Rivastigmine May Delay Dementia in Parkinson's

BY JEFF EVANS Senior Writer

the cholinesterase inhibitor rivastigmine transiently halted cognitive deterioration associated with Parkinson's disease but fell short of actually modifying the course of either Parkinsonism or related dementia, according to the results of a randomized clinical trial reported by Murat Emre, M.D., of Istanbul (Turkey) University and his colleagues.

In the double-blind study of patients with mild to moderately severe dementia associated with Parkinson's disease, scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale were significantly improved in the 329 patients given 24 weeks of treatment with rivastigmine compared with 160 patients who received placebo (N. Engl. J. Med. 2004;351:2509-18).

Patients also showed significant, though moderate, improvement with rivastigmine, compared with placebo, according to scores on the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change. About 80% of the patients who received rivastigmine did not have clinically meaningful improvement on that scale.

Rivastigmine patients received an average 8.6 mg of the drug per day. During the study, 95% of patients took levodopa and 46% took dopamine agonists.

SEROQUEL® (quetiapine fumarate) Tablets

Significantly more rivastigmine patients

reported Parkinsonian symptoms than did placebo patients (27% vs. 16%), but this was not reflected in overall motor function scores on the Unified Parkinson's Disease Rating Scale, the researchers said.

Dr. Emre and many of the other investigators in the study reported being paid for work performed for Novartis, which funded the study and markets rivastigmine as Exelon.

Daniel Z. Press, M.D., of Harvard Medical School, Boston, said in an editorial that clinicians' ability to treat the motor symptoms of Parkinson's disease far outstrips their ability to treat cognitive symptoms (N. Engl. J. Med. 2004;351:2547-9). Yet the optimal approach to the management of motor symptoms remains controversial.

Another randomized study showed that levodopa improved motor symptoms at sufficiently high doses but did not alter the course of Parkinson's disease for better or worse.

Stanley Fahn, M.D., of Columbia University, New York, and his colleagues conducted a double-blind trial of levodopa in patients who were considered not likely to require therapy for the symptoms of Parkinson's disease during the 9 months that followed enrollment.

Clinical deterioration of the symptoms of Parkinson's disease did not occur in 81 patients who received carbidopa and levodopa at 600 mg/day after 42 weeks, according to scores on the Unified Parkinson's Disease Rating Scale. Patients who took lower daily doses of carbidopa and levodopa (150 mg and 300 mg) experienced some deterioration, but significantly less than the 70 placebo patients (N. Engl. J. Med. 2004;351:2498-508).

In a separate substudy using single photon emission CT (SPECT), striatal dopamine transporter density in the 106 patients who received levodopa was similar to that of 29 patients on placebo after 40 weeks of treatment. But when they excluded 19 patients with normal dopaminergic activity, the patients who took levodopa had a significantly greater decrease in the density of striatal dopamine transporters than did patients on placebo.

Counter to the neuroprotective effects of levodopa seen in the clinical part of the study, the result of the SPECT study "suggests the possibility of a levodopa-induced toxic effect on dopamine neurons," according to the investigators.

All of the patients took levodopa during the SPECT study. Levodopa could have had a pharmacologic effect on the dopamine transporter by interfering with and reducing the binding of the radioligand used to detect the density of dopamine transporters.

But the small number of patients in the study and the relatively short period of treatment make it impossible to "exclude the possibility that levodopa may simply downregulate the dopamine transporter," said Dr. Fahn, who has served as an unpaid consultant to Teva Pharmaceuticals, which supplied the drugs used in the study.

Only levodopa at doses of 600 mg/day was associated with a significantly higher adverse event (dyskinesia, headache, hypertonia, infection) rate than placebo. ■

Prescribing Information.

INDICATIONS AND USAGE Bipolar Mania: SEROOUEL is indicated for the treatment of acute manic ensioneds associated with bipolar of disorder, as either monotherapy or adjunct therapy to lithium or divalprox. The efficacy of SEROOUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar plants initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials former than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROOUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. Schizophrenia. SEROOUEL is indicated for the treatment of schizophrenia. The efficacy of SEROOUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROOUEL in ong-term use, that is, or more than 50 weeks, has not be easy systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROOUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. usefulness of the drug for the individual patient.

CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to

CONTAMINIOLATIONS. SCHOOLET IS CONTINUATIONAL TOWN.

