PROVIGIL® (modafinil) tablets, for oral use, C-IV
Initial U.S. Approval: 1998

INDICATIONS AND USAGE
PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder (SWD). (1)

Limitations of Use
In OSA, PROVIGIL is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction.

DOSE AND ADMINISTRATION
The recommended dosage of PROVIGIL for each indication is as follows:
• Narcolepsy or OSA: 200 mg once a day in the morning. (2.1)
• SWD: 200 mg once a day, taken approximately one hour prior to start of the work shift. (2.2)
• Severe Hepatic Impairment: reduce dose to half the recommended dose. (2.3, 12.3)
• Geriatric Patients: consider lower dose. (2.4, 12.3)

DOSE FORMS AND STRENGTHS
Tablets: 100 mg and 200 mg. (3)

CONTRAINDICATIONS
PROVIGIL is contraindicated in patients with known hypersensitivity to modafinil or armodafinil. (4)

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage in Narcolepsy and Obstructive Sleep Apnea (OSA)
2.2 Dosage in Shift Work Disorder (SWD)
2.3 Dosage Modifications in Patients with Severe Hepatic Impairment
2.4 Use in Geriatric Patients
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Rash, including Stevens-Johnson Syndrome
5.2 Angioedema and Anaphylaxis Reactions
5.3 Multi-organ Hypersensitivity Reactions
5.4 Persistent Sleepiness
5.5 Psychiatric Symptoms
5.6 Effects on Ability to Drive and Use Machinery
5.7 Cardiovascular Events
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Narcolepsy
14.2 Obstructive Sleep Apnea (OSA)
14.3 Shift Work Disorder (SWD)
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

PROVIGIL® (modafinil) tablets [C-IV]

WARNINGS AND PRECAUTIONS
• Serious Rash, including Stevens-Johnson Syndrome: Discontinue PROVIGIL at the first sign of rash, unless the rash is clearly not drug-related. (5.1)
• Angioedema and Anaphylaxis Reactions: If suspected, discontinue PROVIGIL. (5.2)
• Multi-organ Hypersensitivity Reactions: If suspected, discontinue PROVIGIL. (5.3)
• Persistent Sleepiness: Assess patients frequently for degree of sleepiness and, if appropriate, advise patients to avoid driving or engaging in any other potentially dangerous activity. (5.4)
• Psychiatric Symptoms: Use caution in patients with a history of psychosis, depression, or mania. Consider discontinuing PROVIGIL if psychiatric symptoms develop. (5.5)
• Known Cardiovascular Disease: Consider increased monitoring. (5.7)

ADVERSE REACTIONS
Most common adverse reactions (≥5%): headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Steroidal contraceptives (e.g., ethinyl estradiol): Use alternative or concomitant methods of contraception while taking PROVIGIL and for one month after discontinuation of PROVIGIL treatment. (7)
• Cyclosporine: Blood concentrations of cyclosporine may be reduced. (7)
• CYP2C19 substrates, such as omeprazole, phenytoin, and diazepam: Exposure of these medications may be increased. (7)

USE IN SPECIFIC POPULATIONS
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2018

FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder (SWD). (1)

Limitations of Use
In OSA, PROVIGIL is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction.

2 DOSAGE AND ADMINISTRATION
2.1 Dosage in Narcolepsy and Obstructive Sleep Apnea (OSA)
The recommended dosage of PROVIGIL for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning. Doses up to 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/day dose. (see Clinical Pharmacology (12.3) and Clinical Studies (14.1, 14.2)).

The recommended dosage of PROVIGIL for patients with SWD is 200 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.

2.3 Dosage Modifications in Patients with Severe Hepatic Impairment
In patients with severe hepatic impairment, the dosage of PROVIGIL should be reduced to one-half of that recommended for patients with normal hepatic function. [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].
have been reported in adults and children in worldwide postmarketing experience. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years. There are no factors that are known to predict the risk of occurrence or the severity of rash associated with modafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., 3 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes may occur with PROVIGIL, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, PROVIGIL should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

5.2 Angioedema and Anaphylaxis Reactions
Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm), were observed in patients treated with armodafinil, the R enantiomer of modafinil (which is the racemic mixture). No such cases were observed in modafinil clinical trials. However, isolated cases have been reported in postmarketing experience. Although beni其 rashes may occur with PROVIGIL, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, PROVIGIL should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

