July 2002 Volume 7 - Number 7

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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Diffusion Tensor Imaging of the Central Nervous System: Clinical Applications

X. Li, X. Leclerc, T. Huisman, and A.G. Sorensen

https://doi.org/10.1017/S1092852900018009 Published online by Cambridge University Press

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.

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:* choreaathetosis, 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

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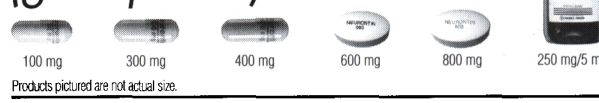
Rev. 0, July 2001

NEURONTIN®
(gabapentin)



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He's the

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STRONG SILENT TYPE.
LIKE HIS NEURONTIN.

ADD-ON PARTIAL-SEIZURE CONTROL WITH EXCELLENT TOLERABILITY

Efficacy in a range of patients

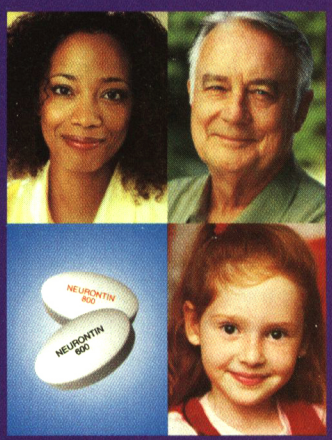
Well tolerated

Effective starting dose

Rapid titration to maximum efficacy

Simple, safe pharmacokinetics

Available in 100-mg, 300-mg, and 400-mg capsules, 600-mg and 800-mg tablets, and an oral solution



NEURONTIN is indicated as adjunctive treatment for partial seizures in pediatric patients (3-12 years old) and for partial seizures with and without secondary generalization in adults (>12 years old). NEURONTIN is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. NEURONTIN use in pediatric patients aged 3 to 12 years has been associated with mild to moderate neuropsychiatric adverse events, including emotional lability, hostility, thought disorder, and hyperkinesia.

In controlled clinical trials, the most common adverse events reported with NEURONTIN vs placebo in adults (>12 years old) were somnolence (19.3% vs 8.7%), dizziness (17.1% vs 6.9%), ataxia (12.5% vs 5.6%), fatigue (11.0% vs 5.0%), and nystagmus (8.3% vs 4.0%); the most common adverse events in pediatric patients (3-12 years old) were viral infection (10.9% vs 3.1%), fever (10.1% vs 3.1%), nausea and/or vomiting (8.4% vs 7.0%), somnolence (8.4% vs 4.7%), and hostility (7.6% vs 2.3%).

Please see brief summary of full prescribing information on adjacent pages.

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https://doi.org/10.1017/S1092852900018009 Published online by Cambridge University Press

CNS SPECTRUMS

The International Journal of Neuropsychiatric Medicine

DIFFUSION TENSOR IMAGING: ITS PAST, PRESENT, AND POSSIBLE FUTURE

page 505

"While the Gaussian diffusion model posited by DT-MRI greatly simplifies the analysis and interpretation of diffusion imaging experiments, the assumption of Gaussian diffusion obscures many phenomena. For example, the tensor model is incapable of describing truly restricted diffusion or fiber crossing. Recent progress to overcome these limitations has been possible with the development of a more nearly model-independent DT-MRI method termed diffusion spectrum imaging (DSI), which can resolve such fiber crossing. With DSI, the basic assumption of Gaussian diffusion is cast aside, and replaced by a measurable diffusion propagator formalism that allows discrete edges in the microscopic environment to shape the mobility of molecules, and thus the probability cloud of their position at a later time, in a non-Gaussian way."

BUILDING THE BRAIN

page 510

"Other rotationally invariant scalar quantities can be constructed from the DT to measure different features of anisotropic diffusion. One of these measures is the skewness of the eigenvalues. While anisotropy indices measure the degree to which the diffusion ellipsoid's shape deviates from being spherical, the skewness of the eigenvalues measures whether the ellipsoid is prolate (cigar-shaped) or oblate (pancake-shaped). Prolate water-displacement profiles are typically found in white matter regions with parallel arrangement of fibers, such as the corpus callosum and pyramidal tract. Oblate ellipsoids correspond to white matter regions having a particular architectural arrangement of fibers, such sheets of parallel fibers with different orientations, or bundles of fibers that are randomly oriented in a plane."