WARNINGS. Neuroleptic Malignant Syndrom (NMS): A potentially fatal symptom complex synthemises referred to as SNMS has been reported in association with administration of antipsychotic drugs. including SEROQUEL. Pare cases of MMS have been reported with SEROQUEL. Clinical manifestations of MMS are byperyrexia, muscle rigidity, attender omental status, and evidence of autonomic instability. See full Prescribing information for more information on the manifestations, diagnosis and management of MMS. In a patient requires antipsychotic drug treatment after recovery from MMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of MMS have been reported. Tardive Dysinesiz: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients freated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elidery, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative does of antipsychotic drug administered to the patient treatment, and the syndrome and remainspechotic treatment, seek, the syndrome and evelop, although much less commonly, after relatively brief treatment periods allow doess. There is no known treatment for established cases of tardive dyskinesia. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and the reflect that symptomatic suggression has upon the long-term course of the syndrome is unknown. The reflect that symptomatic suggression has upon the long-term course of the syndrome is unknown. symptoms of the syndrome and thereby may possibly mask the underlying pricess. 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 courrence of tardite dyskiness. Chronic antispsychotic treatment should generally be reserved for patients who appear to suffer from a chronic liliness that (1) is known to respond to antispsychotic drugs, and (2) for whomal alternative, equally effective, but potentially less farmult 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 mean of continued treatment should be crossived 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. Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketacoldosis or hypersomalor come or death, has been reported in platentist treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotics use and glucose antomeralities to complicated by the possibility of an increased background risk of antipsychotics, including SEROUEL. Assessment of the relationship between atypical antipsychotic uses and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes melitus in patients with schizophrenia and the increasing incidence of diabetes melitus in the general population. Given these confounders, the relationship between atypical antipsychotic uses and hyperdycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperdycemia-related adverse events in patients treated with the abpical antipsychotics. Precise risk estimates for hyperdycemia-related adverse events in patients treated with adypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on applical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, parish knotney of diabetes) with a cartain in texterned with abunical antipsychotics. regularly for worsening of guicose control. Patients with risk factors for diabetes melituits (et, obest), family history of diabetes) who are starting treatment with atypical antispsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antispsychotics should be monitored for symptoms of hypertylocanic including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hypertylocania during retarment with atypical antispsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antispsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-thration period, probably reflecting its c, aderengic antagonist properties. Syncope was reported in 1% (28/2567) of the patients treated with SEROQUEL, compared with 5% (0067) on placebo and about 0.4% (26/27) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascural disease (history of myocardia inflaction or sichemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (elelydration, hypovolemia and treatment with antilhypertensive medications). 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 detun to the previous dose in the titration schedule is appropriate. Cataracts: The development of cataracts was observed in patients during long-terms PSROQUEL terms can be seen schanges have also been observed in patients during long-terms PSROQUEL sense. The propriate cataract formation, such as still lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment rule appropriately sensitive methods, is recommended at initiation of the treatment scharges courred in 0.5% (18/2792) op platests treated Learnet to minimum, such as shift rating exam in under appropriatery sensitive minemous, is recom-mendered. The intermediate of the property es for placebo patients. These changes were only weakly related to the increases in weight observed in SEROULEL tracked patients. Megnotachinenia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROULEL, increased protectin 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 protectin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detated breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with productin-levelst puriously compounds, the clinical significance of elevated serum prodactin levels su winknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between bronge administration of this clease of drugs and tumoringensis in humans an association between bronges administration of this clease of drugs and tumoringensis in humans and accordant and the contractions of the clease of drugs and tumoringensis in humans and accordant and the contractions and the contraction of this clease of drugs and tumoringensis in humans and accordant and the contractions of the clease of drugs and tumoringensis in humans and accordant and the contraction of this clease of drugs and tumoringensis in humans and accordant and the contraction of the clease of drugs and tumoringensis in humans and accordant and the contractions and the contraction of the clease of drugs and tumoringensis in humans and accordant and the contractions are drugged and the contraction of the clease of drugs and tumoringensis in humans and accordant and the contraction and the contraction of the clease of drugs and tumoringensis in humans and accordant and the contraction of the clease of drugs and tumoringensis in hu reforfed. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference rangine in pool of 3- to 8-week placebro-controlled trials were approximately 6% for SEROULEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of 2.5 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROULEL and placebo. These hepatic enzyme elevations of succurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing freatment with SEROULEL. **Potential for Cognitive and Indust Impairment:** Sommolence was a commonly reported adverse event reported in patients treated with SEROULEL especially during the 3-5 day period of initial dose-tiliation. In schizophrenia trials, sommolence was reported in 18% of patients on SEROULEL compared to 11% of patients on SEROULEL compared to 11% of patients. In acute bipolar mania trials using SEROULEL as sommolence was reported in 16% of patients on SEROULEL compared to 9% of placebo patients. In acute bipolar mania trials using SEROULEL as sommolence was reported in 16% of patients on SEROULEL compared to 9% of placebo patients. In acute bipolar mania trials using SEROULEL as patients should be cautioned about performing activities requiring ment, thinking, or mothor skills, patients should be cautioned about performing activities requiring SEROULEL compared to 9% of placebo patients. Since SEROULEL 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 SEROULEL theray bose not affect them adversely. Prajasim: One case of principsm in a patient receiving SEROULEL has been reported prior to market introduction. While is causal relationship to use of SEROULEL has other edups with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROULEL may strate this capacity. Severe priapism may require surgical intervention. Body Emperature Regulation: Although not reported with SEROULEL factor in the work of the severe program may require surgical intervention. Body ender the present of the propers of the