5.3 Multi-organ Hypersensitivity Reactions
Multi-organ hypersensitivity reactions, including at least one fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days: range 4-33) to the initiation of modafinil. Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, hematological abnormalities (leukopenia, thrombocytopenia), pruritus, and asthma. Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

If a multi-organ hypersensitivity reaction is suspected, PROVIGIL should be discontinued. Although there are no case reports to indicate cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

5.4 Persistent Sleepiness
Patients with abnormal levels of sleepiness who take PROVIGIL should be advised that their level of alertness may not return to normal. Patients with excessive sleepiness, including those taking PROVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specified activities.

5.5 Psychiatric Symptoms
Psychiatric adverse reactions have been reported in patients treated with modafinil. In the adult PROVIGIL controlled trials, psychiatric symptoms resulting in treatment discontinuation (at a frequency ≥0.3%) and reported more often in patients treated with PROVIGIL compared to placebo were anxiety (1%), nervousness (1%), insomnia (>1%), confusion (<1%), agitation (<1%), and depression (<1%). Postmarketing adverse reactions associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation, and aggression, some resulting in hospitalization. Many, but not all, patients had a prior psychiatric history. One healthy male volunteer developed ideas of reference, expanded delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL (three times the recommended dose) 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, depression, or mania. Consideration should be given to the possible emergence or exacerbation of psychiatric symptoms in patients treated with PROVIGIL. If psychiatric symptoms develop in association with PROVIGIL administration, consider discontinuing PROVIGIL.

5.6 Effects on Ability to Drive and Use Machinery
Although PROVIGIL 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 it is reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.

5.7 Cardiovascular Events
In modafinil clinical studies, cardiovascular adverse reactions, including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG occurred in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. In a Canadian clinical trial, a 35 year old obese narcoleptic male with a prior history of hypertension had a B-second episode of asystole after 27 days of modafinil treatment (300 mg/day in divided doses). PROVIGIL is not recommended in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Findings suggestive of mitral valve prolapse syndrome include but are not limited to ischemic ECG changes, chest pain, or arrhythmia. If new onset of any of these findings occurs, consider cardiac evaluation. Consider increased monitoring in patients with a recent history of myocardial infarction or unstable angina. Blood pressure monitoring in short term (≥ 3 months) controlled trials showed no clinically significant changes in mean systolic and diastolic blood pressure in patients treated with PROVIGIL as compared to placebo. However, a retrospective analysis of the use of antihypertensive medication in these studies showed that a greater proportion of patients on PROVIGIL required new or increased use of antihypertensive medications (2.4%) compared to patients on placebo (0.7%). The difference was clinically larger when only studies in OSA were included, with 3.4% of patients on PROVIGIL and 1.1% of patients on placebo requiring such alterations in the use of antihypertensive medication. Increased monitoring of heart rate and blood pressure may be appropriate in patients on PROVIGIL. Caution should be exercised when prescribing PROVIGIL to patients with known cardiovascular disease.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Serious Rash, including Stevens-Johnson Syndrome [see Warnings and Precautions (5.1)]
- Angioedema and Anaphylaxis Reactions [see Warnings and Precautions (5.2)]
- Multi-organ Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- Persistent Sleepiness [see Warnings and Precautions (5.4)]
- Psychiatric Symptoms [see Warnings and Precautions (5.5)]
- Effects on Ability to Drive and Use Machinery [see Warnings and Precautions (5.6)]
- Cardiovascular Events [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. PROVIGIL has been evaluated for safety in over 3,500 patients, of whom more than 2,000 patients had excessive sleepiness associated with OSA, SWD, and narcolepsy.

