of the other outcome measures, there were no consistent statistically significant differences between drug and placebo on these measures.

Nighttime sleep measured with nocturnal polysomnography was not affected by the use of PROVIGIL.

The effectiveness of modafinil in long-term use (greater than 9 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe PROVIGIL tablets for an extended time should periodically re-evaluate long-term usefulness for the individual patient.

INDICATIONS AND USAGE

PROVIGIL is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

CONTRAINDICATIONS

PROVIGIL is contraindicated in patients with known hypersensitivity to modafinil.

PRECAUTIONS

General

Although modafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking or motor skills. Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.

Cardiovascular System

In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use.

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

Modafinil has not been systematically evaluated in patients with hypertension. Periodic monitoring of hypertensive patients may be appropriate.

Central Nervous System

One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation. Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.

Patients with Severe Renal Impairment

In patients with severe renal impairment (mean creatinine clearance = 16.6 mL/min), a 200 mg single dose of modafinil did not lead to increased exposure to modafinil but resulted in much higher exposure to the inactive metabolite, modafinil acid, than is seen in subjects with normal renal function. There is little information available about the safety of such levels of this metabolite (See **CLINICAL PHARMACOLOGY**).

Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment, with or without cirrhosis (See **CLINICAL PHARMACOLOGY**), PROVIGIL should be administered at a reduced dose as the clearance of modafinil was decreased compared to that in normal subjects (See **DOSAGE AND ADMINISTRATION**).

Elderly Patients

To the extent that elderly patients may have diminished renal and/or hepatic function, dosage reductions should be considered (See **DOSAGE AND ADMINISTRATION**).

Patients Using Contraceptives

The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL tablets and for one month after discontinuation of therapy (See *Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes*). Alternative or concomitant methods of contraception are recommended for patients treated with PROVIGIL tablets, and for one month after discontinuation of PROVIGIL.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe PROVIGIL tablets.

Pregnancy

Animal studies to assess the effects of modafinil on reproduction and the developing fetus were not conducted at adequately high doses or according to guidelines which would ensure a comprehensive evaluation of the potential of modafinil to adversely affect fertility, or cause embryolethality or teratogenicity (See *Impairment of Fertility* and **Pregnancy**).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL tablets and for one month after discontinuation of therapy.

Nursing

Patients should be advised to notify their physician if they are breast feeding an infant.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, because of the potential for interactions between PROVIGIL tablets and other drugs.

Alcohol

Patients should be advised that the use of PROVIGIL in combination with alcohol has not been studied. Patients should be advised that it is prudent to avoid alcohol while taking PROVIGIL tablets.

Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions

CNS Active Drugs

Methylphenidate - In a single-dose study in healthy volunteers, coadministration of modafinil (200 mg) with methylphenidate (40 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of PROVIGIL may be delayed by approximately one hour when coadministered with methylphenidate.

Clomipramine - The coadministration of a single dose of clomipramine (50 mg) on the first of three days of treatment with modafinil (200 mg/day) in healthy volunteers did not show an effect on the pharmacokinetics of either drug. However, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported in a patient with narcolepsy during treatment with modafinil (See *Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes*).

Triazolam - In a single-dose pharmacodynamic study with PROVIGIL in healthy volunteers (50, 100 or 200 mg) and triazolam (0.25 mg), no clinically important alterations in the safety profile of modafinil or triazolam were noted.

Monoamine Oxidase (MAO) Inhibitors - Interaction studies with monoamine oxidase inhibitors have not been performed. Therefore, caution should be used when concomitantly administering MAO inhibitors and modafinil.

Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes

In a controlled study in patients with narcolepsy, chronic dosing of PROVIGIL at 400 mg/day once daily resulted in a ~20% mean decrease in modafinil plasma trough concentrations by week 9, relative to those at week 3, suggesting that chronic administration of PROVIGIL might have caused induction of its metabolism. In addition, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the levels of modafinil due to the partial involvement of that enzyme in the metabolic elimination of the compound.