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular control with advanced Abahemer's demental as ENROUEL and other artifosychoic drog should be used cautiously in patients at risk for aspiration pneumonia. Suicide: The possibility of a suicide attempt is inchement in bipolar disorder and schizophrenia: close supervision of high risk patients should accompare the properties of the properties of the procession of high risk patients should accompare the properties of the properties of the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. Use in Patients ownsistent with concomitant litiness: Clinical experience with SEPROUEL: in patients with carcomitant litiness: Clinical experience with SEPROUEL in patients with concomitant systemic litiness is made to premarked the properties of the state of the properties with research application of the actent 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). Intermation for Patients: Physicians are advised to consult the full Prescribing information for details of the following issues to disease with patients for whom they prescribe SEROUDEL: Orthostatic hypotension, interference with Cognitive and Motor Performance, Pregnancy, Nursing, Concomitant Medication, Alcohol, and relat Exposure and Dehydration. Laboratory Tests. No specific laboratory tests are recommended. Drug Interactions: The risks of using SEROUDEL in properties and the primary CNS effects of SEROUDEL. caution should be used when it is taken in combination with other drugs have not been activately evaluated in systematic studies. Given the primary CNS effects of SEROUDEL as probentiated the coughing phyotension. SEROUDEL prohamace the primary CNS effects of certain antitypertensive agents. SEROUDEL but appreniation of combination with other certaily acting drugs. SERO 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 Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetapine (300 mg bid) by 65%. Climedian: Administration of multiple daily obess of cimediane (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetapine (150 mg bid). Dosage adjustment for ketoconazole (200 mg once daily for 4 days), a potent inhibitor of ortochrome P450 3A, reduced oral elearance of quetapine by 84%, resulting in a 35% increase in maximum plasma concentration of quetapine. Caution is indicated when SERGOUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A, equal to a consideration of quetapine. Caution is indicated when SERGOUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A, equ., attracazole, fluctorazole, and erythromycin. Fluoretine, imipramine, Haloperidol, and Risperidone: Caudiministration of fluovetine (60 mg once daily) rimipramine (75 mg bid), alloperidol (7 mg bid), or risperidone (8 mg bid) with quetapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetapine. Effect of Quetapine on Offmusy. Curazepam The mean oral clearance of total propers. The mean maximum constitution and extend of security of the constitution of th many neoplasms have been found in rodents after chronic administration of other antiposychotic drugs and are considered to be protection-mediated. The relevance of this increased incidence of protection-mediated mammary gland tumors in rats to human risk is unknown (see Phyperprotectinema in PRE-CAUTIONS, General). Mutagenesis: The mutagenic potential of quelapine was tested in six in vitro to bacterial gene mutation assays and in an in vitro mammalian gene mutation assay in Chinese Hamster Ovary calls. Notwers sufficiently high concentrations of quelapine may not have been used for all tester strains. Quelapine did produce a reproducible increase in mutations in one Sainnorella typhirmurum tester strain in the presence of metabolic activation. No evidence of calsogenic potential the strains of the produce are reproducible increase in mutations in one Sainnorella typhirmurum tester strain in the presence of metabolic activation. No evidence of calsogenic potential was obtained in an in vitro chromosomal aberration assay in cultured human lymphorytes or in the In vivo micronucleus assay in rast. Impairment of Fertility; Ouethapen 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 mgm has in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg or 0.6 times the maximum human dose on a mgm and fertility in male Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mgm and fertility in relate Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mgm and fertility in relate Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mgm basis. There offect dose for interest of the strain of to SEROOUEL, or cause pusumacokinetic clearance, increase the pharmacodynamic response to SEROOUEL, or cause poorer blerance or orthosaks, should lead to consideration of a lower starting dose, slower thration, and careful monitoring during should lead to consideration of a lower starting has a clearance of SEROOUEL was reduced by 30% to 50% in elderly patients when compared to younger patients.