AT THE CROSSROADS: A LOOK AT THE CINGULUM BUNDLE

page 522

"There are some limitations to the DT-MRI technique, such as spatial resolution, that affect imaging time and anatomical interpretation. More precisely, visual inspection of anatomy and the tractography solutions rely on high signal-to-noise ratio. The desired signal-to-noise ratio to produce robust tract solutions should be included in any tractography study. To obtain images richer in signal, a higher number of images is needed. This in turn, results in an increase of acquisition time. In addition, the geometric form of voxels should be as isotropic as possible. The trade-off between isotropic voxel dimensions and small voxels needs to be considered in a case-by-case study. Minimizing the voxel anisotropy is a difficult endeavor when specific anatomic hypotheses have to be met that require relatively small voxels, because smaller voxels result in lower magnetic resonance signal."

MULTI-DIMENSIONAL ANALYSIS OF WHITE MATTER

page 529

"There are several limitations in these first-generation approaches. For example, it is known that there are many regions in the brain that contain axonal tracts with various orientations that are mixed in a microscopic scale. DT-MRI data may contain pixels in which diffusion ellipsoids have two large axes and one short axis (disk-shaped); therefore, it does not make sense to determine one preferential orientation as the fiber orientation.The line propagation techniques are also known to accumulate errors produced by noise as the line gets longer. While some of these limitations are fundamental and may not be solved completely, many techniques have been postulated to extract the best possible information about the tract trajectories. For example, there are techniques in which energy minimization approaches are employed. In this approach, unlike the deterministic method of line propagation techniques (one line is determined from one seed pixel), they provide the probability of connectivity between two arbitrary pixels."

PRACTICAL USES FOR DT-MRI

page 535

"The measurement of anisotropic diffusion may yield information about the integrity of the tissue. Many investigators have hypothesized that changes in white matter anisotropic diffusion could represent an early indicator of tissue injury by various diseases. The degree of anisotropic diffusion is measured by first assessing the full diffusion tensor at each voxel. Once this is obtained, a variety of scalar metrics can be used to quantify the degree of anisotropy; one popular metrics is termed fractional anisotropy (FA). FA values range between 0 and 1, with 0 representing maximally isotropic diffusion, and 1 representing the hypothetical case of maximal anisotropic diffusion. Consequently, CSF is hyperintense, whereas the brain parenchyma is hypointense. On FA maps, the highest degree of anisotropy is found in the white matter, typically appearing as bright signal. Conversely, the lowest degree of anisotropy is seen in the CSF, which appears dark. In routine clinical practice, DWI images are evaluated in combination with ADC maps to exclude the so-called 'T2-shine through' phenomena. This phenomenon is due to the fact that, unlike ADC maps, diffusion-weighted images are not pure diffusion maps but include a component of T2-weighting." CNS

Year 2002

The September 11th Commemorative Double Issue

Geriatric Psychiatry

Neuropsychiatric HIV Infection

Coming Soon in

CNS SPECTRUMS®

Administration of *Paxil CR* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug.

Concomitant use of *Paxil CR* and alcohol in depressed patients is not advised. Undertake concurrent use of *Paxil CR* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil CR* with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been reported with immediate-release paroxetine treatment co-administration; monitoring theophylline levels is recommended.

A significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell sarcomas vs. animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with *Paxil CR*.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) showed a reduced pregnancy rate.

Pregnancy Category C: Reproduction studies performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits, approximately 8 (rat) and 2 (rabbit) times the MRHD on a mg/m^2 basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. *Paxil CR* should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of paroxetine on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when *Paxil CR* is administered to a nursing woman. Safety and effectiveness in the pediatric population have not been established.