In *in vitro* studies using primary human hepatocyte cultures, modafinil was shown to slightly induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner. Although induction results based on *in vitro* experiments are not necessarily predictive of response *in vivo*, caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on these three enzymes for their clearance. Specifically, lower blood levels of such drugs could result. In the case of CYP1A2 and CYP2B6, no other evidence of enzyme induction has been observed. A modest induction of CYP3A4 by modafinil has been indicated by other results, hence the clearance of CYP3A4 substrates such as cyclosporine, steroidal contraceptives and, to a lesser degree, theophylline, may be increased.

One case of an interaction between modafinil and cyclosporine has been reported in a 41 year old woman who had undergone an organ transplant. After one month of administration of 200 mg/day of modafinil, cyclosporine blood levels were decreased by 50%. The interaction was postulated to be due to the increased metabolism of cyclosporine, since no other factor expected to affect the disposition of the drug had changed.

The exposure of human hepatocytes to modafinil *in vitro* produced an apparent concentration-related suppression of expression of CYP2C9 activity. The clinical relevance of this finding is unclear, since no other indication of CYP2C9 suppression has been observed. However, monitoring of prothrombin times is suggested as a precaution for the first several months of coadministration of PROVIGIL and warfarin, a CYP2C9 substrate, and thereafter whenever PROVIGIL dosing is changed. In addition, patients receiving PROVIGIL and phenytoin, a CYP2C9 substrate, concomitantly should be monitored for signs of phenytoin toxicity.

In vitro studies using human liver microsomes showed that modafinil has little or no capacity to inhibit the major CYP enzymes except for CYP2C19, which is reversibly inhibited at pharmacologically relevant concentrations of modafinil. Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin or S-mephenytoin may have prolonged elimination upon coadministration with PROVIGIL and may require dosage reduction.

In addition, CYP2C19 provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine and desipramine) that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased. PROVIGIL may cause elevation of the levels of the tricyclics in this subset of patients. Physicians should be aware that a reduction in the dose of tricyclic agents might be needed in these patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which modafinil was administered in the diet to mice for 78 weeks and to rats for 104 weeks at doses of 6, 30 and 60 mg/kg/day. The highest dose studied represents 1.5 times (mouse) or 3 times (rat) greater than the maximum recommended human daily dose of 200 mg on a mg/m^2 basis. There was no evidence of tumorigenesis associated with modafinil administration in these studies, but because the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose, the carcinogenic potential of modafinil has not been fully evaluated.

Mutagenesis

There was no evidence of mutagenic or clastogenic potential of modafinil in a series of assays. It was not mutagenic in the *in vitro* Ames bacterial reverse mutation test, the *in vitro* mouse lymphoma/TK locus assay in the presence or absence of metabolic activation; and it was not clastogenic in the *in vitro* human lymphocyte chromosomal aberration assay in the presence or absence of metabolic activation, or in two *in vivo* mouse bone marrow micronucleus assays. Modafinil did not increase unscheduled DNA synthesis in rat hepatocytes. In a cell transformation assay in BALB/3T3 mouse embryo cells, modafinil did not cause an increase in the frequency of transformed foci in the presence or absence of metabolic activation.

Impairment of Fertility

When modafinil was administered orally to male and female rats prior to and throughout mating and gestation at doses up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m^2 basis) no effects on fertility were seen. The study to evaluate these effects, however, did not use sufficiently high doses or large enough sample size to adequately assess effects on fertility.

Pregnancy

Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral modafinil throughout the period of organogenesis. At a dose of 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m^2 basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m^2 basis). When rabbits received oral modafinil throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m^2 basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with modafinil in pregnant women and this drug should be used during pregnancy only if the potential benefit outweighs the potential risk.

Labor and Delivery

The effect of modafinil on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received modafinil during pregnancy. One patient gave birth 3 weeks earlier than the expected range of delivery dates (estimated using ultrasound) to a healthy male infant. One woman with a history of spontaneous abortions suffered a spontaneous abortion while being treated with modafinil.

Nursing Mothers

It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROVIGIL tablets are administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in individuals below 16 years of age have not been established.

