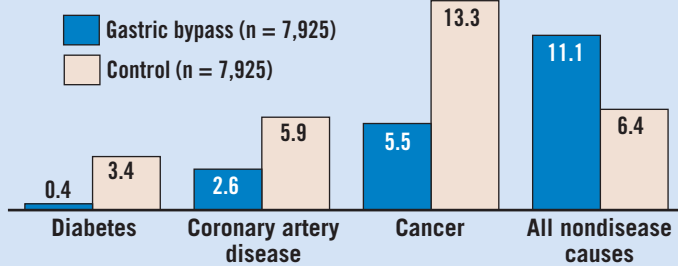


Mortality in Obese Patients During Mean 7.1-Year Follow-Up (per 10,000 person-years)



Note: All differences between groups are statistically significant.

Source: New England Journal of Medicine

Gastric Bypass Also Cuts Cancer, Diabetes, Heart Disease Mortality

BY FRAN LOWRY
Orlando Bureau

Severely obese individuals who opt to have gastric bypass surgery not only reduce their waistlines, they reduce their long-term total mortality as well, Utah researchers have reported.

Rates of death from diabetes, coronary artery disease, and cancer were all significantly lower in 7,925 patients who underwent gastric bypass between

1984 and 2002, Ted D. Adams, Ph.D., and his associates wrote.

Compared with a group of similarly obese control subjects who did not have the surgery, the gastric bypass group had a statistically significant, 40% decrease in adjusted long-term mortality from any cause during the mean follow-up of 7.1 years (37.6 vs. 57.1 deaths/10,000 person-years, *P* less than .001).

Deaths from coronary artery disease decreased by 56% (2.6 vs. 5.9/10,000 person-years, *P* = .006); deaths from diabetes were reduced by 92% (0.4 vs. 3.4/10,000 person-years, *P* = .005), and deaths from cancer dropped by 60% (5.5 vs. 13.3/10,000 person-years, *P* less than .001).

However, the rate of death from all nondisease causes, such as accidents and suicides, was 58% higher in the surgery group than in the control group, wrote Dr. Adams, professor in the division of cardiovascular genetics at the University of Utah, Salt Lake City, and his associates (*N. Engl. J. Med.* 2007;357:753-61).

The retrospective cohort study compared long-term mortality among severely obese men and women who had chosen gastric bypass surgery with that of an equal number (7,925) of severely obese persons who had applied for driver's licenses in the state of Utah. The two groups were matched for age, gender, and body mass index. The rates of death from any cause and from specific causes were determined with the use of the National Death Index.

Dr. Adams said that the reduced mortality from disease likely is related to the improvements in health that follow significant weight loss, such as reduced blood pressure, lower diabetes and coronary artery disease risk, and reduced sleep apnea. Dr. Adams also is a program director at the Health and Fitness Institute at Latter Day Saints Hospital, Salt Lake City.

When asked what he thought might be the reason for the higher rate of nondisease deaths in the bariatric surgery group, he commented that it was difficult to know. "We don't have any information about patients' psychosocial makeup or anything like that. There have been suggestions that some individuals who have undergone gastric bypass surgery may go on to increase their intake of alcohol."

He also suggested that the significant weight loss associated with bariatric surgery may lead patients to become more physically active, and thus at greater exposure to accidents. "Patients lose, on average, more than 100 pounds."

The finding that cancer deaths were lower after bypass surgery was a surprise, especially because this occurred within the relatively short time frame of 7.1 years, Dr. Adams said.

"This reduction persisted even after we excluded prevalent cancers and deaths from cancer occurring within 5 years after baseline. It really interested us that in such a short period of time we would see such a dramatic reduction in cancer."

PROVIGIL® (modafinil) TABLETS [C-IV]

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information
INDICATIONS AND USAGE: PROVIGIL is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypoxemia syndrome, and shift work sleep disorder. In OSAS, PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating PROVIGIL. If PROVIGIL is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary. In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

CONTRAINDICATIONS: Known hypersensitivity to modafinil, amodafinil (the R-enantiomer of PROVIGIL) or its inactive ingredients.