Table 1. Adverse Reactions in Pooled Placebo-Controlled Trials in Narcolepsy, OSA, and SWD

<table>
<thead>
<tr>
<th>Reaction</th>
<th>PROVIGIL (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34</td>
<td>23</td>
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<tr>
<td>Nausea</td>
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<tr>
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</tr>
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</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Abnormal Liver Function</td>
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<td>Constipation</td>
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<td>1</td>
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<tr>
<td>Depression</td>
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PROVIGIL® (modafinil) tablets [C-IV]

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category C

There are no adequate and well-controlled studies of modafinil in pregnant women. Intrauterine growth restriction and spontaneous abortion have been noted in association with modafinil (a mixture of R- and S-modafinil) and armodafinil (the R-enantiomer of modafinil). Although the pharmacology of modafinil is not identical to that of the sympathomimetic amines, it does share some pharmacologic properties with this class. Certain of these drugs have been associated with intrauterine growth restriction and spontaneous abortions. Whether the cases reported with modafinil are drug-related is unknown. In studies of modafinil and armodafinil conducted in pregnant rats throughout organogenesis, caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of visceral and skeletal variations in the offspring at the highest dose tested. The higher no-effect dose for embryofetal development in rats (100 mg/kg/day) was associated with a plasma modafinil AUC less than that in humans at the recommended human dose (RHD) of PROVIGIL (200 mg/day). However, in a subsequent study of up to 480 mg/kg/day of modafinil, no adverse effects on embryofetal development were observed. Oral administration of armodafinil (60, 200, or 600 mg/kg/day) to pregnant rats throughout organogenesis resulted in increased incidences of fetal visceral and skeletal variations and decreased fetal body weight at the highest dose tested. The highest no-effect dose for embryofetal developmental toxicity in rats (200 mg/kg/day) was associated with a plasma armodafinil AUC less than that in humans at the RHD of PROVIGIL (200 mg/day).

Modafinil administered orally to pregnant rabbits throughout organogenesis at doses of up to 100 mg/kg/day had no effect on embryofetal development; however, the doses used were too low to adequately assess the effects of modafinil on embryofetal development. In a subsequent developmental toxicity study evaluating doses of 2.8, 28, and 280 mg/kg/day in rabbits at the RHD of PROVIGIL, Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200 mg/kg/day resulted in a decrease in body weight gain of the offspring, a lower plasma armodafinil AUC compared to the high dose and no reproductive toxicity at 20 mg/kg/day, a dose resulting in a plasma modafinil AUC less than that in humans at the RHD of PROVIGIL. No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring.

**8.2 Postmarketing Experience**

The following adverse reactions have been identified during post approval use of PROVIGIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Cardiovascular:** Stroke

**Hematologic:** agranulocytosis

**Psychiatric disorders:** psychomotor hyperactivity

**Dose-Dependent Adverse Reactions**

In the placebo-controlled clinical trials which compared doses of 200, 300, and 400 mg/day of PROVIGIL and placebo, the following adverse reactions were dose related: headache and anxiety.

**Adverse Reactions Resulting in Discontinuation of Treatment**

In placebo-controlled clinical trials, 74 of the 934 patients (8%) who received PROVIGIL discontinued due to an adverse reaction compared to 3% of patients that received placebo. The most frequent reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (each <1%).

**Laboratory Abnormalities**

Clinical chemistry; hematology, and urinalysis parameters were monitored in the studies. Mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be higher following administration of PROVIGIL, but not placebo. Few patients, however, had GGT or AP elevations outside of the normal range. Shifts to higher, but not clinically significantly abnormal, GGT and AP values appeared to increase with time in the population treated with PROVIGIL in the placebo-controlled clinical trials. No differences were apparent in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, or total bilirubin.

**6.2 Postmarketing Experience**

**Effects of PROVIGIL on CYP3A4/5 Substrates**

The clearance of drugs that are substrates for CYP3A4/5 (e.g., steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by PROVIGIL via induction of metabolic enzymes, with resultant higher systemic exposure. In individuals with moderately or severely reduced cirrhosis, it is especially applicable to the use of lower doses and close monitoring in this population to one-half of that recommended for patients with normal hepatic function.

In patients with severe hepatic impairment, the dose of PROVIGIL should be reduced to the use of lower doses and close monitoring in this population to one-half of that recommended for patients with normal hepatic function.

In patients with severe hepatic impairment, the dose of PROVIGIL should be reduced to the use of lower doses and close monitoring in this population. The higher no-effect dose for embryofetal developmental toxicity in rats (200 mg/kg/day) was associated with a plasma armodafinil AUC less than that in humans at the RHD of PROVIGIL (200 mg/day).

Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200 mg/kg/day resulted in a decrease in body weight gain of the offspring, a lower plasma armodafinil AUC compared to the high dose and no reproductive toxicity at 20 mg/kg/day, a dose resulting in a plasma modafinil AUC less than that in humans at the RHD of PROVIGIL. No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring.

**Pregnancy Registry**

A pregnancy registry has been established to collect information on the pregnancy outcomes of women exposed to PROVIGIL. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106 (toll free).

**8.3 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 is administered to a nursing woman.

**8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established. PROVIGIL is not approved in this population for any indication.

Serious skin rashes, including exanthema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS) have been associated with modafinil use in pediatric patients [see Warnings and Precautions (5.1)].

In a controlled 18-week study in premenarcheal girls (aged 5–17 years) with narcolepsy were treated with modafinil (n=123), or placebo (n=42). There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT, or in perceptions of sleepiness as determined by the clinical global impression-clinician scale (CGI-C).

In a randomized, double-blind, placebo-controlled and open-label clinical studies, treatment emergent adverse reactions of the psychiatric and nervous system included Tourette's syndrome, insomnia, hostility, increased cataplexy, increased hypnagogic hallucinations, and suicidal ideation. Transient leukopenia, which resolved without medical intervention, was also observed. In the controlled clinical study, 3 of 38 girls, ages 12 or older, treated with modafinil experienced dysmenorrhea compared to 0 of 10 girls who received placebo. There were three 7 to 9 week, double-blind, placebo-controlled, parallel group studies in children and adolescents (aged 6–17 years) with Attention-Deficit Hyperactivity Disorder (ADHD). Two of the studies were flexible-dose studies (up to 425 mg/day), and the third was a fixed-dose study (340 mg/day for patients <30 kg and 425 mg/day for patients ≥30 kg). Although these studies showed statistically significant differences favoring modafinil over placebo in reducing ADHD symptoms as measured by the ADHD-RS (school version), there were 3 cases of serious rash including one case of possible SJS among 933 patients exposed to modafinil in this program. Modafinil is not approved for use in treating ADHD.

**8.5 Geriatric Use**

In clinical trials, experience in a limited number of modafinil-treated patients who were greater than 65 years of age showed an incidence of adverse reactions similar to other age groups. In elderly patients, elimination of modafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.

**Dose-Dependent Adverse Reactions**

Provision should be made when concomitantly administering MAO inhibitors and PROVIGIL.
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 behaviors). Modafinil produced psychoactive and euphoric effects and feelings consistent with other stimulants (e.g., methylphenidate, dextroamphetamine).

9.3 Dependence

In one placebo-controlled clinical trial, the effects of modafinil withdrawal were monitored following 9 weeks of modafinil use. There were no reported withdrawal symptoms with modafinil during 14 days of observation, although sleepiness returned in some patients.

10 OVERDOSAGE

In clinical trials, a total of 151 protocol-specified doses ranging from 1000 to 1600 mg/day (5 to 8 times the recommended daily dose of PROVIGIL) have been administered to 32 subjects, including 13 subjects who received doses of 1000 or 1200 mg/day for 7 to 21 consecutive days. In addition, several intentional acute overdoses occurred; the two largest being 4500 mg and 4000 mg taken by two subjects participating in foreign depression studies. None of these study subjects experienced any unexpected or life-threatening effects. Adverse reactions that were reported at these doses included excitement or agitation, insomnia, and slight or moderate elevations in liver enzymes. 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.

From postmarketing experience, there have been reports of fatal overdoses involving modafinil alone or in combination with other drugs. Symptoms most often accompanying PROVIGIL overdose have been agitation, restlessness, disorientation, confusion, hallucination, delirium, and seizures. Overdose may result in death.

11 DESCRIPTION

PROVIGIL (modafinil) is a racemic compound, whose enantiomers have different pharmacokinetics (e.g., the half-life of R-modafinil is approximately three times that of S-modafinil in adult humans). The enantiomers do not interconvert. At steady state, total exposure to R-modafinil is approximately three times that for S-modafinil. The trough concentration (Cmin) of circulating modafinil after once daily dosing consists of 90% of R-modafinil and 10% of S-modafinil. 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 R-modafinil are reached after 2-4 days of dosing.

