

Medical Students Not Immune to Club Drug Use

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CORONADO, CALIF. — One out of six medical students at a private Midwestern medical school reported prior use of at least one club drug, results from a survey found.

“Therefore, physicians should be cognizant, when treating medical students, physicians, or other health care workers, that we are not excluded from substance abuse,” Dr. Alex Horowitz said in an in-

terview after presenting the study as a poster at the annual meeting of the American Academy of Addiction Psychiatry.

“The same principles should be applied when assessing health care workers for substance use as when assessing the rest of the population,” he asserted.

In what he said is the first study of its kind, Dr. Horowitz and his associates asked 340 students at a private Midwestern medical school to complete an anonymous survey about their use of and attitudes

about club drugs. Generation I club drugs were defined as cocaine and LSD; generation II club drugs included methylenedioxymethamphetamine (also known as ecstasy), methamphetamine, gamma hydroxybutyrate (GHB), Rohypnol, ketamine, and dextromethorphan. Nearly half (46%) of the respondents were first-year medical students; 34% were in their second year; and 20% were third-year students.

The overall prevalence of lifetime club drug use was 17%, with ecstasy and co-

caine as the most popular agents of choice (12% and 6%, respectively), reported Dr. Horowitz, psychiatric unit chief of the methadone treatment program at Bellevue Hospital Center, New York.

The prevalence of medical students' lifetime ecstasy use was similar to that of their peers in the general population, as reported in the National Institute on Drug Abuse's 2004 “Monitoring the Future” survey. However, the use of generation I club drugs by medical students was lower than that of their peers in the general population, an association that remains unclear.

Compared with students aged 21-25 years, those aged 26 and older were more likely to have used the generation I drugs (cocaine, 16% vs. 4%, respectively; LSD, 14% vs. 2%). However, no relationship was found between age and use of generation II club drugs in general.

Students who reported never using club drugs perceived regular cocaine use as posing the greatest risk to health (89%), followed by ecstasy (72%). For students who reported lifetime use of at least one club drug, the perceived risk of using cocaine and ecstasy regularly was significantly lower (75% and 58%, respectively). The use of club drugs did not differ between men and women, but women found them to be generally more harmful than men did.

“There appears to be a correlation between knowledge/perceived harmfulness of each drug and drug use,” said Dr. Horowitz, of the department of psychiatry at New York University, also in New York. “Therefore, increasing formal medical student education on club drugs would help them be aware of dangers of club drug use, and also would help them know how to then assess and treat their patients who use club drugs.”

A greater number of students thought it would be necessary to revoke the license of physicians who were currently using generation I club drugs than those who were using generation II club drugs (27% vs. 20%, respectively). Women were more likely than men to endorse license revocation for physicians currently using generation I club drugs (33% vs. 22%, respectively) and for those currently using generation II club drugs (26% vs. 15%, respectively).

Dr. Horowitz acknowledged that the self-reported nature of the study is a limitation. “Some medical students may underreport their drug use for fear of having anyone find out, despite the anonymity of the survey,” he said.

Another limitation is that the data were collected in a classroom setting, which means that participants were limited to students more likely to attend class. However, the survey was administered in a class that was considered mandatory. ■

BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seven placebo-controlled trials (total duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. **GEODON XR** (ziprasidone mesylate) for injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS—QT Prolongation: Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, procabrol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see **Boxed Warning**). **QT Prolongation and Risk of Sudden Death:** GEODON use should be avoided in combination with other drugs that are known to prolong the QT interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QTc-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QTc from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QTc prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QTc, prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QTc interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see **CONTRAINDICATIONS**, and see **Drug Interactions** under **PRECAUTIONS**). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QTc measurements ≥ 500 msec. **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. 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. 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 (TD):** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is possibly not yet upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if hyperglycemia is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS—General:** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. **Orthostatic Hypotension:** GEODON 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 0.6% of GEODON patients. GEODON 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 that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). **Seizures:** In clinical trials, seizures occurred in 0.4% of GEODON patients. There were no confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON 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. **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, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed Warning**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**). **Hyperprolactinemia:** As with other drugs that antagonize dopamine D₂ receptors, GEODON elevates prolactin levels in humans. 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. 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. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON 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 GEODON therapy does not affect them adversely. **Priapism:** One case of priapism was reported in the premarketing database. **Body Temperature Regulation:** Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. **Suicide:** The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. **Use in Patients with Concomitant Illness:** Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON 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 QTc prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see **QT Prolongation and Risk of Sudden Death in WARNINGS** and **Orthostatic Hypotension in PRECAUTIONS**). **Information for Patients:** To ensure safe and effective use of GEODON, the