WARNINGS: Serious Rash, including Stevens-Johnson Syndrome

Serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children in association with the use of PROVIGIL. PROVIGIL is not approved for use in pediatric patients for any indication. In clinical trials of PROVIGIL, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in pediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome (SJS) and 1 case of apparent multi-organ hypersensitivity reaction. Several of the cases were associated with fever and other abnormalities (e.g., vomiting, leukopenia). The median time to rash that resulted in discontinuation was 13 days. No such cases were observed among 380 pediatric patients who received placebo. No serious skin rashes have been reported in adult clinical trials (0 per 4,254) of PROVIGIL. Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. The reporting rate of TEN and SJS associated with PROVIGIL 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 PROVIGIL. Nearly all cases of serious rash associated with PROVIGIL 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 also occur with PROVIGIL, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, PROVIGIL should ordinarily 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.

Angioedema and Anaphylactoid Reactions: One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm), were observed among 1,595 patients treated with amodafinil. No such cases were observed in PROVIGIL clinical trials. Angioedema has been reported in postmarketing experience with PROVIGIL. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness). **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 PROVIGIL. 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 associated with PROVIGIL. 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 (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. 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.

Persistent Sleepiness: Patients with abnormal levels of sleepiness who take PROVIGIL should be advised that their level of wakefulness may not return to normal. Patients should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. **Psychiatric Symptoms:** Psychiatric adverse experiences have been reported in patients treated with PROVIGIL. Postmarketing adverse events associated with the use of PROVIGIL have included mania, delusions, hallucinations, and suicidal ideation, some resulting in hospitalization. Many, but not all, patients had a prior psychiatric history. In the adult PROVIGIL controlled trial database, psychiatric symptoms resulting in treatment discontinuation (at a frequency ≥0.3%) and reported more often in patients treated with PROVIGIL compared to those treated with placebo were anxiety (1%), nervousness (1%), insomnia (<1%), confusion (<1%), agitation (<1%), and depression (<1%). 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.

PRECAUTIONS: Diagnosis of Sleep Disorders: PROVIGIL should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of narcolepsy, OSAS, and/or SWSD has been made in accordance with ICSD or DSM diagnostic criteria. **General:** 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 they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities. **CPAP Use in Patients with OSAS:** If PROVIGIL is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary. **Cardiovascular System:** PROVIGIL has not been evaluated in patients with a recent history of myocardial infarction or unstable angina, and such patients should be treated with caution. It is recommended that PROVIGIL tablets not be used 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. Such signs may include but are not limited to ischemic ECG changes, chest pain, or arrhythmia. If new onset of any of these symptoms occurs, consider cardiac evaluation. Increased monitoring of blood pressure may be appropriate in patients on PROVIGIL. **Patients Using Steroidal Contraceptives:** The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL tablets and for one month after discontinuation of therapy (See **PRECAUTIONS, Drug Interactions**). Alternative or concomitant methods of contraception are recommended for patients treated with PROVIGIL tablets; and for one month after discontinuation of PROVIGIL. **Patients Using Cyclosporine:** The blood levels of cyclosporine may be reduced when

used with PROVIGIL (See **PRECAUTIONS, Drug Interactions**). Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when these drugs are used concomitantly. **Patients with Severe Hepatic Impairment:** In patients with severe hepatic impairment, with or without cirrhosis, PROVIGIL should be administered at a reduced dose. **Patients with Severe Renal Impairment:** There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment. **Elderly Patients:** 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. **Information for Patients:** Physicians are advised to discuss the following with patients for whom they prescribe PROVIGIL. PROVIGIL is indicated for patients who have abnormal levels of sleepiness. PROVIGIL has been shown to improve, but not eliminate this abnormal tendency to fall asleep. Therefore, patients should not alter their previous behavior with regard to potentially dangerous activities (e.g., driving, operating machinery) or other activities requiring appropriate levels of wakefulness, until and unless treatment with PROVIGIL has been shown to produce levels of wakefulness that permit such activities. Patients should be advised that PROVIGIL is not a replacement for sleep. Patients should be informed that it may be critical that they continue to take their previously prescribed treatments. Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking PROVIGIL. Patients should be advised to contact their physician if they experience chest pain, rash, depression, anxiety, or signs of psychosis or mania. **Pregnancy:** Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should notify their physician if they are breast feeding. **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 drug interactions.

