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 seventeen placebo controlled trials (modal 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® (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, probucol, 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_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c 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 QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c 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 QT_c 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/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c 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/QT_c 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 QT_c 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 QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c 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 QT_c 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 QT_c 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 QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c 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 QT_c 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, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c 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 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 GEODON 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 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 D_2 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 QT_c 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 QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not 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 bid 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 benztropine, 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 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. 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/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 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 ≥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, hypesthesia, 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, hypertonia, 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 ≥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" 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:*** GEODON is associated with an increase in the QT_c 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 1/100 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, 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, phlebitis, pulmonary embolus, 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, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders— *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System— *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System— *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, 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:* gynecomastia, 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 (≥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 >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥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, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, 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 overdosage 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).

References: 1. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology.* 2001;155:128-134. **2.** Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry.* 2001;62:12-18. **3.** Brook S, Walden J, Benattia I, Su CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology.* 2005;178:514-523. **4.** Brook S, Lucey JV, Gunn KP, for the Ziprasidone IM Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry.* 2000;61:933-941. **5.** Data on file. Pfizer Inc, New York, NY.

Revised November 2006

Control acute agitation with

GEODON®

for ***Injection*** *(ziprasidone mesylate)*

In schizophrenia. . .

Rapid control* with low EPS[1-4]

- **Low incidence of movement disorders[1-4]**
- **Smooth transition, with continued improvement, from IM to oral therapy[3,4]**
- **May be used concomitantly with benzodiazepines[2,3,5]**

*In 2 pivotal studies vs control, significance was achieved at the 2-hour primary end point (10 mg study) and at the 4-hour primary end point (20 mg study).

GEODON for Injection is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with GEODON is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_c interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

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 GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence ≥5%) and observed at a rate in the higher GEODON dose groups (10 mg, 20 mg) of at least twice that of the lowest GEODON dose group (2 mg control) were somnolence (20%), headache (13%), and nausea (12%).

Please see brief summary of prescribing information on adjacent page.

Call for Papers
***Epidemiologic Reviews* Theme Issue**
The Epidemiology of Mental Disorders

Epidemiologic Reviews, a sister publication of the *American Journal of Epidemiology*, is devoted to publishing comprehensive and critical reviews on specific themes once a year. The next issue will address the epidemiology of mental disorders. We are soliciting manuscripts on topics such as schizophrenia, depression, anxiety, suicide, dementia, eating disorders, life course approaches, international variation, genetic and social risk factors, and epidemiologic approaches to taxonomy.

Please note that papers on other aspects of the epidemiology of mental disorders are welcome. Manuscripts can be up to 6,000 words in length exclusive of the abstract, tables, figures, and references. Give details of the method of literature search and use systematic reviews or meta-analysis, if appropriate.

Submit completed manuscripts as email attachments to Harriett Telljohann (htelljoh@jhsph.edu) by November 30, 2007.

