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Volume 8 - Number 2

The International Journal of Neuropsychiatric Medicine

Sleep Disorders

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Author Guidelines

Introduction

CNS Spectrums is an Index Medicus journal that publishes original scientific literature and reviews on a wide variety of neuroscientific topics of interest to the clinician. CNS Spectrums will publish 12 issues in 2003. As the immense prevalence of comorbid diseases among patients seen by psychiatrists and neurologists increases, these physicians will jointly diagnose and treat the neuropsychiatrically ill. Our mission is to provide these physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry; therefore, manuscripts that address crossover issues germane to neurology and psychiatry will be given immediate priority.

Scope of Manuscripts

CNS Spectrums will consider the following types of articles for publication:

Original Reports: Original reports present methodologically sound original data.

Reviews: Reviews are overview articles that summarize and synthesize the literature on various topics in a scholarly and clinically relevant fashion. Suitable topics include mood disorders, schizophrenia and related disorders, personality disorders, substance-use disorders, anxiety disorders, neuroscience, psychosocial aspects of psychiatry, child psychiatry, geriatric psychiatry, and other topics of interest to clinicians. Original flowcharts designed to aid the clinician in diagnosis and treatment will be considered for publication in reviews and are encouraged.

Case Reports: Single or multiple case reports will be considered for publication.

Letters to the Editor: Letters will be considered for publication.

Manuscript Submission

General information: Two copies of the manuscript with a letter on the author's letterhead should be submitted to Jack M. Gorman, Editor (or, in Europe, to Joseph Zohar, International Editor), c/o MBL Communications, 333 Hudson Street, 7th Floor, New York, NY 10013; (F) 212.328.0600. Authors are also required to submit their manuscripts on computer disk in Microsoft Word format. Disks should be labeled with the word processing program, title of paper, and lead author's name. Accepted manuscripts and letters will be edited for clarity and style.

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Manuscript Preparation

Length: Reviews and Original Reports should not exceed 5,000 words (excluding References). Letters should not exceed 1,500 words. Single Case Reports should not exceed 3,750 words and may be submitted with a photograph, if applicable. Diagnostic/treatment algorithms (see Reviews) should contain an extensive introduction, flowchart or series of graphs that fill 8–12 journal pages, and a concise summary.

Spacing: One space should be left after commas and periods. Manuscripts should be double-spaced.

Abstract: Authors must provide a brief abstract.

References: American Medical Association style. See the following examples:

- 1. Jones J. Necrotizing Candida esophagitis. JAMA. 1980;244:2190-2191.
- 2. Stryer L. Biochemistry. 2nd ed. San Francisco, Calif: WH Freeman Co; 1980:559-596.

Continuing Medical Education: Authors must submit four multiple-choice questions (two Type A and two Type K), with answers.

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Submission Checklist

- □ Original manuscript plus one copy, with cover letter on author's letterhead
- Copies of permission letters to reproduce previously published and unpublished material
- \square A brief abstract of the article

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- $\hfill\square$ Four CME multiple-choice questions with answers
- □ Disk labeled with the word processing program, title of paper, and lead author's name
- □ Names and addresses of five potential reviewers



Time for wakefulness

PROVIGIL® (modafinil) TABLETS

BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information

INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy

CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL

PRECAUTIONS: 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.

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 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.

Central Nervous System: 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

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 treatment.

Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL: Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased of the potential increased of the potential increased of the potential increased of the potential of the potential increased of the potential increased of the potential increased of the potential incre risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. *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, coadministration of PROVIGIL 200 mg with methylphenidate 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The 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 a single-dose study with PROVIGIL (50, 100 or 200 mg) and triazolam 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with monoamine oxidase (MAO) inhibitors, caution should be exercised. monoamme oxidase (MAQ) inhibitors, caution should be exercised. Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P-A50 Isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in ~20% mean decrease in PROVIGIL plasma trough

concentration suggesting that PROVIGIL may have caused induction

of its metabolism. Coadministration of potent inducers of CYP3A4 (eg, ketoconazole, itraconazole) could (eg, carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) could alter the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant in vivo effects of PROVIGIL based on in vitro data are:

A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed

A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).

An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, phenytoin). A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol,

phenytoin, S-mephenytoin).

In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg, clomipramine, desipramine).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended 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*: When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m² basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects on fertility

Pregnancy: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m² basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m² basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m² basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk

investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy. Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to a nursing woman. PEDIATRIC USE: Safely and effectiveness in individuals below 16 years of age have not been established.

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically

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 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate The most commonly observed adverse events (\geq 5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of \geq 1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.