Alcohol: Patients should be advised that it is prudent to avoid alcohol while taking PROVIGIL. **Allergic Reactions:** Patients should be advised to stop taking PROVIGIL and to notify their physician if they develop a rash, hives, mouth sores, blisters, peeling skin, trouble swallowing or breathing or a related allergic phenomenon. **Drug Interactions: CNS Active Drugs:** Concomitant administration of PROVIGIL with methylphenidate or dextroamphetamine produced no significant alterations on the pharmacokinetic profile of PROVIGIL or either stimulant, even though the absorption of PROVIGIL was delayed by approximately one hour. The coadministration of a single dose of clomipramine (50 mg) on the first three days of treatment with PROVIGIL (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 PROVIGIL. In the drug interaction study between PROVIGIL and ethinyl estradiol (EE), 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 C_{max} and AUC_{0-12} of triazolam were decreased by 42% and 53%, respectively, and its elimination half-life was decreased by approximately 1 hour after the PROVIGIL treatment. Interaction studies with monoamine oxidase (MAO) inhibitors have not been performed. Therefore, caution should be used when concomitantly administering MAO inhibitors and PROVIGIL. **Other Drugs:** More frequent monitoring of prothrombin times/INR is advised when PROVIGIL is coadministered with warfarin. Administration of PROVIGIL 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 C_{max} and 18% decrease in AUC_{0-12} of ethinyl estradiol. One case of an interaction between PROVIGIL 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 PROVIGIL 200 mg/day, cyclosporine blood levels were decreased by 50%. Dosage adjustment for cyclosporine may be needed.

Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: In vitro studies using primary human hepatocyte cultures, PROVIGIL was shown to slightly induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on these enzymes for their clearance, since lower blood levels of such drugs could result (See **Other Drugs** above). The exposure of human hepatocytes to PROVIGIL in vitro produced an apparent concentration-related suppression of expression of CYP2C9 activity suggesting that there is a potential for a metabolic interaction between PROVIGIL and the substrates of this enzyme (e.g., S-warfarin and phenytoin). In vitro studies using human liver microsomes showed that PROVIGIL reversibly inhibited CYP2C19 at pharmacologically relevant concentrations of PROVIGIL. CYP2C19 is also reversibly inhibited, with similar potency, by a circulating metabolite, modafinil sulfone. The combined effect of both compounds could produce sustained partial inhibition of the enzyme. Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination upon coadministration with PROVIGIL and may require dosage reduction and monitoring for toxicity. CYP2C19 also 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, 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. In addition, due to the partial inhibition of CYP3A4 in the metabolic elimination of PROVIGIL, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the plasma levels of PROVIGIL. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in which PROVIGIL was administered in the diet to mice for 78 weeks and to rats for 104 weeks. The highest dose studied is 1.5 (mouse) or 3 (rat) times greater than the recommended adult human daily dose of PROVIGIL (200 mg) on a mg/m² basis. There was no evidence of tumorigenicity associated with PROVIGIL administration in these studies. However, since the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose, a subsequent carcinogenicity study was conducted in the Tg.AC transgenic mouse. Doses evaluated in the Tg.AC assay were 125, 250, and 500 mg/kg/day, administered daily. There was no evidence of tumorigenicity associated with PROVIGIL administration; however, this dermal model may not adequately assess the carcinogenic potential of an orally administered drug. **Mutagenesis:** PROVIGIL demonstrated no evidence of mutagenic or clastogenic potential in a series of in vitro assays in the absence or presence of metabolic activation, or in vivo assays. PROVIGIL was also negative in the unscheduled DNA synthesis assay in rat hepatocytes. **Impairment of Fertility:** Oral administration of PROVIGIL (doses of up to 480 mg/kg/day) to male and female rats prior to and throughout mating, and continuing in females through day 7 of gestation produced an increase in the time to mate at the highest dose; no effects were observed on other fertility or reproductive parameters. The no-effect dose of 240 mg/kg/day was associated with a plasma modafinil exposure (AUC) approximately equal to that in humans at the recommended dose of 200 mg. **Pregnancy: Pregnancy Category C:** In studies conducted in rats and rabbits, developmental toxicity was observed at clinically relevant exposures. There are no adequate and well-controlled studies in pregnant women. Two cases of intrauterine growth retardation and one case of spontaneous abortion have been reported in association with amodafinil and modafinil. Whether the cases reported are drug-related is unknown. PROVIGIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. **Nursing Mothers:** It is not known whether PROVIGIL or its metabolites are excreted in human milk. Caution should be exercised

when PROVIGIL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients, below age 16, have not been established. Serious skin rashes, including erythema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS) have been associated with PROVIGIL use in pediatric patients (See **WARNINGS, Serious Rash, including Stevens-Johnson Syndrome**). In the controlled and open-label clinical studies, treatment emergent adverse events 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 PROVIGIL experienced dysmenorrhea compared to 0 of 10 girls who received placebo.