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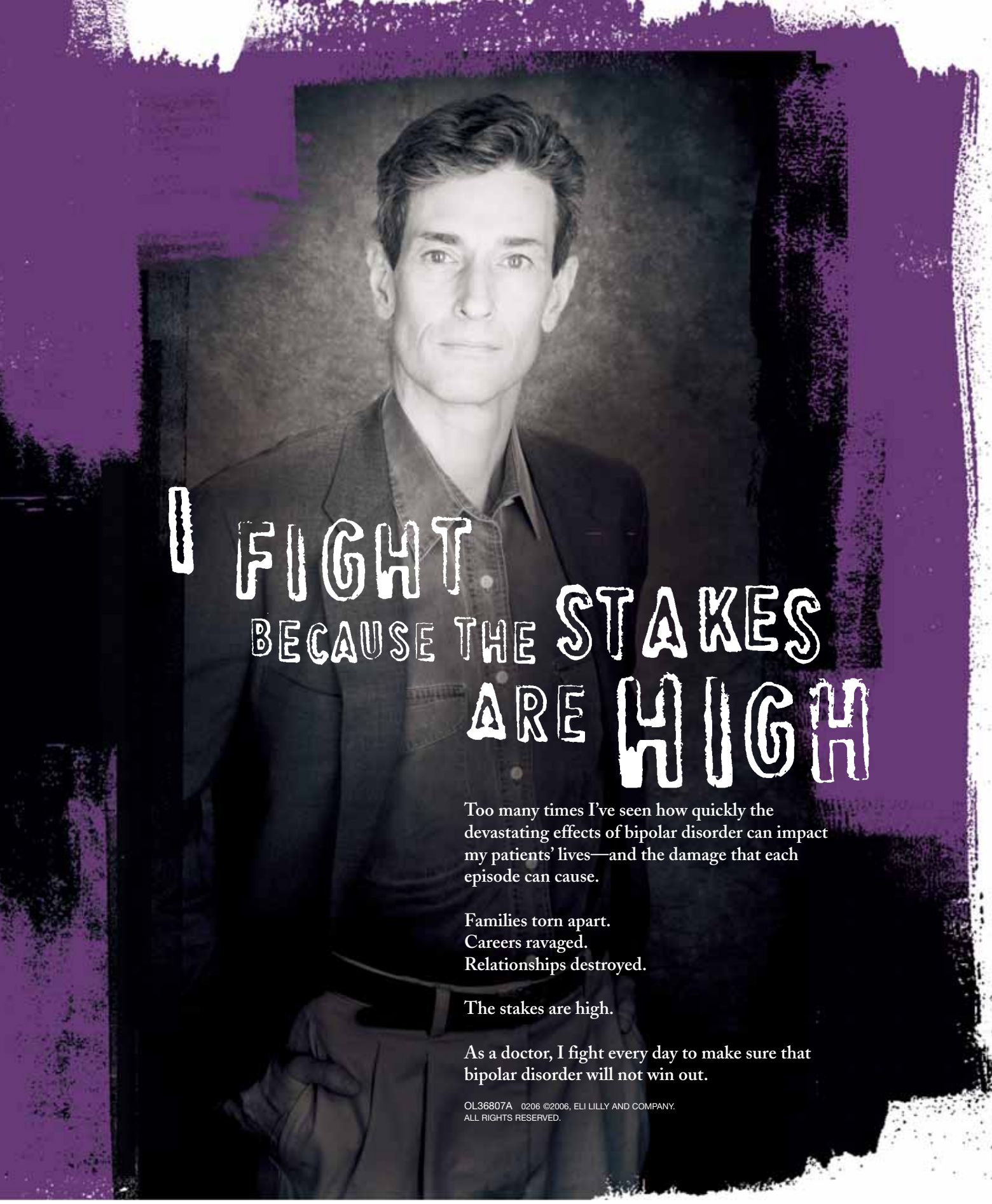


I FIGHT BECAUSE THE STAKES ARE HIGH

Too many times I've seen how quickly the devastating effects of bipolar disorder can impact my patients' lives—and the damage that each episode can cause.

Families torn apart.
Careers ravaged.
Relationships destroyed.

The stakes are high.

As a doctor, I fight every day to make sure that bipolar disorder will not win out.

