April 2002 Volume 7 - Number 4

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

4

Neuropsychology Circa 2002: Methodological Developments

CNS Spectrums is indexed by EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis, and is the official journal of the International Neuropsychiatric Assoc.

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Use in Nursing Mothers** Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Neurontin® should be used in women who are nursing only if the benefits clearly outweigh the risks. **Pediatric Use** Effectiveness in pediatric patients below the age of 3 years has not been established (see CLINICAL PHARMACOLOGY, Clinical Studies). **Geriatric Use** Clinical studies of Neurontin did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections).

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of Neurontin® in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of Neurontin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see WARNINGS, Neuropsychiatric Adverse Events). Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received Neurontin® in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%). **Incidence in Controlled Clinical Trials** Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin® group. In these studies, either Neurontin® or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity. The prescriber should be aware that these figures, obtained when Neurontin® was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 Years of Age
(Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin®[a] N=543 %	Placebo[a] N=378 %	Body System/ Adverse Event	Neurontin®[a] N=543 %	Placebo[a] N=378 %
Body As A Whole			**Nervous System (cont'd)**		
Fatigue	11.0	5.0	Tremor	6.8	3.2
Weight Increase	2.9	1.6	Nervousness	2.4	1.9
Back Pain	1.8	0.5	Dysarthria	2.4	0.5
Peripheral Edema	1.7	0.5	Amnesia	2.2	0.0
Cardiovascular			Depression	1.8	1.1
Vasodilatation	1.1	0.3	Thinking Abnormal	1.7	1.3
Digestive System			Twitching	1.3	0.5
Dyspepsia	2.2	0.5	Coordination Abnormal	1.1	0.3
Mouth or Throat Dry	1.7	0.5	**Respiratory System**		
Constipation	1.5	0.8	Rhinitis	4.1	3.7
Dental Abnormalities	1.5	0.3	Pharyngitis	2.8	1.6
Increased Appetite	1.1	0.8	Coughing	1.8	1.3
Hematologic and Lymphatic Systems			**Skin and Appendages**		
Leukopenia	1.1	0.5	Abrasion	1.3	0.0
Musculoskeletal System			Pruritus	1.3	0.5
Myalgia	2.0	1.9	**Urogenital System**		
Fracture	1.1	0.8	Impotence	1.5	1.1
Nervous System			**Special Senses**		
Somnolence	19.3	8.7	Diplopia	5.9	1.9
Dizziness	17.1	6.9	Amblyopia[b]	4.2	1.1
Ataxia	12.5	5.6	**Laboratory Deviations**		
Nystagmus	8.3	4.0	WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy. [b] Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne. Among the treatment-emergent adverse events occurring at an incidence of at least 10% of Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with Neurontin®. The incidence of adverse events increased slightly with increasing age in patients treated with either Neurontin® or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race. Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of Neurontin-treated patients 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin group. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial
(Events in at least 2% of Neurontin patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin®[a] N=119 %	Placebo[a] N=128 %	Body System/ Adverse Event	Neurontin®[a] N=119 %	Placebo[a] N=128 %
Body As A Whole			**Nervous System**		
Viral Infection	10.9	3.1	Somnolence	8.4	4.7
Fever	10.1	3.1	Hostility	7.6	2.3
Weight Increase	3.4	0.8	Emotional Lability	4.2	1.6
Fatigue	3.4	1.6	Dizziness	2.5	1.6
Digestive System			Hyperkinesia	2.5	0.8
Nausea and/or Vomiting	8.4	7.0	**Respiratory System**		
			Bronchitis	3.4	0.8
			Respiratory Infection	2.5	0.8

[a] Plus background antiepileptic drug therapy.