Absorption

PROVIGIL is readily absorbed after oral administration, 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 testing. Oral bioavailability of modafinil in rats is approximately 60%, mainly to albumin. The potential for interactions of PROVIGIL with highly protein-bound drugs is considered to be minimal.

Distribution

PROVIGIL has an apparent volume of distribution of approximately 0.9 L/kg. In human plasma, modafinil is moderately bound to plasma protein (approximately 60%), mainly to albumin. The major route of elimination is metabolism (approximately 90%), primarily by the liver, with subsequent renal elimination of the metabolites. Urine alkalinization has no effect on the elimination of modafinil.

Metabolism and Elimination

Metabolism occurs through hydrolytic deamination, 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 and modafinil sulfone, 2-p-(lactic acid)-2'-hydroxy-1-phenyl-1-propionic acid and 2-hydroxy-1-phenyl-1-propanol, were inactive or did not appear to mediate the arousing effects of modafinil. In adults, decreases in trough levels of modafinil have sometimes been observed after multiple weeks of dosing, suggesting auto-induction, but the magnitude of the decreases and their inconsistency with the occurrence of clinical significance is minimal. Significant accumulation of modafinil sulfone has been observed after multiple doses due to its long elimination half-life of 40 hours. Auto-induction of metabolizing enzymes, most importantly cytochrome P-450 CYP3A4, has also been observed in vitro after incubation of primary cultures of human hepatocytes with modafinil and in vivo after extended administration of modafinil at 400 mg/day.

Specific Populations

Age

A slight decrease (approximately 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 not likely 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 (2.4) and Use in Specific Populations (8.5)].

Gender

The pharmacokinetics of modafinil are not affected by gender.

Race

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.
Hepatic Impairment

The pharmacokinetics and metabolism of modafinil were examined in patients with cirrhosis of the liver (6 men and 3 women). Three patients had stage B or C+ cirrhosis and 6 patients had stage C or C+ cirrhosis (per the Child-Pugh score criteria). 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 plasma concentrations of modafinil were doubled compared to normal patients [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

Drug Interactions

In vitro data demonstrated that modafinil weakly induces CYP1A2, CYP2B6, and possibly CYP3A activities in a concentration-related manner and that CYP2C19 activity is reversibly inhibited by modafinil. In vitro data also demonstrated that modafinil produced an apparent concentration-related suppression of expression of CYP2C9 activity. Other CYP activities did not appear to be affected by modafinil.

Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P450 Isoenzymes and Other Hepatic Enzymes

The existence of multiple pathways for modafinil metabolism, as well as the fact that a non-CYP-related pathway is the most rapid in metabolizing modafinil, suggest that there is a low probability of substantive effects on the overall pharmacokinetic profile of PROVIGIL due to CYP inhibition by concomitant medications. However, due to the partial involvement of CYP3A enzymes in the metabolic elimination of modafinil, coadministration of potent inducers of CYP3A4/5 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4/5 (e.g., ketoconazole, erythromycin) could alter the plasma concentrations of modafinil.

The Potential of PROVIGIL to Alter the Metabolism of Other Drugs by Enzyme Induction or Inhibition

- **Drugs Metabolized by CYP3A4/5**
  - In vitro data demonstrated that modafinil is a weak inducer of CYP3A activity in a concentration-related manner. Therefore, the blood levels and effectiveness of drugs that are substrates for CYP3A enzymes (e.g., steroidal contraceptives, cytosporine, cyclosporine, and triazolam) may be reduced after initiation of concomitant treatment with PROVIGIL [see Drug Interactions (7)].
  - Ethinyl Estradiol - Administration of modafinil to female volunteers once daily at 200 mg/day for 7 days followed by 400 mg/day for 21 days resulted in a mean 11% decrease in mean Cmax and 16% decrease in mean AUC(0→∞) of ethinyl estradiol (EE2; 0.035 mg; administered orally with norgestimate). There was no apparent change in the elimination rate of ethinyl estradiol.
  - Triazolam - In the drug interaction study between PROVIGIL and ethinyl estradiol (EE2), on the same days as those for the plasma sampling for EE, pharmacokinetics, a single dose of triazolam (0.125 mg) was also administered. Mean Cmax and AUC of triazolam were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment.
  - Cyclosporine - One case of an interaction between modafinil and cyclosporine, a substrate of CYP3A4, 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.
  - Midazolam - In a clinical study, concomitant administration of armodafinil 250 mg/day for 7 days resulted in a reduction in systemic exposure to midazolam by 32% after a single oral dose (5 mg) and 17% after a single intravenous dose (2 mg).
  - Quetiapine - In a separate clinical study, concomitant administration of armodafinil 250 mg with quetiapine (300 mg to 600 mg daily doses) resulted in a reduction in the mean systemic exposure of quetiapine by approximately 29%.