information and instructions in the *Patient Information Section* should be discussed with patients. **Laboratory Tests:** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QTc measurements ≥ 500 msec (see **WARNINGS**). **Drug Interactions:** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. **Effect of Other Drugs on GEODON:** **Carbamazepine**, 200 mg qd for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. **Ketoconazole**, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. **Cimetidine**, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztrone, propranolol, or lorazepam. **Effect of GEODON on Other Drugs:** In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of *lithium*. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*: ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, *dextrorphan*. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidence of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia**). **Mutagenesis:** There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. **Impairment of Fertility:** GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced. **Pregnancy—Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of GEODON on labor and delivery in humans is unknown. **Nursing Mothers:** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. **Pediatric Use:** The safety and effectiveness of GEODON in pediatric patients have not been established. **Geriatric Use:** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, 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 for some elderly patients. **ADVERSE REACTIONS—Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week, flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. **Adverse Events Associated with Discontinuation:** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. **Adverse Events at an Incidence $\geq 5\%$ and at Least Twice the Rate of Placebo:** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: **Body as a Whole**—asthenia, accidental injury, chest pain. **Cardiovascular**—tachycardia. **Digestive**—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. **Nervous**—extrapyramidal symptoms, somnolence, akathisia, dizziness. **Respiratory**—respiratory tract infection, rhinitis, cough increased. **Skin and Appendages**—rash, fungal dermatitis. **Special Senses**—abnormal vision. Bipolar Mania: **Body as a Whole**—headache, asthenia, accidental injury. **Cardiovascular**—hypertension. **Digestive**—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. **Musculoskeletal**—myalgia. **Nervous**—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hyposthesia, speech disorder. **Respiratory**—pharyngitis, dyspnea. **Skin and Appendages**—fungal dermatitis. **Special Senses**—abnormal vision. **Dose Dependence:** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hyperreflexia, somnolence, tremor, rhinitis, rash, and abnormal vision. **Extrapyramidal Symptoms (EPS):** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. **Vital Sign Changes:** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain:** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain ($>7\%$ of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a “low” BMI (<23) compared to normal (23-27) and overweight (>27) kg mean weight loss for patients with a “high” BMI. **ECG Changes:** GEODON is associated with an increase in the QTc interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. **Other Adverse Events Observed During the Premarketing Evaluation of GEODON:** Frequent adverse events are those occurring in at least 1/1000 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. Schizophrenia: **Body as a Whole**—Frequent: abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. **Cardiovascular System**—Frequent: tachycardia, hypertension, postural hypotension. **Infrequent:** bradycardia, angina pectoris, atrial fibrillation. **Rare:** first degree AV block, bundle branch block, pleuritis, pulmonary embolism, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. **Digestive System**—Frequent: anorexia, vomiting. **Infrequent:** rectal hemorrhage, dysphagia, tongue edema. **Rare:** gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. **Endocrine**—Rare: hypothyroidism, hyperthyroidism, thyroiditis. **Hemic and Lymphatic System**—Infrequent: anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy. **Rare:** thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polythemia, thrombocytosis. **Metabolic and Nutritional Disorders**—Infrequent: thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesterolemia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia. **Rare:** BUN increased, creatinine increased, hyperlipidemia, hypercholesterolemia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hypercholesterolemia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. **Musculoskeletal System**—Frequent: myalgia. **Infrequent:** tenosynovitis. **Rare:** myopathy. **Nervous System**—Frequent: agitation, extrapyramidal syndrome, tremor, dystonia, hyperreflexia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hyposthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy. **Infrequent:** paralysis. **Rare:** myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonus, reflexes increased, trismus. **Respiratory System**—Frequent: sinusitis. **Infrequent:** pneumonia, epistaxis. **Rare:** hemoptysis, laryngismus. **Skin and Appendages**—Frequent: maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. **Special Senses**—Frequent: fungal dermatitis. **Infrequent:** conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia. **Rare:** eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. **Urogenital System**—Infrequent: impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria. **Rare:** glycocostasia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON ($\geq 5\%$) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence $\geq 1\%$ in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in $\geq 1\%$ of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. **Body as a Whole**—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. **Cardiovascular**—postural hypotension, hypertension, bradycardia, vasodilation. **Digestive**—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. **Nervous**—dizziness, anxiety, insomnia, speech disorder, akathisia, agitation, extrapyramidal syndrome, hyperreflexia, cogwheel rigidity, paresthesia, personality disorder, psychosis, somnolence. **Respiratory**—rhinitis. **Skin and Appendages**—fungal dermatitis, sweating. **Urogenital**—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE—Controlled Substance Class:** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdose of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).