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials Neurontin® has been administered to 2074 patients >12 years of age during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to Neurontin® who experienced an event of the type cited on at least one occasion while receiving Neurontin®. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Body As A Whole:** *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect. **Cardiovascular System:** *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis. **Digestive System:** *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perleche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm. **Endocrine System:** *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance. **Hematologic and Lymphatic System:** *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased. **Musculoskeletal System:** *Frequent:* arthralgia; Infrequent: tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture. **Nervous System:** *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture. **Respiratory System:** *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema. **Dermatological:** *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling. **Urogenital System:** *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain. **Special Senses:** *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell. Adverse events occurring during clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are: **Body As A Whole:** dehydration, infectious mononucleosis. **Digestive System:** hepatitis. **Hemic and Lymphatic System:** coagulation defect. **Nervous System:** aura disappeared, occipital neuralgia. **Psychobiologic Function:** sleepwalking. **Respiratory System:** pseudocroup, hoarseness. **Postmarketing and Other Experience** In addition to the adverse experiences reported during clinical testing of Neurontin®, the following adverse experiences have been reported in patients receiving marketed Neurontin®. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, Stevens-Johnson syndrome.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Neurontin® has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation. Acute oral overdoses of Neurontin® up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care. Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Neurontin® is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established. Neurontin® is given orally with or without food. **Patients >12 Years of Age:** The effective dose of Neurontin® is 900 to 1800 mg/day and given in divided doses (three times a day) using 300- or 400-mg capsules or 600- or 800-mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300- or 400-mg capsules or 600- or 800-mg tablets three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours. **Pediatric Patients Age 3-12 Years:** The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of Neurontin in patients 5 years of age and older is 25–35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day). (See CLINICAL PHARMACOLOGY, Pediatrics.) Neurontin® may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin® therapy. Further, because there are no significant pharmacokinetic interactions among Neurontin® and other commonly used antiepileptic drugs, the addition of Neurontin® does not alter the plasma levels of these drugs appreciably. If Neurontin® is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week. Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $C_{Cr} = (0.85)(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

for males $C_{Cr} = (140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL. Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows:

TABLE 3. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 T.I.D.
30–60	600	300 B.I.D.
15–30	300	300 Q.D.
<15	150	300 Q.O.D.[a]
Hemodialysis	—	200-300[b]

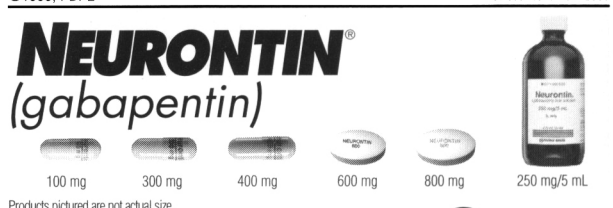
[a] Every other day. [b] Loading dose of 300 to 400 mg in patients who have never received Neurontin®, then 200 to 300 mg Neurontin® following each 4 hours of hemodialysis.

The use of Neurontin® in patients <12 years of age with compromised renal function has not been studied.

℞ only

Distributed by:
PARKE-DAVIS
Div of Warner-Lambert Co
A Pfizer Company

0416G641
Revised November 2000



Products pictured are not actual size.

 Printed in USA/February 2002

Pfizer U.S. Pharmaceuticals

NEURONTIN® (gabapentin) capsules
NEURONTIN® (gabapentin) tablets
NEURONTIN® (gabapentin) oral solution

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Neurontin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3–12 years.