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

ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 3500 patients, of whom more than 2000 patients with excessive sleepiness associated with primary disorders of sleep and wakefulness were given at least one dose of PROVIGIL. In clinical trials, PROVIGIL has been found to be generally well tolerated and most adverse experiences were mild to moderate. The most commonly observed adverse events (≥5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in the placebo-controlled clinical studies in primary disorders of sleep and wakefulness were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. In the placebo-controlled clinical trials, 8% of the 934 patients who received PROVIGIL discontinued due to an adverse experience. 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%). **Incidence in Controlled Trials:** The incidence of adverse experiences that occurred at a rate of ≥1% and were more frequent in adult patients treated with PROVIGIL than in placebo-treated patients in the principal trials are listed below. Consult full prescribing information on adverse events. **Body as a Whole:** Headache, back pain, flu syndrome, chest pain, chills, neck rigidity. **Cardiovascular:** Hypertension, tachycardia, palpitation, vasodilatation. **Digestive:** Nausea, diarrhea, dyspepsia, dry mouth, anorexia, constipation, abnormal liver function, flatulence, mouth ulceration, thirst. **Hemic/Lymphatic:** Eosinophilia. **Metabolic/Nutritional:** Edema. **Nervous:** Nervousness, insomnia, anxiety, dizziness, depression, paresthesia, somnolence, hypotonia, dyskinesia, hyperkinesia, agitation, confusion, tremor, emotional lability, vertigo. **Respiratory:** Rhinitis, pharyngitis, lung disorder, epistaxis, asthma. **Skin/Appendages:** Sweating, herpes simplex. **Special Senses:** Amblyopia, abnormal vision, taste perversion, eye pain. **Urogenital:** Urine abnormality, hematuria, pyuria. **Dose Dependence of Adverse Events:** In the adult placebo-controlled clinical trials which compared doses of 200, 300, and 400 mg/day of PROVIGIL and placebo, the only adverse events that were clearly dose related were headache and anxiety. **Vital Sign Changes:** The requirement for antihypertensive medication was slightly greater in patients on PROVIGIL compared to placebo. **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 Phase 1, 2, and 3 studies. In these 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 subjects, 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 on PROVIGIL. No differences were apparent in alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. **ECG Changes:** No treatment-emergent pattern of ECG abnormalities was found in placebo-controlled clinical trials following administration of PROVIGIL. **Postmarketing Reports:** The following adverse reactions have been identified during post-marketing use of PROVIGIL. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to PROVIGIL.

Hematologic: agranulocytosis

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: 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 psychotropic and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In some studies, PROVIGIL was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant abuse, for signs of misuse or abuse. **Withdrawal:** Following 9 weeks of PROVIGIL use in one US clinical trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcotic-dependent patients.

OVERDOSAGE: Human Experience: 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 200 mg) 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 experiences that were reported at these doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. 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 post-marketing experience, there have been no reports of fatal overdoses involving PROVIGIL alone (doses up to 12 grams). Overdoses involving multiple drugs, including PROVIGIL, have resulted in fatal outcomes. Symptoms most often included insomnia, restlessness, disorientation, excitation, confusion, hallucination, nausea, diarrhea, tachycardia, bradycardia, hypotension, and chest pain. Cases of accidental ingestion/overdose have been reported in children as young as 11 months of age. The highest reported accidental ingestion on a mg/kg basis occurred in a three-year-old boy who ingested 800-1000 mg (50-63 mg/kg) of PROVIGIL. The child remained stable. The symptoms associated with overdose in children were similar to those observed in adults. **Overdose Management:** No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. 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.

Manufactured for: Cephalon, Inc., Frazer, PA 19355

For more information about PROVIGIL, please call Cephalon Medical Services at 1-800-896-5855 or visit our Web site at www.PROVIGIL.com

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