ADVERSE REACTIONS: The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. Of these approximately 3000 subjects, approximately 2700 (2300 in exhicophrenia and 46 in acute bioploar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. Refer to the nveness trans, and mer experience corresponded to approximately 914.3 patient-years. Refer to the III Prescribing Information for details of adverse sevent data collection. Adverse Findings Observed in Short-Term, Controlled Trials: Adverse Events Associated with Dissontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Biplard Mania: Overall, discontinuations due to adverse events were 5.7 % for SEROULEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROULE vs. 5.5% for placebo in dijunct therapy. Schizophrenia: Overall, there was fittle difference in the incidence of discontinuation due to adverse events (4% for SEROULEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to summerce and hypotension vive considered to be drug related (see PREADUTIONS). Sommolence 0.8% vs. 0% for placebo and Hypotension 0.4% vs. drug related (see PRECAUTIONS): Somnolence 0.8% vs 0% for placebo and Hypotension 0.4% vs 0% for placebo. Adverse Events Occurring at an Incidence of 1% or More Among SEROOUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The following treatment-emergent diverse events that occurred during acute theracy of schizolyneria (up to 6 weeks) and hipotar mania (up to 12 weeks) in 1% or more of patients treated with SEROOUEL (doses ranging from 75 to 800 mg/dga) where the incidence in patients treated with SEROOUEL vsa greater than the incidence in placebo-treated patients. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials* for the Treatment of Schizophrenia and Bippolar Mania Inconditionary: Body as a Whole: Headache, Palin, Asthenia, Abdominal Pain, Back Pain, Fever, Cardiovascular: Tachycardia, Postural Hypotension; Digestive: Dry Mouth, Constipation, Vorniting, Dyspepsia, Gastroenteritis, Camma Glutamyl, Transpeptidase Increased, Metabolic and Muritinosat. Weight Gain, SGPT Increased, SG0T Increased; Nervous: Agitation, Sommolence, Dizziness, Anxiety;