CONTRAINDICATIONS

Neurontin® is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events—Pediatric Patients 3-12 Years of Age *Gabapentin use in pediatric patients* with epilepsy 3–12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity. In controlled trials in pediatric patients 3–12 years of age the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability. **Withdrawal Precipitated Seizure, Status Epilepticus** Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency. In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving Neurontin® was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients treated with Neurontin® across all studies (controlled and uncontrolled) 31(1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with Neurontin® is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with Neurontin®. **Tumorigenic Potential** In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans. In clinical studies comprising 2085 patient-years of exposure, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of Neurontin®. Without knowledge of the background incidence and recurrence in a similar population not treated with Neurontin®, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment. **Sudden and Unexplained Deaths** During the course of premarketing development of Neurontin®, 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure). Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving Neurontin® (ranging from 0.0005 for the general population of epileptics, to 0.003 for a clinical trial population similar to that in the Neurontin® program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the Neurontin® cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients Patients should be instructed to take Neurontin® only as prescribed. Patients should be advised that Neurontin® may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Neurontin® to gauge whether or not it affects their mental and/or motor performance adversely. **Laboratory Tests** Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin®. The value of monitoring Neurontin® blood concentrations has not been established. Neurontin® may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs. **Drug Interactions** Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs. The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy. **Phenytoin:** In a single and multiple dose study of Neurontin® (400 mg T.I.D.) in epileptic patients (N = 8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics. **Carbamazepine:** Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration. **Valproic Acid:** The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid. **Phenobarbital:** Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N=12) are identical whether the drugs are administered alone or together. **Cimetidine:** In the presence of cimetidine at 300 mg Q.I.D. (N=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated. **Oral Contraceptive:** Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D., N=13). The Cmax of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance. **Antacid (Maalox®):** Maalox reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration. **Effect of Probenecid:** Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid. **Drug/Laboratory Tests Interactions** Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear. Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans. Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin. No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on an mg/m^2 basis). **Pregnancy** Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m^2 basis. When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (*500, 1000 and 2000 mg/kg/day*) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

He's the

https://doi.org/10.1017/S1092852900019624 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

CNS SPECTRUMS

The International Journal of Neuropsychiatric Medicine

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

KEPPRA® (levetiracetam)

250 mg, 500 mg and 750 mg tablets ℞ only

BRIEF SUMMARY (for full prescribing information, consult package insert)

INDICATIONS AND USAGE: Keppra (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

CONTRAINDICATIONS: This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra tablets.

WARNINGS: Neuropsychiatric Adverse Events: Keppra use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities. In controlled trials of patients with epilepsy, 14.8% of Keppra treated patients reported somnolence, compared to 8.4% of placebo patients. *There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about* 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of Keppra treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were *hospitalized due to somnolence. In controlled trials of patients with epilepsy,* 14.7% *of treated patients* reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced. A total of 3.4% of Keppra treated patients experienced coordination difficulties (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. *A total of 0.4% of patients in controlled trials discontinued Keppra treatment due to ataxia,* compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of preexisting ataxia. Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment. In controlled trials of patients with epilepsy, 5 (0.7%) of Keppra treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) Keppra treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In one patient experiencing psychotic depression occurring within a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of Keppra patients experienced other behavioral symptoms (reported as agitation, hostility, anxiety, apathy, emotional lability, depersonalization, depression, etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized. In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months. **Withdrawal Seizures:** Antiepileptic drugs, including Keppra, should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS: Hematologic Abnormalities: Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 10^6/mm^3), mean hemoglobin (0.09 g/dL), and mean hematocrit *(0.38%) were seen in Keppra treated patients in controlled trials. A total of 3.2% of treated and 1.8% of* placebo patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤1.0 x 10^9/L) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts. **Hepatic Abnormalities:** There were no meaningful changes in mean liver function tests *(LFT) in controlled trials;* lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%). No patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) epilepsy patient receiving open treatment. **Information For Patients:** Patients should be instructed to take Keppra only as prescribed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised that Keppra may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery or engage in other hazardous activities until they have gained sufficient experience on Keppra to gauge whether it adversely affects their performance of these activities. **Laboratory Tests:** Although most laboratory tests are not systematically altered with Keppra treatment, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests. **Use in Patients With Impaired Renal Function:** Caution should be taken in dosing patients with moderate and severe renal impairment and patients undergoing hemodialysis. Dosage should be reduced in patients with impaired renal function receiving Keppra and supplemental doses should be given to patients after dialysis (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function). **Drug Interactions:** *In vitro* data on metabolic interactions indicate that Keppra is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, warfarin, digoxin, oral contraceptive) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients. Drug-Drug Interactions Between Keppra and Existing Antiepileptic Drugs (AEDs): Potential drug interactions between Keppra and existing AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of existing AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam. **Other Drug Interactions:** Oral Contraceptives: Keppra (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the *pharmacokinetics of levetiracetam. Digoxin: Keppra (1000 mg twice daily) did not influence the* pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam. Warfarin: Keppra (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of *levetiracetam. Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose* of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of Keppra on probenecid was not studied. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis: Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m^2 or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied. Mutagenesis: Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay. Impairment of Fertility: No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis). **Pregnancy: Pregnancy Category C:** *In animal studies, levetiracetam produced evidence of* developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg *[MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a* dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses *≥600 mg/kg/day (approximately 4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and* increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day. When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the *MRHD*). 1200 mg/kg/day (4 times the *MRHD*) was a developmental no effect dose. There was no evidence of maternal toxicity in this study. Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Keppra should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women exposed to Keppra physicians are encouraged to register patients, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free). **Labor and Delivery:** The effect of Keppra on labor and delivery in humans is unknown. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Keppra is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in patients below the age of 16 have not been established. **Geriatric Use:** Of the total number of subjects in clinical studies of levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Keppra in these patients. A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses for 10 days showed no pharmacokinetic differences related to age alone. Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. **Use in Patients With Impaired Renal Function:** Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. The dosage should be reduced in patients with impaired renal function receiving Keppra and supplemental doses should be given to patients after dialysis (see DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