GERIATRIC USE

Safety and effectiveness in individuals above 65 years of age have not been established. Experience in a limited number of patients (15) who were greater than 65 years of age in US clinical trials showed an incidence of adverse experiences similar to other age groups.

ADVERSE REACTIONS

Modafinil has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least one dose of modafinil. Modafinil has been found to be generally well-tolerated. In controlled clinical trials, most adverse experiences were mild to moderate.

The most commonly observed adverse events (≥5%) associated with the use of modafinil more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia.

In US placebo-controlled Phase 3 clinical trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). In foreign, controlled clinical trials, reasons for discontinuation were similar to those in US trials. In a Canadian clinical trial, a 35 year old obese narcoleptic male with a prior history of syncopal episodes experienced a 9-second episode of asystole after 27 days of modafinil treatment (300 mg/day in divided doses).

Incidence in Controlled Trials

The following table presents the adverse experiences that occurred in narcolepsy patients at a rate of 1% or more and were more frequent in patients treated with PROVIGIL than in placebo patients in US placebo-controlled clinical trials.

The prescriber should be aware that the figures provided below cannot be used to predict the frequency of adverse experiences in the course of usual medical practice, where patient characteristics and other factors may differ from those occurring during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. Review of these frequencies, however, provides prescribers with a basis to estimate the relative contribution of drug and non-drug factors to the incidence of adverse events in the population studied.

Table 3. Incidence of Treatment-Emergent Adverse Experiences in US 9-Week Placebo-Controlled Clinical Trials[1] with PROVIGIL (200 mg and 400 mg) Daily

Body System	Preferred Term	Modafinil (n = 369)	Placebo (n = 185)
Body as a Whole	Headache	50%	40%
	Chest pain	2%	1%
	Neck pain	2%	1%
	Chills	2%	0%
	Rigid Neck	1%	0%
	Fever/Chills	1%	0%
Digestive	Nausea	13%	4%
	Diarrhea	8%	4%
	Dry mouth	5%	1%
	Anorexia	5%	1%
	Abnormal liver function[2]	3%	2%
	Vomiting	2%	1%
	Mouth ulcer	1%	0%
	Gingivitis	1%	0%
	Thirst	1%	0%
Respiratory System	Rhinitis	11%	8%
	Pharyngitis	6%	3%
	Lung disorder	4%	2%
	Dyspnea	2%	1%
	Asthma	1%	0%
	Epistaxis	1%	0%
Nervous System	Nervousness	8%	6%
	Dizziness	5%	4%
	Depression	4%	3%
	Anxiety	4%	1%
	Cataplexy	3%	2%
	Insomnia	3%	1%
	Paresthesia	3%	1%
	Dyskinesia[3]	2%	0%
	Hypertonia	2%	0%
	Confusion	1%	0%
	Amnesia	1%	0%
	Emotional lability	1%	0%
	Ataxia	1%	0%
	Tremor	1%	0%
Cardiovascular	Hypotension	2%	1%
	Hypertension	2%	0%
	Vasodilation	1%	0%
	Arrhythmia	1%	0%
	Syncope	1%	0%
Hemic/Lymphatic	Eosinophilia	2%	0%
Special Senses	Amblyopia	2%	1%
	Abnormal vision	2%	0%
Metabolic/Nutritional	Hyperglycemia	1%	0%
	Albuminuria	1%	0%
Musculo-skeletal	Joint disorder	1%	0%
Skin/Appendages	Herpes simplex	1%	0%
	Dry skin	1%	0%
Urogenital	Abnormal urine	1%	0%
	Urinary retention	1%	0%
	Abnormal ejaculation[4]	1%	0%

*Notes and abbreviations are in next column.

[1] Events reported by at least 1% of patients treated with PROVIGIL that were more frequent than in the placebo group are included; incidence is rounded to the nearest 1%. The adverse experience terminology is coded using a standard modified COSTART Dictionary.