Respiratory: Pharyngitis, Rhinitis; Skin and Appendages: Rash; Special Senses: Amblyopia. In these studies. the most commonly observed adverse events associated with the use of SEROQUEL ficidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo w somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5 weight gain (5%), and dyspepsia (5%). Table 2 enumerates the incidence of treatment-emerg placebo are not listed, but included the following accidental injury, akathisia, chest pain, cough noreased, depression, diarhea, extrapyramidal syndrome, bostility, hypedrension, hypotension, increased appetite, infection, insomna, leukopenia, malaise, nausea, nervousness, parasthesia, peripheral edmas, aveating, terror, and weight loss. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials* for the Treatment of Bipolar Mania (Adjunt Therapy): Body as a Whole: Hadache, Asthenia, Addominal Pain, Rask Pain; Cardiovascular: Postural Hypotension; Digestive: Dry Mouth, Constipation; Metabolic and Autritional: Weight Gain; Nervous: Somolence, Diziness, Termor, Agitation; Respiratory: Pharyngiis, In these studies, the most commonly observed adverse events associated with the use of SEROOUEL Incidence of 5% or graetely and observed at a rate on SEROOUEL to Historia, and pain (7%), bostural hypotension (7%), plaryngiis (6%), and weight gain (6%). Events for which the SEROOUEL incidence was equal to or less than placebo are not listed in the table, but included the following; adversities, diarrhea, insomnia, and nausea. Dose Dependency of Adverse Events is Montarion, and aversity of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose-related Adverse Events: Logistic regression analyses revealed a positive dose response (6/L05) for the following adverse events: dyspepsia, adominal pain, and weight gain. Etrapyramidal Symptoms: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROOUEL (75), 500, 500, 705, 91, and gady provided evidence for the lack of treatment-emergent extrapyramidal Symptoms (PcS) and dose-relatedness for PS associated with SEROOUEL treatment. Three methods were used to measure PS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of Spontaneous complaints of PS (Sakhisiaa, akinesa, coupwherl rigidity, extrapyramidal symptomia, hypotenia, hypokinesia, neck schizophrenia revealing a 1% (4/39) incidence for SEROQUEL compared to 0.6% (17156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients medium the relation to tachwardia was 0.5% (1792) for SEROQUEL compared to 0% (0/178) incidence for place-bo. In acute bipolar mania (adjunct) frists the proportions of patients meeting the same criteria was 0.6% (17166) for SEROQUEL compared to 0% (0/171) incidence for place-bo. SEROQUEL compared to 2.6% (17166) for SEROQUEL compared to 2.6% (1716) incidence for place-bo. SEROQUEL see was associated with a mean increase in heart rate, assessed by ECG, 07 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 solvents and increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL solvents and increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL solvents are categorized by body system and listed in order of decreasing relatation of SEROQUEL solvents are categorized by body system and listed in order of decreasing in fequency according to the following definitions: frequent adverse events are those occurring in 1700 to 17000 patients. Place place to the solvents are those occurring in 1700 to 17000 patients, grade events are those occurring in 1700 to 17000 patients. Personal related to 1700 patients. events are tridse occurring in Hruto frou Trulo patients; rare events are tridse occurring in tever to 17000 patients. Nervous System: Frequent: hyperional, dysarthris. Infrequent ahonomal dreams, oyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, cordiusion, anne-sa, psychosis, fallucitations, hyperinesia, libido increased "unitary retention, incoordination, para-noid reaction, abnormal gait, mycolonus, delusions, manic reaction, apathy, ataxia, depersonalization, support, brushing, calabine reaction, hemiplegia, *Bare: aphasia, buccoglosal syntome, choreoa-thetosis, delitium, emotional lability, euphoria, libido decreased "neuralgia, stuttering, subtor-thematoma. Body as a Whole: *Frequent fit syntome; infrequent: here kep ain; pelvic pain", suicide attempt, malaise, photosensitivity reaction, chilis, face edema, monitasis; *Bare: abdomen entagria, plustary transpeptidase increased, gingiptis, dysphagia, fallutione, gastroenteritis, gastrisis, hemo-rious, stomatilis, fibrist, tooth caries, fecal inconfinence, gastroesophage relius, guith memorrhage, mouth ulceration, rectal hemorrhage, longue edema, *Bare: glossiis, hemalemess; intestial obstruo-tion, melena, parcetalis, Cardiovascular system: *Prequent: palpitation, Infrequent: vascollatation, Of interval prolonget, migraine, bradycardis, cerebral stotema, irregular pluse; Invaer altorium, bundle branch block, cerebrovascular accident, deep thromotophelisis, Traver intersion, *Fare: angi-losphelbitis, Traver litatening, ST abnormality increased of PS duration. Respiratory Systems *Frequent: pharquits sensition, Metabolic and Nutritional System: *Frequent: perspirat defens. *Fare: hickup, hyperentilation. Metabolic and Nutritional System: *Frequent: perspirat defens. *Popicalemia, water individual on Store and Appendiagents System: *Frequent: perspirat defens.

anu steven Johnson syndrome (SJS).

DRUG ARUSE AND DEPRÜDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-sekling behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CINS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed dosely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE: Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute OVERDOSAGE: Human experience: Experience with SEROULE (quelapine furnante) in acute overdosage was initied in the clinical trial database (freports) with estimated doses ranging from 1200 mp to 9900 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exagenetion of the drug's known pharmacological effects (e. drowsienses and sedation tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypotealemia and ritis degree heard tooks: In post-invariently experience, there have been very are reports of overdose of SEROULE alone resulting in death, orna or OTE protongation. Management of Dverdosage. In case of acute overdosage, establish and malarial an altway and ensure adequate oxygenation and verifiation. Gastric large (after intuitation, in patient is unconscious) and administration of activated charcal logether with a laxifive should be considered. The possibility of otheridation, seizure or dystomic reaction of the head and neck following overdose ray create a risk of aspiration with induced emissis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is detected, and the continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is decised to expect that the alpha-adrenegro-blocking properties of prelythmi might be additive to those of quellagine, resulting in problematic hypotension. overoosage of Schouluc L Similarly it is reasonation to expect that the alpha-adhereligic-licosidity in propellines of previous might be additive to those of queltaipine, resulting in problematic hypotension. There is no specific antidote to SEROOUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetra degrates (peinperine and dopamine should not be used, since bets stimulation may worsen hypotension in the setting of queltapine-induced alpha blockade). In cases of severe extragyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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