ADVERSE REACTIONS: In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness. Table 1 lists treatment-emergent adverse events that occurred in at least 1% of patients with epilepsy treated with Keppra participating in placebo-controlled studies and were numerically more common in patients treated with Keppra than placebo. In these studies, either Keppra or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity. The prescriber should be aware that these figures, obtained when Keppra was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied. **Table 1: Incidence (%) of Treatment-emergent Adverse Events in Placebo-controlled, Add-on Studies by Body System (Adverse Events Occurred in at Least 1% of Keppra-treated Patients and Occurred More Frequently than Placebo-treated Patients)** Keppra (N=769) vs Placebo (N=439): **Body System/Adverse Event: Body as a Whole:** Asthenia (15% vs 9%); Headache (14% vs 13%); Infection (13% vs 8%); Pain (7% vs 6%). **Digestive System:** Anorexia (3% vs 2%). **Nervous System:** Amnesia (2% vs 1%); Anxiety (2% vs 1%); Ataxia (3% vs 1%); Depression (4% vs 2%); Dizziness (9% vs 4%); Emotional Lability (2% vs 0%); Hostility (2% vs 1%); Nervousness (4% vs 2%); Paresthesia (2% vs 1%); Somnolence (15% vs 8%); Vertigo (3% vs 1%). **Respiratory System:** Cough Increased (2% vs 1%); Pharyngitis (6% vs 4%); Rhinitis (4% vs 3%); Sinusitis (2% vs 1%). **Special Senses:** Diplopia (2% vs 1%). Other events reported by 1% or more of patients treated with Keppra but as or more frequent in the placebo group were: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain. **Time Course of Onset of Adverse Events:** Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra. **Discontinuation or Dose Reduction in Well-Controlled Clinical Studies:** In well-controlled clinical studies, 15.0% of patients receiving Keppra and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in Table 2. **Table 2: Adverse Events Most Commonly Associated With Discontinuation or Dose Reduction in Placebo-controlled Studies in Patients With Epilepsy** Keppra (N=769) vs Placebo (N=439): [Number (%)]: Asthenia [10 (1.3%) vs 3 (0.7%)]; Convulsion [23 (3.0%) vs 15 (3.4%)]; Dizziness [11 (1.4%) vs 0]; Somnolence [34 (4.4%) vs 7 (1.6%)]; Rash [0 vs 5 (1.1%)]. **Comparison of Gender, Age and Race:** The overall adverse experience profile of Keppra was similar between females and males. There are insufficient *data to support a statement regarding the distribution of adverse experience reports by age and race.*

DOSAGE AND ADMINISTRATION: Keppra is indicated as adjunctive treatment of partial onset seizures in adults with epilepsy. In clinical trials, daily doses of 1000 mg, 2000 mg and 3000 mg, given as twice a day dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose (see CLINICAL STUDIES in package insert), a consistent increase in response with increased dose has not been shown. Treatment should be initiated with a daily dose of 1000 mg/day, given as twice daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Long term experience at doses greater than 3000 mg/day is relatively minimal, and there is no evidence that doses greater than 3000 mg/day confer additional benefit. Keppra is given orally with or without food. **Patients With Impaired Renal Function:** Keppra dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose are shown in the Table below. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CLcr = \frac{[140\text{-}age\ (years)] \times weight\ (kg)}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