Body as a whole: Headache,' chest pain, neck pain, chills, rigid neck, fever/chills

Digestive: Nausea,1 diarrhea,1 dry mouth,1 anorexia,1 abnormal liver function,2 vomiting, mouth ulcer, gingivitis, thirst Respiratory system: Rhinitis, pharyngitis, lung disorder, dyspnea, asthma, epistaxis Nervous system: Nervousness, dizziness, depression, anxiety, cataplexy, insomnia, paresthesia,

dyskinesia,1 hypertonia, confusion, amnesia, emotional lability, ataxia, tremor

Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope

Hemic/Lymphatic: Eosinophilia

Special senses: Amblyopia, abnormal vision

Metabolic/Nutritional: Hyperglycemia, albuminuria

Musculo-skeletal: Joint disorder Skin/Appendages: Herpes simplex, drv skin

Urogenital: Abnormal urine, urinary retention, abnormal ejaculation

Incidence ≥5%,² Elevated liver enzymes,³ Oro-facial dyskinesias,⁴ Incidence adjusted for gender

Dose Dependency: In US trials, the only adverse experience more frequent (\geq 5% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.

Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.

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

Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not

clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilitubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.

ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL Postmarketing Reports

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

DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to 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. Patients should be observed for signs of misuse or abuse (eg. incrementation of doses or drug-seeking behavior). 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 trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

OVERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Overdose Management:** No specific antidote to the toxic effects of 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 suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician Should consider contacting a poison-control center on the treatment of any overdose. Manufactured for: **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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Time for wakefulness

A unique wake-promoting agent

PROVIGIL promotes daytime wakefulness, improving patients' ability to participate in daily activities—with no effect on nighttime sleep.¹⁻³

Long-term safety

The long-term safety profile of PROVIGIL has been demonstrated for up to 136 weeks.⁴

PROVIGIL was generally well tolerated. Most frequently reported adverse events in clinical trials were headache, nausea, nervousness, anxiety, infection, and insomnia. Most adverse events were mild to moderate. PROVIGIL may interact with drugs that inhibit, induce, or are metabolized by cytochrome P450 isoenzymes.

Dosing

Recommended dose for PROVIGIL is 200 mg taken orally once daily in the morning. Both PROVIGIL doses, 200 mg and 400 mg QD, were effective.

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

References: 1. PROVIGIL full prescribing information. **2.** US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol.* 1998;43:88-97. **3.** US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology.* 2000;54:1166-1175. **4.** Data on file, Cephalon, Inc.



Please see brief summary of prescribing information on adjacent page. For more information, call 1-800-896-5855 or visit our Website at www.PROVIGIL.com.

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CNS Spectrums' editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. It serves as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of centeral nervous system disease, illness, or trauma. BRIEF SUMMARY. See package insert for full prescribing information. CONTRAINDICATIONS: Hypersensitivity to venlataxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. WARNINGS: Potential for Interaction with Monoamine Oxidase Oxidase Inhibitors (MAUIs) is contraindicated, wahnings, rotential for interaction with monitorianine oxidase inhibitors—Adverse reactions, some services, have been reported in patients who were recently discontinued from an MAOI and started on ventataxine, or who recently had ventataxine therapy discontinued prior to initiation of an MAOI. These reactions included themor, myocionus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic mailignant syndrome, seizures, and death. It is recommended that Effexor XR not be used in combination with an MAOI, or within at least 14 days of continuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Sustained Hypertension—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Experience with immediate release venlafaxine showed that sustained hypertension was dose related. It is recommended that patients receiving Effexor XR have regular monitoring of BP. For patients who experience a sustained increase in BP either dose reduction or discontinuation should be considered. PRECAUTIONS: General-Insomnia and Nervousness: Treatment-emergent insomnia and nervousness have been reported. Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients The rousiness have been reported. Insomina and nervous ress each red to brig discontinuation in 0.2% of the patients in Phase 3 depression studies. In Phase 3 deneralized Anxiety Disorder (GAD) trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of patients. *Changes in Appetite/Weight*: Treatment-emergent anorexia has been reported. A loss of 5% or more of body weight occurred in 7% of patients in placebo-controlled depression trials. A loss of 7% or more of body weight occurred in 3% of patients in placebo-controlled GAD trials. The safety and efficacy of ventativane therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. **Activation of Mania/Hypomania**: Mania or hypomania has occurred during short-term depression studies. Effexor XR should be used cautiously in patients with a history of mania. Hyponatremia: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example volume-depleted, elderly, or taking diuretics. *Mydriasis*: Mydriasis has been reported; therefore patients with raised Transcutar pressure or at risk of acute narrow-angle glaucoma should be monitored. Seizures: In all premarketing depression traits with Effexor, seizures were reported in 0.3% of venlataxine-treated patients. Use Effexor XR cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. Abnormal Bleeding: There have been reports of abnormal bleeding (most commonly ecchymosis). Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. The same precautions should be observed when treat-ing patients with GAD. Use in Patients With Concomitant Illness: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. In short-term depression studies electrocardiographic changes in corrected QT interval (QTc) showed a mean increase of 4.7 msec, and the mean change from baseline heart rate was 4 beats per minute. In GAD studies, mean changes in QTc did not differ significantly from placebo and the mean change from baseline heart rate was 3 beats per minute. In a flexible dose study with immediate release Effexor (mean dose >300 mg/day), patients had a mean increase in heart rate of 8.5 beats per minute. Caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent MI). In patients with renal impairment or cirrhosis of the liver, the pagents with hyperhypolicitism, hear training, on recent min, in pagents with relial impaintment of unitiss of the rever, use clearances of ventalaxine and its active metabolities were decreased, thus prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that veniafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. Laboratory Tests—There are no specific laboratory tests recommended. Drug Interactions—Alcohol: A single dose of ethanol bad no effect on the pharmacokinetics of ventafaxine of