- **Drugs Metabolized by CYP1A2**
  - In vitro data demonstrated that modafinil is a weak inducer of CYP1A2 in a concentration-related manner. However, in a clinical study with armodafinil using caffeine as a probe substrate, no significant effect on CYP1A2 activity was observed.

- **Drugs Metabolized by CYP2B6**
  - In vitro data demonstrated that modafinil is a weak inducer of CYP2B6 activity in a concentration-related manner.

- **Drugs Metabolized by CYP2C9**
  - In vitro data demonstrated that modafinil produces an apparent concentration-related suppression of expression of CYP2C9 activity suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin and phenytoin) [see Drug Interactions (7)].
  - Warfarin: Concomitant administration of modafinil with warfarin did not produce significant changes in the pharmacokinetic profiles of R- and S-warfarin. However, since only a single dose of warfarin was tested in this study, an interaction cannot be ruled out [see Drug Interactions (7)].

- **Drugs Metabolized by CYP2C19**
  - In vitro data demonstrated that modafinil is a reversible inhibitor of CYP2C19 activity. CYP2C19 is also reversibly inhibited, with similar potency, by a circulating metabolite, modafinil sulfone. Although the maximum plasma concentrations of modafinil sulfone are much lower than those of parent modafinil, the combined effect of both compounds could produce sustained partial inhibition of the enzyme. Therefore, exposure to some drugs that are substrates for CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be increased when used concomitantly with PROVIGIL. [see Drug Interactions (7)].

PROVIGIL® (modafinil) tablets [C-IV]
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. 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 PROVIGIL showed a statistically significantly enhanced ability to remain awake on the MWT at each dose compared to placebo at final visit (Table 2). A statistically significantly greater number of patients treated with PROVIGIL at each dose showed improvement in overall clinical condition as rated by the CGI-C scale at final visit (Table 3). Nighttime sleep measured with polysomnography was not affected by the use of PROVIGIL.

14.2 Obstructive Sleep Apnea (OSA)

The effectiveness of PROVIGIL in improving wakefulness in patients with obstructive sleep apnea was associated with OSA was established in two multi-center, placebo-controlled clinical studies of patients who met the criteria for OSA. The criteria included (1) excessive sleepiness or insomnia, plus frequent episodes of impaired breathing during sleep, and associated features such as loud snoring, morning headaches and dry mouth upon awakening; or (2) excessive sleepiness or insomnia and polysomnography demonstrating one of the following: more than five obstructive apneas, each greater than 10 seconds in duration, per hour of sleep and one or more episodes of hypopnea. The MSLT was performed during a simulated night shift at the final visit (Table 2). A statistically significantly greater number of patients treated with PROVIGIL at each dose showed improvement in overall clinical condition as rated by the CGI-C scale at final visit (Table 3). A statistically significant greater number of patients treated with PROVIGIL showed improvement in overall clinical condition as rated by the CGI-C scale at final visit (Table 3). Nighttime sleep measured with polysomnography was not affected by the use of PROVIGIL.

Table 2. Average Baseline Sleep Latency and Change from Baseline at Final Visit (MWT and MSLT in minutes)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Measure</th>
<th>PROVIGIL 200 mg*</th>
<th>PROVIGIL 400 mg*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy</td>
<td>MWT</td>
<td>5.8</td>
<td>2.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Narcolepsy II</td>
<td>MWT</td>
<td>6.1</td>
<td>2.2</td>
<td>5.9</td>
</tr>
<tr>
<td>OSA</td>
<td>MWT</td>
<td>13.1</td>
<td>1.6</td>
<td>13.6</td>
</tr>
<tr>
<td>SWD</td>
<td>MSLT</td>
<td>2.1</td>
<td>1.7</td>
<td>-</td>
</tr>
</tbody>
</table>