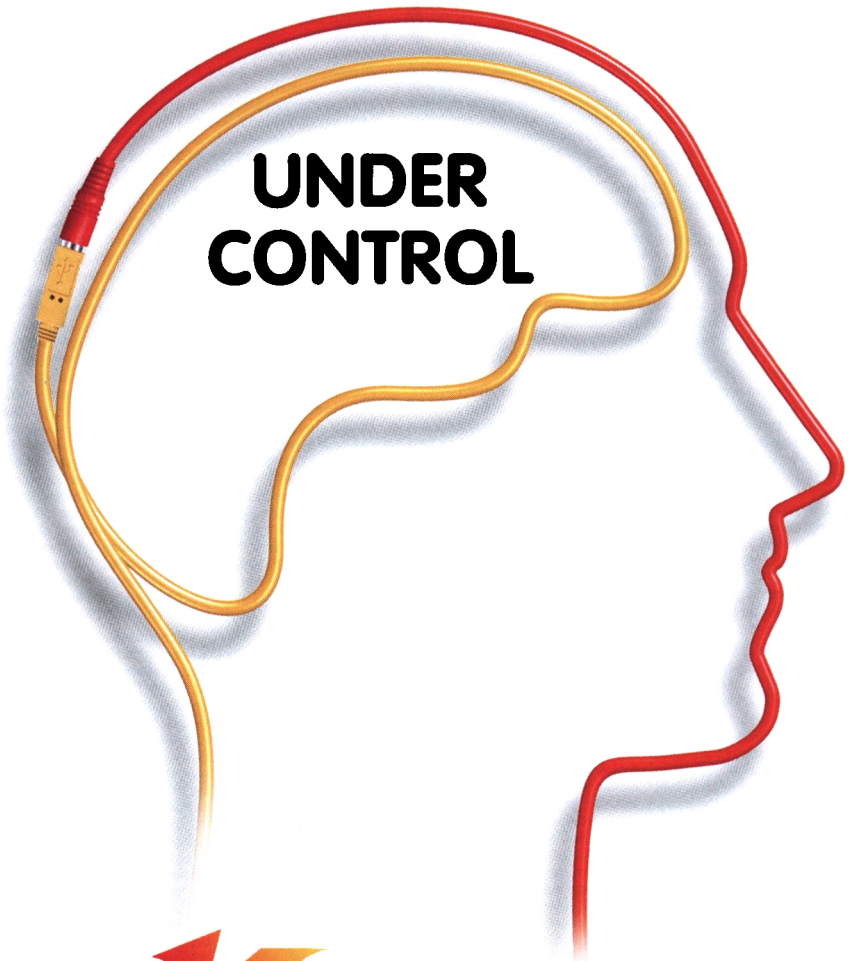
Dosing Adjustment Regimen for Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 h
Mild	50 – 80	500 to 1,000	Every 12 h
Moderate	30 – 50	250 to 750	Every 12 h
Severe	< 30	250 to 500	Every 12 h
ESRD patients using dialysis	—	500 to 1,000	Every 24 h*

*Following dialysis, a 250 to 500 mg supplemental dose is recommended.

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL ONSET SEIZURES IN ADULTS WITH EPILEPSY



Keppra®

levetiracetam

250 • 500 • 750 mg tablets

SIMPLIFYING SEIZURE CONTROL

- PROVIDES UP TO 4 OUT OF 10 REFRACTORY PATIENTS WITH ≥50% PARTIAL ONSET SEIZURE REDUCTION
- NO DRUG/DRUG INTERACTIONS WITH AEDs INCLUDED IN WELL-CONTROLLED STUDIES, A COMBINATION ORAL CONTRACEPTIVE, WARFARIN, OR DIGOXIN
- GENERALLY WELL TOLERATED

Keppra® use is associated with the occurrence of central nervous system adverse events, classified as somnolence and fatigue, coordination difficulties, and behavioral abnormalities; and with minor, but statistically significant, hematological abnormalities. Keppra® dosing must be individualized according to renal function status.