0-desmethylvenlafaxine (ODV) when venlafaxine was administered and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. *Cimetidine*: Use with caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. Diazepam: A single dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or

ODV. Venlafaxine did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced b diazepant of the border final bonic, desine unyolated part of a first of the psycholic and psycholic effect of the offer of the bonic of the bonic and the psycholic and the Inhibiting Cytochrome P4502D6 Metabolism: Venlataxine is metabolized to its active metabolite, ODV, via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of ventariation in FVD2DD, brugs initiating uns software une potential to interease plasma levels of ventafaxine and ODV since ventafaxine and decrease concentrations of ODV. Since the composite plasma levels of ventafaxine and ODV are essentially unchanged in CYP2D6 poor metabolizers, no dosage adjustment is required when ventafaxine is coadministered with a CYP2D6 inhibitor. The concomitant use of ventafaxine with a drug treatment(s) that potentially inhibits both (VP2D6 and CYP3A4, the primary metabolizing erzymes for ventafaxine, has not been studied. Caution is advised should a patient's therapy include veniataxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems. Drugs Metabolized by Cytochrome P450 Isoenzymes: Studies indicate that veniafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. Imipramine: Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by 2.5-4.5 fold. Imigrarine did not affect the pharmacokinetics of ventilatavine and DDV. **Risperidone**: Ventative slightly inhibited the CVP2De-mediated metabolism of risperidone to its active metabolite, 9-hydroxy-risperidone, resulting in an approximate 32% increase in risperidone AUC. Ventatavine coadministration did not significantly alter the pharmacokinetic profile of the total active molety (risperidone plus 9-hydroxyrisperidone). Indinavir: In a study of 9 healthy volunteers, venlafaxine resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. MAOIs: See "Contraindications" and "Warnings." CNS-Active Drugs: Caution is advised if the concomitant administration of venlafaxine and CNS-active drugs is required. Carcinogenesis, Mutagenesis, Impairment of Fertility-Carcinogenesis: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. Mutagenesis: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. Impairment of Fertility: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. Pregnancy---Teratogenic Effects—Prognancy Category C. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a Ingrim basis revealed no manufacture in one of the second se Delivery, Nursing — The effect on labor and delivery in humans is unknown. Venlafavine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, to be excreted in numan milk. Because of the potential for serious adverse reactions in nursing infants from Energy AH, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in pediatric patients have not been established. **Geriatric Use**—Approximately 4% and 6% of Effexor XR-treated patients in placebo-controlled premar-keting depression and GAD trials, respectively, were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients. However, greater sensitivity of some older individuals conclude and the Saveral case of burnoarbania and surformer of inacroarban additionation burnoarban. individuals cannot be ruled out. Several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone Individuals cannot be ruled out. Several cases or nyponatremia and syndrome or inappropriate andiourenc normone secretion (SIADH) have been reported, usually in the elderly. ADVERSE REACTIONS: Associated with Discontinuation of Treatment—The most common events leading to discontinuation in depression and GAD trials included: nausea, anorexia, dry mouth, dizziness, insomnia, somnolence, hypertension, diarthea, paresthesia, tremor, anormal (mostly blurred) vision, anormal (mostly delayed) eliculation, asthenia, vomiting, nervousness, and sweating. Commonly Observed Adverse Events in Controlled Clinical Trials for Depression and GAD—Body as a Whole:

asthenia. Cardiovascular: vasodilatation, hypertension. Digestive: nausea, constipation, anorexia, vomiting, flatulence. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation. <u>Respiratory System</u>: pharyngitis, vawn, Skin: sweating, Special Senses; abnormal vision, Urogenital System; abnormal ejaculation, impotence anorgasmia (female). Vital Sign Changes: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min. (See the "Sustained Hypertension" section of "Warnings.") Laboratory Changes: Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled depression trials was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively. Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL. This increase was duration excersion that had a mean initial orienteracy increase in total choicesterior of s. In figure. This increase was duration dependent over the 12-month study period and tended to be greater with higher doses. An increase in serum choicesterol from baseline by \geq 50 mg/dL and to values >260 mg/dL at any time after baseline, has been recorded in 8.1% of patients. *ECG Changes*: See the "Use in Patients with Concomitant linesses" section of PRECAUTIONS. *Other* Events Observed During the Premarketing Evaluation of Effexor and Effexor XR—N=5079. "Frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = fewer than 1/1000 patients. Body as a whole - Frequent: chest pain substemal, chills, fever, neck pain; infrequent: face edema, intentional injuy; malaise, monillasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. Cardiovascular system - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardía, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, Digestive system - Frequent; eructation, increased appetite; Infrequent; bruxism, colitis, dysphagia, tongue edema, esophagitis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, proctitis, increased salivation, soft stools, tongue discoloration. <u>Endocrine system</u> - Rare: goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. <u>Hemic and lymphatic</u> system - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura. Metabolic and nutritional - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. Musculoskeletal system - Frequent: arthralgia; infrequent: arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: pathological fracture, myopathy, osteoporosis, osteosclerosis, rheumatoid arthritis, tendon rupture. Nervous system -Frequent: amnesia, confusion, depersonalization, emotional lability, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myodonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, twitching; Rare: akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, libido increased, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. Respiratory system - Frequent: cough increased, dyspnea, Infrequent: asthma, chest congestion, epistaxis, hyper Institution i providente provi

VENLAFAXINE HCI EFFEXOR XR EXTENDED RELEASE CAPSULES

dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae. Special senses - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: cataract, conjunctivitis, comeal lesion, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal

hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. Urogenital system - Frequent: dysuria, metrorrhagia," prostatic disorder (prostatitis and enlarged prostate)," urination impaired, vaginitis"; infrequent: albuminuria, amenormea," cystitis, hematuria, leukormea," menormagia," nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage"; Rare: abortion," anuria, breast discharge, breast engorgement, balanitis," breast enlargement, endometriosis," female lactation," fibrocystic breast, calcium crystalluria, cervicitis," orchitis," ovarian enargement, encontenuoss, remaine lacuation, notovisto pressi, valotin organizati da votos, organizati oyst, prolonged erection, gynecomastia (male), hypomorrhea, kiloney calculus, kidney pain, kidney function abnormal, mastitis, menopause, "pyelonephritis, oliguria, sapingotis," urolithiasis, uterine hermorrhage, "uterine spasm." ("Based on the number of men and women as appropriate). **Postmarketing Reports**: agranulocytosis, anaptiylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vieit htrombophiebits, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachyc ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly). There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy. DRUG ABUSE AND DEPENDENCE: Effexor XR is not a controlled substance. Evaluation patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. OVER-DOSAGE: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diversis, dialysis, hemo-perfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In perusion, and exclusing a dataset are tunnery to be of certain to specific antibutes for ventaging a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). DOSAGE AND ADMINISTRATION: Please consult full prescribing information for detailed dosing instructions. Discontinuing Effector XR—When discontinuing Effexor XR, the dose should be tapered gradually, based upon the dose, duration of therapy and the individual patient. Discontinuation symptoms reported include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo Ingrimitates, sensory obsurbances (including sinck-line electrical sensations), sommelence, sweating, termin, vertugo and vomiting, Switching Patients Too r From a Monoamine Oxidase inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see "Contraindications" and "Warnings"). This brief summary is based on the circular CI 7509-4, revised April 11, 2002.



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Something extra

...approximately **1/3 more** patients got their life back

In a pooled analysis of over 2,000 patients, against leading SSRIs (fluoxetine, paroxetine, fluvoxamine), EFFEXOR XR/EFFEXOR offered something extra in depression, remission* of symptoms in approximately 1/3 more patients.¹ Remission of symptoms is a first step on the road to recovery.²

> *Remission is defined as minimal or no symptoms (HAM-D ≤7).¹

Indicated in Depression and Generalized Anxiety Disorder



EXTENDED RELEASE CAPSULES

EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI. The most common adverse events reported in EFFEXOR XR placebocontrolled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, delayed ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, delayed ejaculation, anorexia, constipation, nervousness, and sweating. Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.5% in GAD studies (doses of 37.5 to 225 mg/day) had sustained BP elevations. Less than 1% discontinued treatment because of elevated BP. Regular BP monitoring is recommended. Patients should not be abruptly discontinued from antidepressant medication, including EFFEXOR XR. See the Dosage and Administration section of the Prescribing Information. References: 1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with ventafaxine or selective serotonin reputake inhibitors. Br J Psychiatry. 2001;178:234-241. 2. Kupfer DL Long-term treatment of depression. J Clin Psychiatry. 1991;52(5, suppl):28-34. Please see brief summary of Prescribing Information on adjacent page.

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