In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended. However, there were no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in complete prescribing information). In a controlled study focusing specifically on elderly patients with major depressive disorder, *Paxil CR* was demonstrated to be safe and effective in the treatment of elderly patients (>60 years of age) with major depressive disorder. (See CLINICAL TRIALS and ADVERSE REACTIONS—Table 2 in complete prescribing information.)

ADVERSE REACTIONS: Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with *Paxil CR*:

Adverse Events Associated with Discontinuation of Treatment

Ten percent (21/212) of *Paxil CR* patients discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for *Paxil CR* compared to placebo) included: nausea (3.7% vs. 0.5%); asthenia (1.9% vs. 0.5%), dizziness (1.4% vs. 0.0%); somnolence (1.4% vs. 0.0%), respectively. In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of *Paxil CR* patients discontinued due to these adverse events: nausea (2.9% vs. 0.0%), headache (1.9% vs. 0.9%), depression (1.9% vs. 0.0%), LFT's abnormal (1.9% vs. 0.0%), for *Paxil CR* and placebo, respectively. Eleven percent (50/444) of *Paxil CR* patients in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included: nausea (2.9% vs. 0.4%); insomnia (1.8% vs. 0.0%); headache (1.4% vs. 0.2%), asthenia (1.1% vs. 0.0%) for *Paxil CR* and placebo, respectively.

The most commonly observed adverse events associated with *Paxil CR* in a pool of two trials for major depressive disorder (incidence of 5.0% or greater and incidence for *Paxil CR* at least twice that for placebo) were: abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning. Using the same criteria, the adverse events associated with the use of *Paxil CR* in a study of elderly patients with major depressive disorder were: abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

In the pool of panic disorder studies, the adverse events meeting these criteria were: abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Incidence in Controlled Clinical Trials

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥1% of patients with major depressive disorder were: **Body as a Whole:** Headache (27% vs. 20%), asthenia (14% vs. 9%), infection (8% vs. 5%), abdominal pain (7% vs. 4%), back pain (5% vs. 3%), trauma (5% vs. 1%), pain (3% vs. 1%), allergic reaction (2% vs. 1%); **Cardiovascular System:** tachycardia (1% vs. 0%), vasodilatation (2% vs. 0%); **Digestive System:** Nausea (22% vs. 10%), diarrhea (18% vs. 7%), dry mouth (15% vs. 8%), constipation (10% vs. 4%), flatulence (6% vs. 4%), decreased appetite (4% vs. 2%), vomiting (2% vs. 1%); **Nervous System:** somnolence (22% vs. 8%), insomnia (17% vs. 9%); dizziness (14% vs. 4%); libido decreased (7% vs. 3%), tremor (7% vs. 1%), hypertonia (3% vs. 1%), paresthesia (3% vs. 1%), agitation (2% vs. 1%), confusion (1% vs. 0%); **Respiratory System:** yawn (5% vs. 0%), rhinitis (4% vs. 1%), cough increased (2% vs. 1%), bronchitis (1% vs. 0%); **Skin and Appendages:** sweating (6% vs. 2%), photosensitivity (2% vs. 0%); **Special Senses:** abnormal vision (5% vs. 1%), taste perversion (2% vs. 0%); **Urogenital System:** abnormal ejaculation (26% vs. 1%), female genital disorder (10% vs. <1%), impotence (5% vs. 3%), urinary tract infection (3% vs. 1%), menstrual disorder (2% vs. <1%), vaginitis (2% vs. 0%).

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥5% of elderly patients with major depressive disorder were: **Body as a Whole:** headache (17% vs. 13%), asthenia (15% vs. 14%), trauma (8% vs. 5%), infection (6% vs. 2%); **Digestive System:** dry mouth (18% vs. 7%), diarrhea (15% vs. 9%), constipation (13% vs. 5%), dyspepsia (13% vs. 10%), decreased appetite (12% vs. 5%), flatulence (8% vs. 7%); **Nervous System:** somnolence (21% vs. 12%), insomnia (10% vs. 8%), dizziness (9% vs. 5%), libido decreased (8% vs. <1%), tremor (7% vs. 0%); **Skin and Appendages:** sweating (10% vs. <1%); **Urogenital System:** abnormal ejaculation (17% vs. 3%), impotence (9% vs. 3%).