*Significantly different than placebo for all trials (p<0.01 for all trials but SWD, which was p<0.05)

Table 3. Clinical Global Impression of Change (CGI-C) (Percent of Patients Who Improved at Final Visit)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Measure</th>
<th>PROVIGIL 200 mg*</th>
<th>PROVIGIL 400 mg*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy I</td>
<td></td>
<td>64%</td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>Narcolepsy II</td>
<td></td>
<td>58%</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>OSA</td>
<td></td>
<td>61%</td>
<td></td>
<td>68%</td>
</tr>
<tr>
<td>SWD</td>
<td></td>
<td>74%</td>
<td></td>
<td>-----</td>
</tr>
</tbody>
</table>

*Significantly different than placebo for all trials (p<0.01)
PROVIGIL® (modafinil) tablets [C-IV]

MEDICATION GUIDE
PROVIGIL® (pro-vij-el) C-IV
(modafinil)
Tablets

Read this Medication Guide before you start taking PROVIGIL and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about PROVIGIL?
PROVIGIL may cause serious side effects including a serious rash or a serious allergic reaction that may affect parts of your body such as your liver or blood cells. Any of these may need to be treated in a hospital and may be life-threatening.

Stop taking PROVIGIL and call your doctor right away or get emergency help if you have any of these symptoms:
• skin rash, hives, sores in your mouth, or your skin blisters and peels
• swelling of your face, eyes, lips, tongue, or throat
• trouble swallowing or breathing
• fever, shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine

If you have a severe rash with PROVIGIL, stopping the medicine may not keep the rash from becoming life-threatening or causing you to be permanently disabled or disfigured.

PROVIGIL is not approved for use in children for any medical condition. It is not known if PROVIGIL is safe or effective in children under 17 years of age.

What is PROVIGIL?
PROVIGIL is a prescription medicine used to improve wakefulness in adults who are very sleepy due to one of the following diagnosed sleep disorders:
• narcolepsy
• obstructive sleep apnea (OSA). PROVIGIL is used to treat excessive sleepiness, but not the obstruction or medical condition that is causing OSA. You should talk with your doctor about treatments for OSA before you start taking PROVIGIL and during treatment with PROVIGIL. PROVIGIL does not take the place of treatments that your doctor has prescribed for OSA. It is important that you continue to use these treatments as prescribed by your doctor.
• shift work disorder (SWD)
PROVIGIL will not cure these sleep disorders. PROVIGIL may help the sleepiness caused by these conditions, but it may not stop all your sleepiness. PROVIGIL does not take the place of getting enough sleep. Follow your doctor’s advice about good sleep habits and using other treatments.

PROVIGIL is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep PROVIGIL in a safe place to prevent misuse and abuse. Selling or giving away PROVIGIL may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Who should not take PROVIGIL?
Do not take PROVIGIL if you:
• are allergic or developed a rash to modafinil or armodafinil (NUVIGIL®) or any of the ingredients in PROVIGIL. See the end of this Medication Guide for a complete list of ingredients in PROVIGIL.

What should I tell my doctor before taking PROVIGIL?
Tell your doctor about all of your medical conditions including, if you:
• have a history of mental health problems, including psychosis
• have heart problems or had a heart attack
• have high blood pressure. Your blood pressure may need to be checked more often while taking PROVIGIL.
• have liver or kidney problems
• have a history of drug or alcohol abuse or addiction
• are pregnant or planning to become pregnant. It is not known if PROVIGIL will harm your unborn baby.

Pregnancy Registry: There is a registry for women who become pregnant during treatment with PROVIGIL. The purpose of this registry is to collect information about the safety of PROVIGIL during pregnancy. Contact the registry as soon as you learn that you are pregnant, or ask your doctor to contact the registry for you. You or your doctor can get information and enroll you in the registry by calling 1-866-404-4106.

• are breastfeeding. It is not known if PROVIGIL passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take PROVIGIL.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PROVIGIL and many other medicines can interact with each other, sometimes causing side effects. PROVIGIL may affect the way other medicines work, and other medicines may affect how PROVIGIL works. Your dose of PROVIGIL or certain other medicines may need to be changed.

