

Prophylaxis a Must for Cluster Headache Patients

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LAS VEGAS — Every cluster headache patient needs to be on a prophylactic drug, Todd D. Rozen, M.D., said at a symposium sponsored by the American Headache Society.

"I tell them, 'I'm not happy, and you shouldn't be happy, until you're cluster free on prevention,'" noted Dr. Rozen, who is with the Michigan Head-Pain and

Neurological Institute in Ann Arbor.

There are two types of prophylaxis for cluster headache: transitional treatments, which are intended to prevent cluster headaches from occurring for a short period of time (typically 7-14 days), and maintenance preventive treatments, which are designed to keep a patient cluster free in a cluster cycle.

Transitional treatments must kick in quickly. They're used for 10-14 days, after which they're tapered down as the

maintenance preventives are tapered up to a therapeutic dose. The transitional drug and maintenance preventive drug are typically started at the same time, Dr. Rozen said.

Corticosteroids are the most commonly used transitional treatment. Start prednisone at a dosage of 60-80 mg/day, tapering down over a period of 10-12 days, he said.

Naratriptan can be used at a dosage of 2.5 mg b.i.d., but monitor the patient for

rebound headaches. Ergotamine, at a dosage of 2 mg at bedtime or b.i.d., also appears useful.

Dihydroergotamine can be given by daily intramuscular injections over a period of 1-2 weeks, or by an intravenous infusion for 3 days.

For reasons that are unclear, greater occipital nerve blocks seem to work well, giving some patients up to 13 days free of cluster headaches, even when their pain (like that of most cluster patients) is not located in the occipital area. The mechanism of action may involve decreasing afferent impulses to the spinal trigeminal nuclear complex.

For long-term prevention, a number of drugs work well, but many patients will need to be on combination therapy, taking two, three, or even four drugs to fully prevent recurrences.

"Melatonin is really my first-line choice because it is easy to get over the counter and there are no side effects," Dr. Rozen said. "[For] a small percentage of cluster patients, the night I give them melatonin is the last time they're going to have a cluster." The typical dosage is 9 mg at bedtime, although some patients have required higher doses.

Verapamil is the best cluster preventive currently available, Dr. Rozen said. He recommended moving the dosage up quickly, since some patients will need up to 1 g/day. ECGs must be performed at every dosage above 480 mg to monitor for heart block. Lithium carbonate, 300 mg t.i.d., appears to be well tolerated in cluster headache.

Valproic acid, when pushed up to a dosage of 3,000 mg at bedtime, is sometimes effective.

Some small, uncontrolled studies suggest that topiramate may be effective for preventing clusters. When trying topiramate, increase the dosage in 25-mg increments every 4-5 days until the patient is taking 75-100 mg/day. When patients do respond to topiramate, it's usually in a short period, 1-2 weeks after starting the agent, he said.

Other preventive treatments that may be effective are transdermal clonidine, ti-zanidine, indomethacin, nasal capsaicin, gabapentin, baclofen, and histamine desensitization.

For some patients, steroids seem to be the only thing that works, Dr. Rozen noted, and of course patients shouldn't take corticosteroids chronically. He has had success in a single patient with mycophenolate mofetil (CellCept), the steroid-sparing immunosuppressant.

Dr. Rozen acknowledged being a member of the advisory board of Ortho-McNeil Pharmaceuticals Inc., whose products include topiramate (Topamax).

GEDDON® (ziprasidone HCl) Capsules is a psychotropic medication indicated for schizophrenia and patients experiencing acute manic or mixed episodes associated with bipolar I disorder. GEDDON® (ziprasidone mesylate) for injection is indicated for schizophrenia.

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CONTRAINDICATIONS — QT Prolongation: Because of GEDDON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEDDON 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 GEDDON and other drugs that prolong the QT interval have not been performed. An additive effect of GEDDON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEDDON 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, levomefentanyl, doxazosin mesylate, procaboc, or tacrolimus. GEDDON 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**). GEDDON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS** — QT Prolongation and Risk of Sudden Death: GEDDON 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 GEDDON. A study directly comparing the QT/QTc-prolonging effect of GEDDON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QTc from baseline for GEDDON 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 GEDDON on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEDDON 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 22988 (0.06%) GEDDON patients and 1440 (0.23%) placebo patients revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEDDON patients, neither case suggested a role of GEDDON. Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsades de pointes and with sudden unexplained death. The relationship of QT prolongation to torsades de pointes is clearer for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsades de pointes has not been observed in association with the use of GEDDON 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 GEDDON, 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 GEDDON (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 GEDDON 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 GEDDON 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 GEDDON at recommended doses. The premarketing experience for GEDDON did not reveal an excess of mortality for GEDDON 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, GEDDON'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 GEDDON 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 torsades 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. GEDDON 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 GEDDON 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 these electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEDDON 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, GEDDON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEDDON 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 impossible to rely 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 GEDDON, 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 GEDDON, and it is not known if GEDDON is associated with these events. Patients treated with atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS** — **General**: Rash: In premarketing trials, about 5% of GEDDON patients developed rash and/or urticaria, and discontinuation of treatment in about one-third 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 GEDDON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEDDON should be discontinued. **Orthostatic Hypotension**: GEDDON 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 6% of GEDDON patients. GEDDON 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 GEDDON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEDDON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. **Hyperprolactinemia**: As with other drugs that antagonize dopamine D₂ receptors, GEDDON 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 GEDDON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEDDON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEDDON 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 GEDDON therapy does not affect them adversely. **Abuse**: One case of priapism was reported in the premarketing database. **Body Temperature Regulation**: Although not reported with GEDDON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. **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 GEDDON and other antipsychotic drugs should be used cautiously in patients at risk. **Suicide**: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEDDON 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 GEDDON in patients with certain concomitant systemic illnesses is limited. GEDDON 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 GEDDON, 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 GEDDON, the information and instructions in the Patient Information Sections should be discussed with patients. **Laboratory Tests**: Patients being considered for GEDDON 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 GEDDON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEDDON in patients who are found to have persistent QTc measurements >500 msec (see **WARNINGS**). **Drug Interactions**: (1) GEDDON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEDDON, caution should be used when it is taken in

combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEDDON may enhance the effects of certain antihypertensive agents. (4) GEDDON may antagonize the effects of levodopa and dopamine agonists. **Effect of Other Drugs on GEDDON**: Carbamazepine 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEDDON. Ketoconazole, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEDDON by about 35%-40%. Cimetidine, 800 mg qd for 2 days, did not affect GEDDON pharmacokinetics. Coadministration of 30 mL of Maaloxid did not affect GEDDON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benzperone, propranolol, or lorazepam. **Effect of GEDDON on Other Drugs**: In vitro studies revealed little potential for GEDDON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEDDON due to displacement. GEDDON 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. GEDDON 20 mg bid did not affect the pharmacokinetics of concomitantly administered oral contraceptives: ethinylloestradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEDDON 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 GEDDON 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 incidences 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. GEDDON 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**: GEDDON 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. GEDDON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery**: The effect of GEDDON on labor and delivery in humans is unknown. **Nursing Mothers**: It is not known whether, and if so in what amount, GEDDON or its metabolites are excreted in human milk. It is recommended that women receiving GEDDON should not breast feed. **Pediatric Use**: The safety and effectiveness of GEDDON in pediatric patients have not been established. **Geriatric Use**: Of the approximately 4500 patients treated with GEDDON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEDDON or of reduced clearance of GEDDON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEDDON, 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 GEDDON was administered in doses ranging from 10 to 200 mg/day. **Adverse Events Associated with Discontinuation**: Schizophrenia: Approximately 4.1% (29/202) of GEDDON-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 GEDDON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEDDON-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 GEDDON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEDDON 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 5% and at Least Twice the Rate of Placebo**: The most commonly observed adverse events associated with GEDDON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEDDON 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 active therapy, including only those events that occurred in 2% of GEDDON 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 Dependency**: 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, hypertension, somnolence, tremor, rhinitis, rash, and abnormal vision. **Extrapyramidal Symptoms (EPS)**: The incidence of reported EPS for GEDDON 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 GEDDON and placebo. **Vital Sign Changes**: GEDDON is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain**: In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of 7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEDDON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEDDON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEDDON and placebo patients. During long-term therapy with GEDDON, 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" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. **ECG Changes**: GEDDON is associated with an increase in the QTc interval (see **WARNINGS**). In schizophrenia trials, GEDDON 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 GEDDON**: Frequent adverse events are 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. Schizophrenia: **Body as a Whole**—Frequent: abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hyperthermia, 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 embolus, cardiomegaly, cerebral infarction, 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, polycythemia, thrombocytopenia. **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, hypochlosterolemia, hypokalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glycosuria tolerance decreased, gout, hypercholesterolemia, hypernatremia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. **Musculoskeletal System**—Frequent: myalgia; **Infrequent**: tenosynovitis; **Rare**: myopathy. **Nervous System**—Frequent: agitation, extrapyramidal syndrome, tremor, dystonia, hypertension, dyskinesia, hostility, twitching, paresis, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hyposthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccolossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; **Infrequent**: paralysis; **Rare**: myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonus, reflexes increased, trismus. **Respiratory System**—Frequent: dyspnea; **Infrequent**: pneumonia, epistaxis; **Rare**: hemoptysis, laryngismus. **Skin and Appendages**—Infrequent: 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**: gynecosmia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEDDON**: In these studies, the most commonly observed adverse events associated with the use of intramuscular GEDDON (5%) and observed at a rate on intramuscular GEDDON (in the higher dose groups) at least twice that of the lowest intramuscular GEDDON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials**: The following list enumerates the treatment-emergent adverse events that occurred in 1% of GEDDON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEDDON 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, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertension, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. **Respiratory**—rhinitis. **Skin and Appendages**—fungal dermatitis, sweating. **Urogenital**—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE**—**Controlled Substance Class**: GEDDON is not a controlled substance. **OVERDOSEAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdose of GEDDON 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 hyperreflexia (BP 200/75).

REFERENCES: 1. Data on file. Pfizer Inc., New York, NY. 2. Keck PE, Versiani M, Potkin S, West SA, Giller E, Ice K, and the Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003;160:741-748.

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