

CLINICAL CAPSULES

Flu Shot Safe for Children

No evidence of serious adverse events within 2 weeks of vaccination appeared in a population-based study of 251,600 children, mean age 10 years, who received the trivalent inactivated influenza vaccine, said Eric K. France, M.D., of Kaiser Permanente Colorado, Denver, and his colleagues. The study spanned four flu seasons and two half-seasons between 1993 and 1999 (Arch. Pediatr. Adolesc. Med. 2004;158:1031-6). In a primary analysis, only one case of uncomplicated diabetes mellitus was positively associated with vac-

ination. Subanalysis revealed one case each of impetigo, atopic dermatitis, and a renal and ureteral disorder not otherwise specified. Overall, vaccinated children were significantly less likely to visit a doctor for an illness during the postvaccination period, compared with a control period. Reasons for this may include the fact that children are more likely to be vaccinated when they are healthy and that children are less likely to visit a doctor for low-grade fever, limb soreness, and irritability during the postvaccination period, because parents expect these symptoms after vaccination.

Hepatitis B Incidence Declines

Incidence of acute hepatitis B declined by 89% among U.S. children aged 19 years and younger between 1990 and 2002, according to data collected by the Centers for Disease Control and Prevention (MMWR 2004;53:1015-8). A total of 13,829 cases were reported during this period. Overall, incidence per 100,000 children declined by 92% among Asian/Pacific Islanders, 88% among whites, 88% among blacks, and 84% among American Indians/Native Alaskans. The greatest declines coincided with greater hepatitis B vaccination rates in children aged 19-35 months, which increased from 16% in

1992 to 90% in 2002, and in adolescents aged 13-15 years, which increased from almost 0% in 1992 to 67% in 2002.

Iron Deficiency's Role in ADHD

Children with attention-deficit hyperactivity disorder had significantly lower levels of iron, compared with controls in a study of 53 children aged 4-14 years, said Eric Konofal, M.D., of Hôpital de Paris, and his colleagues.

The mean serum iron level was 23 ng/mL in the children with ADHD, compared with 44 ng/mL in the controls. In addition, 42 (84%) of the ADHD children had iron levels considered abnormally low—below 30 ng/mL—compared with 5 (18%) of the 27 controls (Arch. Pediatr. Adolesc. Med. 2004;158:1113-5). Low levels of iron may hamper the development of the central nervous system and consequently contribute to the likelihood of behavioral disorders, so children with ADHD might benefit from iron supplements.

Neighborhoods and Violent Girls

Adolescent girls who mature early and live in economically disadvantaged neighborhoods committed three times as many violent acts as early maturers in less disadvantaged neighborhoods, said Dawn Obeidallah, Ph.D., of Harvard Medical School, Boston, and her colleagues.

The investigators used census data to characterize neighborhoods in the Chicago area and interviewed 501 adolescent girls and their families twice during a 3-year period (J. Am. Acad. Child Adolesc. Psychiatry 2004;43:1460-8).

Overall, 121 girls had engaged in violent behavior at the time of the second interview: 18% of the early maturers, 48% of on-time maturers, and 33% of late maturers. Approximately 50% of the girls were Hispanic, 36% were black, and 14% were white, and 20% of early maturing black girls, 14% of early maturing Hispanic girls, and 7% of early maturing white girls had engaged in violence at the time of the second interview.

Infant Hypoglycemia

Significant risk factors for prolonged hypoglycemia in infants include gestational age, 1-minute Apgar scores, male sex, and weight in the lowest quartile.

Prolonged hypoglycemia was present in 55 of 594 (9%) small-for-gestational-age infants, Dr. Eugenia K. Pallotto said in a poster presented at the annual meeting of the Society for Perinatal and Pediatric Epidemiologic Research in Salt Lake City.

The infants were born between 1998 and 2001 and were in the 10th percentile or below for gestational age. Prolonged hypoglycemia was defined as blood sugar of 40 mg/dL or less occurring beyond 72 hours of life.