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥1% of patients with panic disorder were: **Body as a Whole:** asthenia (15% vs. 10%), abdominal pain (6% vs. 4%); trauma (5% vs. 4%); **Cardiovascular System:** vasodilation (3% vs. 2%); **Digestive System:** nausea (23% vs. 17%), dry mouth (13% vs. 9%), diarrhea (12% vs. 9%), constipation (9% vs. 6%), decreased appetite (8% vs. 6%); **Metabolic/ Nutritional Disorders:** weight loss (1% vs. 0%); **Musculoskeletal System:** Myalgia (5% vs. 3%); **Nervous System:** insomnia (20% vs. 11%), somnolence (20% vs. 9%), libido decreased (9% vs. 4%), nervousness (8% vs. 7%); tremor (8% vs. 2%), anxiety (5% vs. 4%), agitation (3% vs. 2%), hypertonia (2% vs. <1%), myoclonus (2% vs. <1%); **Respiratory System:** sinusitis (8% vs. 5%), yawn (3% vs. 0%); **Skin and Appendages:** sweating (7% vs. 2%); **Special Senses:** abnormal vision (3% vs. <1%); **Urogenital System:** abnormal ejaculation (27% vs. 3%), impotence (10% vs. 1%), female genital disorders (7% vs. 1%), urinary frequency (2% vs. <1%), urination impaired (2% vs. <1%), vaginitis (1% vs. <1%).

Studies in major depressive disorder show a clear dose-dependent relationship for some of the more common adverse events associated with the use of immediate-release paroxetine. The percentage of patients in clinical trials reporting symptoms of sexual dysfunction in non-elderly patients with major depressive disorder and in patients with panic disorder are in males: decreased libido (10% and 9%), ejaculatory disturbance (26% and 27%), impotence (5% and 10%); in females: decreased libido (4% and 8%), orgasmic disturbance (10% and 7%).

Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with *Paxil CR*, or the immediate-release formulation, had minimal weight loss (about 1 pound).

In a study of elderly patients with major depressive disorder, three of 104 *Paxil CR* patients and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern. Two of the *Paxil CR* patients dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, four of 444 *Paxil CR* patients and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of *Paxil CR*. The clinical significance of these findings is unknown. In placebo-controlled clinical trials with the immediate release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Other Events Observed During the Clinical Development of Paroxetine: During premarketing assessment in major depressive disorder and panic disorder, multiple doses of *Paxil CR* were administered to 760 patients in phase 3 double-blind, controlled, outpatient studies. The following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with *Paxil CR* is unknown.

Body as a Whole: *Infrequent were anaphylactoid reaction, chills, flu syndrome, malaise;* also observed were adrenergic syndrome, face edema, neck rigidity, sepsis. **Cardiovascular System:** Frequent were hypertension, hypotension; Infrequent were angina pectoris, bradycardia, bundle branch block, palpitation, postural hypotension, syncope; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, hematoma, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles. **Digestive System:** Infrequent were bruxism, dysphagia, eructation, *gastroenteritis, gastroesophageal reflux, gingivitis, glossitis, gum hyperplasia, hemorrhoids,* hepatosplenomegaly, increased salivation, intestinal obstruction, melena, pancreatitis, peptic ulcer, rectal hemorrhage, stomach ulcer, toothache, ulcerative stomatitis; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, colitis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, throat tightness, tongue discoloration, tongue edema. **Endocrine System:** Infrequent were hyperthyroidism, ovarian cyst, testes pain; also observed were *diabetes mellitus, goiter, hypothyroidism, thyroiditis.* ***Hemic and Lymphatic System:*** *Infrequent* were anemia, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, hypochromic anemia, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia. **Metabolic and Nutritional Disorders:** Infrequent were bilirubinemia, dehydration, generalized edema, hyperglycemia, hyperkalemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, *gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia,* hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. **Musculoskeletal System:** Infrequent were arthritis, bursitis, myasthenia, myopathy, myositis, tendonitis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany. **Nervous System:** Infrequent were amnesia, ataxia, convulsion, diplopia, dystonia, emotional lability, hallucinations, hypesthesia, hypokinesia, incoordination, neuralgia, neuropathy, nystagmus, paralysis, paranoid reaction, vertigo, withdrawal syndrome; also observed were abnormal gait, akathisis, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, *dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion,* hostility, hyperalgesia, irritability, libido increased, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis, trismus. **Respiratory System:** Infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia, stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased. **Skin and Appendages:** Infrequent were acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, pruritus, seborrhea, urticaria; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. **Special Senses:** Infrequent were abnormality of accommodation, conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus, visual field defect; also observed were amblyopia, anisocoria, blepharitis, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss. **Urogenital System:** Infrequent were albuminuria, amenorrhea*, breast enlargement*, breast pain*, cystitis, dysuria, hematuria, kidney calculus, menorrhagia*, nocturia, prostatitis*, urinary incontinence, urinary retention; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, female lactation, fibrocystic breast, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, polyuria, pyuria, salpingitis, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor); status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin co-administration. There has been a report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil CR* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil CR* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