Especially, tell your doctor if you use or take:
• a hormonal birth control method, such as birth control pills, shots, implants, patches, vaginal rings, and intrauterine devices (IUDs). Hormonal birth control methods may not work while you take PROVIGIL. Women who use one of these methods of birth control may have a higher chance for getting pregnant while taking PROVIGIL, and for one month after stopping PROVIGIL. Talk to your doctor about birth control choices that are right for you while taking PROVIGIL.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine. Your doctor or pharmacist will tell you if it is safe to take PROVIGIL and other medicines together. Do not start any new medicines with PROVIGIL unless your doctor has told you it is okay.

How should I take PROVIGIL?
Take PROVIGIL exactly as prescribed by your doctor. Your doctor will prescribe the dose of PROVIGIL that is right for you. Do not change your dose of PROVIGIL without talking to your doctor.
Your doctor will tell you the right time of day to take PROVIGIL.
• People with narcolepsy or OSA usually take PROVIGIL 1 time each day in the morning.
• People with SWD usually take PROVIGIL about 1 hour before their work shift.
• Do not change the time of day you take PROVIGIL unless you have talked to your doctor. If you take PROVIGIL too close to your bedtime, you may find it harder to go to sleep.
• You can take PROVIGIL with or without food.
• If you take more than your prescribed dose or if you take an overdose of PROVIGIL, call your doctor or go to the nearest hospital emergency room right away.

Symptoms of an overdose of PROVIGIL may include:
• trouble sleeping
• restlessness
• confusion
• feeling disoriented
• feeling excited
• hearing, seeing, feeling, or sensing things that are not really there (hallucinations)
• nausea and diarrhea
• a fast or slow heartbeat
• chest pain
• increased blood pressure

What should I avoid while taking PROVIGIL?
• Do not drive a car or do other dangerous activities until you know how PROVIGIL affects you. People with sleep disorders should always be careful about doing things that could be dangerous. Do not change your daily habits until your doctor tells you it is okay.
You should avoid drinking alcohol. It is not known how drinking alcohol will affect you when taking PROVIGIL.

What are possible side effects of PROVIGIL?

PROVIGIL may cause serious side effects. Stop taking PROVIGIL and call your doctor right away or get emergency help if you get any of the following:

- a serious rash or serious allergic reaction. (See “What is the most important information I should know about PROVIGIL?”)
- mental (psychiatric) symptoms, including:
  - depression
  - feeling anxious
  - hearing, seeing, feeling, or sensing things that are not really there (hallucinations)
  - an extreme increase in activity and talking (mania)
  - thoughts of suicide
  - aggressive behavior
  - other mental problems
- symptoms of a heart problem, including chest pain, abnormal heartbeat, and trouble breathing.

Common side effects that can happen in anyone who takes PROVIGIL include:

- headache
- back pain
- nausea
- feeling nervous
- stuffy nose
- diarrhea
- feeling anxious
- trouble sleeping
- dizziness
- upset stomach

PROVIGIL is not approved for use in children for any medical condition including Attention Deficit Hyperactivity Disorder (ADHD). In studies of PROVIGIL in children with narcolepsy, side effects included:

- Tourette's syndrome
- hostile behavior
- increase in sudden loss of muscle tone and severe muscle weakness
- increase in seeing and hearing things when falling asleep
- increase in suicidal thoughts
- low white blood count
- painful menstrual periods

Tell your doctor if you get any side effect that bothers you or that does not go away while taking PROVIGIL. These are not all the side effects of PROVIGIL. For more information, ask your doctor or pharmacist.

Some effects of PROVIGIL on the brain are the same as other medicines called “stimulants”. These effects may lead to abuse or dependence on PROVIGIL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROVIGIL?

- Store PROVIGIL at room temperature between 68° and 77° F (20° and 25° C).
- Keep PROVIGIL and all medicines out of the reach of children.

General information about the safe and effective use of PROVIGIL.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROVIGIL for a condition for which it was not prescribed. Do not give PROVIGIL to other people, even if they have the same symptoms you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about PROVIGIL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about PROVIGIL that is written for health professionals. For more information, call 1-888-483-8279.

What are the ingredients in PROVIGIL?

Active Ingredient: modafinil

Inactive Ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, and magnesium stearate.