One-minute Apgar scores of less than 5, male gender, young gestational age, and birth weight in the lowest quartile of the study group were significantly associated with prolonged hypoglycemia, said Dr. Pallotto of the University of Missouri-Kansas City. Hypoglycemic episodes were longer among premature infants, compared with those born at term. Prospective monitoring of high-risk infants may improve glucose control and reduce unrecognized hypoglycemic episodes, she said.

—From staff reports

PROVIGIL® (modafinil) TABLETS [C-IV]

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL or its inactive ingredients.

WARNINGS: Patients with abnormal levels of sleepiness should be advised that their level of wakefulness 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 specific activities.

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 either narcolepsy, OSAHS, and/or SWSD has been made in accordance with ICD-9 or DSM diagnostic criteria. Such an evaluation usually consists of a complete history and physical examination, and it may be supplemented with testing in a laboratory setting.

CPAP Use in Patients with OSAHS: In OSAHS, 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.

General: 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.

Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after discontinuation of PROVIGIL.

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 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.

Patients with a recent history of MI or unstable angina should be treated with caution.

Blood pressure monitoring in short-term controlled trials showed no clinically significant changes in mean systolic and diastolic blood pressure in patients receiving PROVIGIL as compared to placebo. However, 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 differential use was slightly larger when only studies in OSAHS 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 blood pressure may be appropriate in patients on PROVIGIL.

Central Nervous System: There have been reports of psychotic episodes associated with PROVIGIL use. 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: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.

Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.

Elderly Patients: Elderly patients may have diminished renal and/or hepatic function; therefore, dosage reduction should be considered.

Information for Patients: Physicians are advised to discuss the following with patients taking 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 (eg, 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 (eg, patients with OSAHS receiving CPAP should continue to do so). 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.

Pregnancy: Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation of therapy.

Nursing: Patients should notify their physician if they are breast feeding.

Concomitant Medication: Patients should 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: It is prudent to avoid alcohol while taking PROVIGIL.

Allergic Reactions: Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions: CNS Active Drugs: In a single-dose study, simultaneous administration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour.

In a single-dose study, simultaneous administration of PROVIGIL 200 mg with dextroamphetamine 10 mg delayed absorption of PROVIGIL by approximately 1 hour.

Coadministration of a single dose of clomipramine 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported.

In the drug interaction study between PROVIGIL and ethinyl estradiol (EE₂), on the same days as those for the plasma sampling for EE₂ pharmacokinetics, a single dose of triazolam 0.125 mg was also administered. Mean C_{max} and AUC₀₋₂₄ of triazolam were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment.

In the absence of interaction studies with monoamine oxidase (MOA) inhibitors, caution should be exercised.

Other Drugs: No significant changes in the pharmacokinetics of warfarin occurred in healthy subjects given 1 dose of warfarin 5 mg following chronic administration of PROVIGIL. However, more frequent monitoring of prothrombin times/INR is advised when PROVIGIL is coadministered with warfarin.

PROVIGIL once daily 200 mg/day for 7 days followed by 400 mg/day for 21 days decreased ethinyl estradiol C_{max} and AUC₀₋₂₄ by a mean 11% and 18% with no apparent change in the elimination rate.

One interaction between PROVIGIL and cyclosporine has been reported in a 41-year-old female. After 1 month of PROVIGIL 200 mg/day, cyclosporine blood levels 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 primary human hepatocytes, PROVIGIL slightly induced CYP1A2, CYP2B6 and CYP3A4 in a dose-dependent manner. *In vitro* experiments do not necessarily predict response *in vivo*; caution should be exercised when PROVIGIL is coadministered with drugs that are metabolized by enzymes.

In human hepatocytes, PROVIGIL produced a dose-related suppression of CYP2C9 activity suggesting a potential for metabolic interaction between PROVIGIL and substrates of this enzyme (eg, S-warfarin and phenytoin). In healthy volunteers, chronic PROVIGIL treatment had no significant effect on single-dose pharmacokinetics of warfarin vs placebo.