EFFICACY AND TOLERABILITY IN AN EASY-TO-USE AED—ADD-ON THERAPY STARTS WITH KEPPRA®

Please consult brief summary of prescribing information on adjacent page.

ucb Pharma

Printed in U.S.A. K156-0701

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

Table of Contents

Feature Articles

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 7 • Number 4
April 2002

CNS Spectrums is a peer review journal and is indexed in EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis. *CNS Spectrums* is endorsed by, and is the official journal of, the International Neuropsychiatric Assoc., with members in 30 countries.

CNS Spectrums
ISSN 1092-8529
is published by
MedWorks Media,
333 Hudson Street, 7th Floor
New York, NY 10013

One year subscription rates:
domestic $120;
foreign $185;
in-training $75.
For subscriptions:
Fax: 212-328-0600
E-mail:
jrr@medworksmedia.com

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 7 • Number 4
April 2002

Table of Contents

Departments/Monthly Columns

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

Something extra

...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—**remission* of depression in 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]

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 placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal 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 0.4% in GAD studies (doses of 75 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 venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry.* 2001;178:234-241. **2.** Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry.* 1991;52(5, suppl):28-34.

Please see brief summary of Prescribing Information on adjacent page.

Visit us at www.EFFEXORXR.com

Indicated for Depression and Generalized Anxiety Disorder

ONCE-DAILY VENLAFAXINE HCl

EFFEXOR® XR EXTENDED RELEASE CAPSULES

Expect More

https://doi.org/10.1017/S1092852900017624 Published online by Cambridge University Press

VENLAFAXINE HCl
EFFEXOR® XR
EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information. **CONTRAINDICATIONS**: Hypersensitivity to venlafaxine 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 Inhibitors—Adverse reactions, some serious, have been reported in patients who were recently discontinued from an MAOI and started on venlafaxine, or who recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant 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 discontinuing 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 in Phase 3 depression studies. In Phase 3 Generalized 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. ***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 intraocular pressure or at risk of acute narrow-angle glaucoma should be monitored. ***Seizures:*** In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine-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 treating 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 clearances of venlafaxine and its active metabolites 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 venlafaxine 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 had no effect on the pharmacokinetics of venlafaxine or O-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 by diazepam. ***Haloperidol:*** Venlafaxine decreased total oral-dose clearance of haloperidol which resulted in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life was unchanged. ***Drugs Inhibiting Cytochrome P4502D6 Metabolism:*** Venlafaxine is metabolized to its active metabolite, ODV, via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. Since the composite plasma levels of venlafaxine and ODV are essentially unchanged in CYP2D6 poor metabolizers, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. The concomitant use of venlafaxine with a drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes:*** Studies indicate that venlafaxine 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. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. ***Risperidone:*** Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (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—Pregnancy 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 decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects.*** If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine 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, 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 premarketing 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 cannot be ruled out. Several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone 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, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, 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. Respiratory System: pharyngitis, yawn. 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 dependent over the 12-month study period and tended to be greater with higher doses. An increase in serum cholesterol from baseline by ≥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 Illnesses" 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 substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, 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, bradycardia, 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, gastritis, gastroenteritis, 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. **Endocrine system** - Rare: goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic 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, hypercalciuria, 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, myoclonus, 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, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: rash, pruritus; Infrequent: acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; Rare: erythema nodosum, exfoliative 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, corneal 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, amenorrhea,* cystitis, hematuria, leukorrhea,* menorrhagia,* 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 cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm.* (*Based on the number of men and women as appropriate). **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, 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), night sweats, pancreatitis, panic, prolactin increased, 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. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: 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 diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting 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 Effexor 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 and vomiting. **Switching Patients To or 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 7509-1, revised September 12, 2001.

82155-00