GlaxoSmithKline
Research Triangle Park, NC 27709

BRS–PC:L2

https://doi.org/10.1017/S1092852900018009 Published online by Cambridge University Press

INTRODUCING **NEW *PAXIL CR***

THE POWER OF balance

The efficacy to get them there...the tolerability to keep them going.

NEW PAXIL CR™
PAROXETINE HCl
CONTROLLED-RELEASE TABLETS

EFFICACY THAT BEGINS WITH TOLERABILITY

Most common adverse events (incidence of 5% or greater and incidence for *Paxil CR* at least twice that for placebo) in major depressive disorder and panic disorder studies include trauma, nausea, diarrhea, constipation, somnolence, dizziness, decreased libido, tremor, yawning, sweating, abnormal vision, abnormal ejaculation, female genital disorders and impotence. Patients should not be abruptly discontinued from antidepressant medication, including *Paxil CR*. Concomitant use of *Paxil CR* in patients taking monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated.

GlaxoSmithKline

Please see brief summary of prescribing information adjacent to this advertisement.

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Feature Articles

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

CNS Spectrums is an Index Medicus journal and is available on MEDLINE. It is also indexed by DIALOG, EMBASE/Excerpta Medica, Lexis-Nexis, OVID, and SilverPlatter. *CNS Spectrums* is the official journal of the International Neuropsychiatric Association 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:
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CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 7 • Number 7
July 2002

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Departments/Monthly Columns

BRIEF SUMMARY of PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome: (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS [2/2387 (0.1%)] have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS: General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (22/2162) of the patients treated with SEROQUEL, compared with 0% (0/206) on placebo and about 0.5% (2/420) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). **Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lenticular changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment. **Cholesterol and Triglyceride Elevations:** In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on SEROQUEL Phenytoin:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate). **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Lithium:** Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrine:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis:** Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Saimonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected at doses of 25, 75, 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients.

ADVERSE REACTIONS

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The following treatment-emergent adverse experiences occurred at an incidence rate of 1% or more, and were at least as frequent among SEROQUEL treated patients, treated at doses of 75 mg/day or greater than among placebo treated patients in 3- to 6-week placebo-controlled trials.[1]

Body as a Whole: Headache, Asthenia, Abdominal pain, Back pain, Fever; **Nervous System:** Somnolence, Dizziness; **Digestive System:** Constipation, Dry Mouth, Dyspepsia; **Cardiovascular System:** Postural hypotension, Tachycardia; **Metabolic and Nutritional Disorders:** Weight gain; **Skin and Appendages:** Rash; **Respiratory System:** Rhinitis; **Special Senses:** Ear pain

[1]Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials Dose-related Adverse Events:** Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. **Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain:** The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**). An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo. **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis*; ***Rare:*** abdomen enlarged. **Digestive System:** ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System:** ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation. **Metabolic and Nutritional System:** ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure. **Special Senses:** ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System:** ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia. **Endocrine System:** ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism. *adjusted for gender **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Manufactured for:
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Rev 1/01