In human liver microsomes, PROVIGIL and modafinil sulfone reversibly inhibited CYP2C19. Both compounds combined could produce sustained partial enzyme inhibition. Drugs largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination with PROVIGIL coadministration and may require dose reduction and monitoring for toxicity.

CYP2C19 provides ancillary metabolism of some tricyclic antidepressants (eg, clomipramine and desipramine) primarily metabolized by CYP2D6. In tricyclic users deficient in CYP2D6, CYP2C19 metabolism may be substantially increased. PROVIGIL may elevate tricyclics in this patient subset. A reduction in tricyclic dose may be needed.

Due to partial involvement of CYP3A4 elimination of PROVIGIL, coadministration of potent inducers of CYP3A4 (eg, carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) could alter modafinil plasma levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: The highest dose studied in carcinogenesis studies represent 1.5 times (mouse) or 3 times (rat) the maximum human daily dose of 200 mg on a mg/m² basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated.

Mutagenesis: There was no evidence of mutagenic or clastogenic potential of PROVIGIL.

Impairment of Fertility: PROVIGIL was administered orally to male and female rats prior to and throughout

mating and gestation at up to 23 times the recommended human dose of 200 mg/day on a mg/m² basis with no effect on fertility.

Pregnancy: Pregnancy Category C: PROVIGIL administered orally to pregnant rats throughout the period of organogenesis caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of hydronephrosis and skeletal variations in the offspring at a dose of 200 mg/kg/day (10 times the recommended human dose of 200 mg/day on a mg/m² basis) but not at 100 mg/kg/day. However, in a subsequent study of up to 480 mg/kg/day (23 times the recommended human dose on a mg/m² basis), which included maternally toxic doses, no adverse effects on embryofetal development were seen.

PROVIGIL administered orally to pregnant rabbits throughout the period of organogenesis at doses up to 100 mg/kg/day (10 times the recommended human dose on a mg/m² basis) had no effects on embryofetal development.

However, in a subsequent study in pregnant rabbits, increased resorptions, and increased alterations in fetuses from a single litter (open eye lids, fused digits, rotated limbs), were observed at 180 mg/kg/day (17 times the recommended human dose on a mg/m² basis), a dose that was also maternally toxic.

PROVIGIL administered orally to rats throughout gestation and lactation at doses up to 200 mg/kg/day (5 times the recommended human dose on a mg/m² basis), had no effects on the postnatal development of the offspring. There are no adequate and well-controlled studies in pregnant women. 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 individuals below 16 years of age have not been established. Leukopenia has been reported in pediatric patients taking PROVIGIL.

GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.

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 1 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 (B5%) 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%). The incidence of adverse experiences that occurred at a rate of B1% and were more frequent in patients treated with PROVIGIL than in placebo 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, hypertension, 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 Dependency: In the placebo-controlled clinical trials the only adverse events that were clearly dose related were headache and anxiety.

Vital Sign Changes: While there was no consistent change in mean values of heart rate or systolic and diastolic blood pressure, 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: Mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were 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 Reporting: In addition to the adverse events observed during clinical trials, the following adverse events have been identified during post-approval use of PROVIGIL in clinical practice. Because these adverse events are reported voluntarily from a population of uncertain size, reliable estimates of their frequency cannot be made.

Hematologic: Agranulocytosis

Central Nervous System: Symptoms of psychosis, symptoms of mania

Hypersensitivity: Urticaria (hives), angioedema

DRUG ABUSE AND DEPENDENCE: 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 vitro*, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release.

PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. 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 (eg, methylphenidate, amphetamine, or cocaine) abuse. In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.

Withdrawal: Following 9 weeks of PROVIGIL use in 1 US clinical trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE: Human Experience: In clinical trials, a total of 151 protocol-specified doses B1000 mg/day (5 to 8 times the recommended daily dose of 200 mg) had 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 accompanying PROVIGIL overdose, alone or in combination with other drugs have included insomnia, restlessness, disorientation, confusion, excitation, hallucination, nausea, diarrhea, tachycardia, bradycardia, hypertension, 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 alkalization in enhancing drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

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

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

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