Events for which the PROVIGIL incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: infection, back pain, pain, hypothermia, abdominal pain, flu syndrome, allergic reaction, fever, asthenia, accidental injury, general edema, tachycardia, palpitations, migraine, ventricular extrasystole, bradycardia, dyspepsia, tooth disorder, constipation, flatulence, increased appetite, gastroenteritis, GI disorder, ecchymosis, anemia, leukocytosis, peripheral edema, increased weight, increased SGOT, myalgia, arthritis, arthralgia, somnolence, thinking abnormality, leg cramps, sleep disorder, hallucinations, hyperkinesia, decreased libido, increased cough, sinusitis, bronchitis, pneumonia, rash, sweating, pruritus, skin disorder, psoriasis, ear pain, eye pain, ear disorder, taste perversion, dysmenorrhea[4], urinary tract infection, pyuria, hematuria, cystitis, and disturbed menses[4].

[2] Elevated liver enzymes.

[3] Oro-facial dyskinesias.

[4] Incidence adjusted for gender.

Dose Dependency of Adverse Events

In the US Phase 3 clinical trials, the only adverse experience that was more frequent (≥5% difference) in the PROVIGIL dose group of 400 mg/day than in the PROVIGIL dose group of 200 mg/day and placebo was headache.

Vital Sign Changes

There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL enrolled in the US Phase 3 clinical trials.

Weight Changes

There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo-treated patients.

Laboratory Changes

Clinical chemistry, hematology, and urinalysis parameters were monitored in US Phase 1, 2 and 3 studies. In these studies, mean plasma levels of gamma -glutamyl transferase (GGT) were found to be higher following administration of PROVIGIL, but not placebo. Few subjects (1%), however, had GGT elevations outside of the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time in the population treated with PROVIGIL in the 9-week US phase 3 clinical trials. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin.

Although there were more abnormal eosinophil counts following PROVIGIL administration than placebo in US Phase 1 and 2 studies, the difference does not appear to be clinically significant. Observed shifts were from normal to high.

ECG Changes

No treatment-emergent pattern of ECG abnormalities was found in US Phase 1, 2, and 3 studies following administration of PROVIGIL.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Modafinil (PROVIGIL) is listed in Schedule IV of the Controlled Substances Act.

Abuse Potential and Dependence

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In *in vitro* binding studies, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, modafinil was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (e.g. methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g., incrementation of doses or drug-seeking behavior).

The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).

Withdrawal

The effects of modafinil withdrawal were monitored following 9 weeks of modafinil use in one US Phase 3 controlled clinical trial. No specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE

Human Experience

A total of 151 doses of 1000 mg/day (5 times the maximum recommended daily dose of 200 mg) or more, have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by two patients participating in foreign depression studies. In both cases, the adverse experiences observed were limited, expected, and not life-threatening, and the patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in other instances of doses of more than 1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time.

Overdose Management

No specific antidote to the toxic effects of modafinil overdose has been identified to date. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring. If there are no contraindications, induced emesis or gastric lavage should be considered. There are no data to suggest the utility of dialysis or urinary acidification or alkalinization in enhancing drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

The dose of PROVIGIL is 200 mg/day, given as a single dose in the morning.

Doses of 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose (See **CLINICAL PHARMACOLOGY, CLINICAL TRIALS**).

In patients with severe hepatic impairment, the dose of PROVIGIL should be reduced to one-half of that recommended for patients with normal hepatic function (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

In elderly patients, elimination of PROVIGIL and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses in this population (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

HOW SUPPLIED:

PROVIGIL® (modafinil) Tablets

100 mg Each capsule-shaped, white, uncoated tablet is debossed with "PROVIGIL" on one side and "100 MG" on the other.
NDC 63459-100-01 - Bottles of 100

200 mg Each capsule-shaped, white, scored, uncoated tablet is debossed with "PROVIGIL" on one side and "200 MG" on the other.
NDC 63459-200-01 - Bottles of 100

Store at 20° - 25° C (68° - 77° F).

Caution: Federal law prohibits dispensing without prescription.

Manufactured for:
Cephalon, Inc.
West Chester, PA 19380

By:
Circa Pharmaceuticals, Inc.
Copiague, NY 11726

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