Lilly

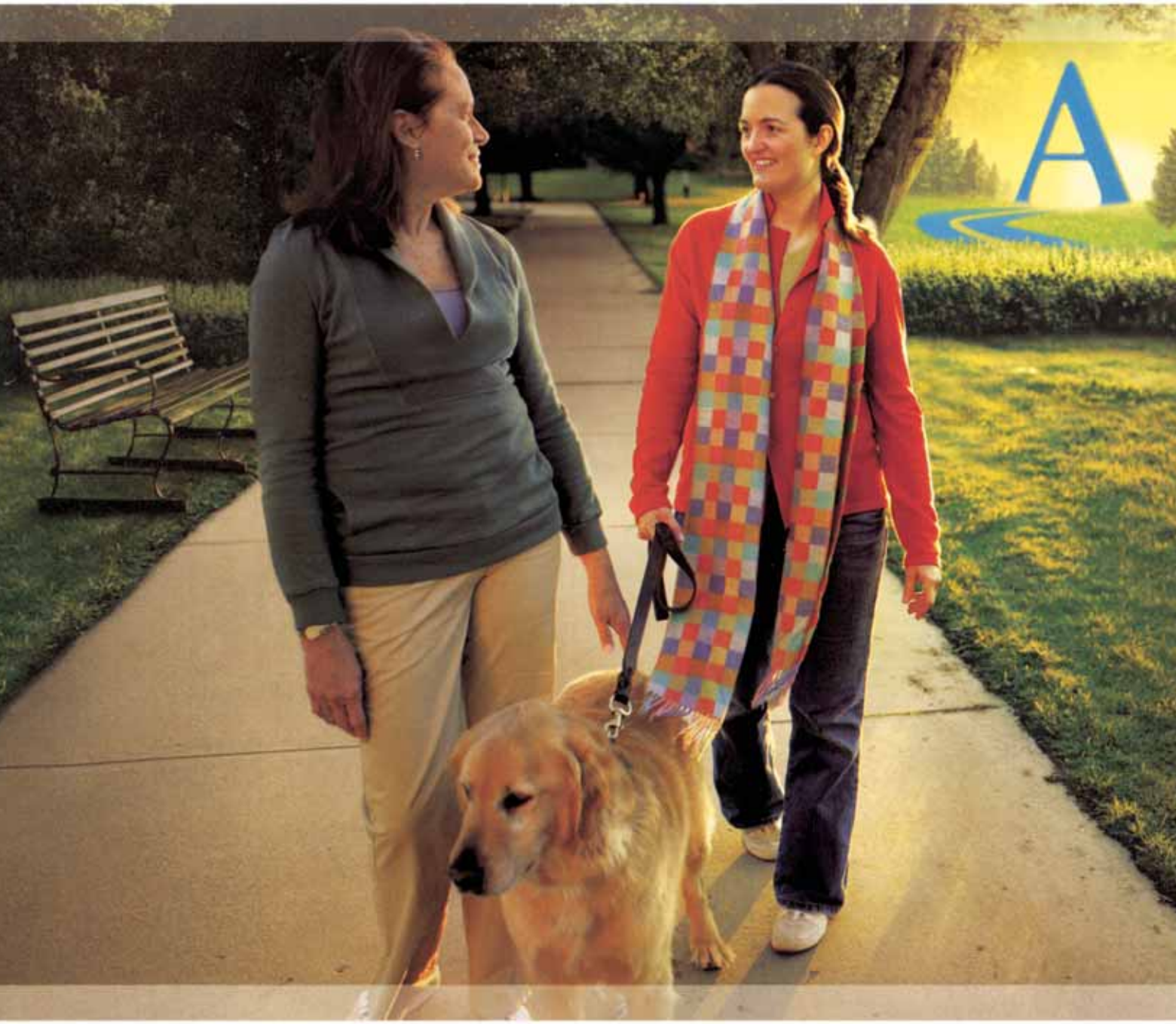
The things that may describe a patient with schizophrenia…

Delusions
Emotional withdrawal
Disorganized behavior

Family history of high cholesterol

…can obscure the person

ABILIFY Helps Reveal



ABILIFY is indicated for the treatment of schizophrenia.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

HELP ILLUMINATE

The Person Within.

Meet Kristen, age 31. She is a patient with schizophrenia, but she's also an animal lover, daughter, and friend. She's so much more than her illness.

Do you have someone like Kristen in your practice?

ABILIFY significantly reduced positive and negative symptoms, as measured by PANSS™ Total Score, at primary endpoint (Week 4) in a 4-week, double-blind, placebo-controlled trial in patients with schizophrenia.[1]

In a long-term (26-week), placebo-controlled trial there were no medically important differences between the ABILIFY and placebo patients in the mean change from baseline in triglyceride, HDL, LDL, and total cholesterol measurements.

PANSS™ (Positive and Negative Syndrome Scale) is a trademark of Multi-Health Systems, Inc.

Please see IMPORTANT SAFETY INFORMATION, including **Boxed WARNING**, on following page.

THE PERSON WITHIN

ABILIFY®
(aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

IMPORTANT SAFETY INFORMATION for ABILIFY

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). ABILIFY is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

- **Neuroleptic malignant syndrome (NMS)**–As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation is recommended
- **Tardive dyskinesia (TD)**–The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely
- **Cerebrovascular adverse events** (eg, stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY
- **Hyperglycemia and diabetes mellitus**–Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY

Treatment-emergent adverse events reported with:

ABILIFY Oral

In short-term trials of patients with schizophrenia (up to 6 weeks) or bipolar disorder (up to 3 weeks), the following were reported at an incidence ≥10% and greater than placebo, respectively: headache (30% vs 25%), anxiety (20% vs 17%), insomnia (19% vs 14%), nausea (16% vs 12%), vomiting (12% vs 6%), dizziness (11% vs 8%), constipation (11% vs 7%), dyspepsia (10% vs 8%), and akathisia (10% vs 4%).

ABILIFY Injection

In short-term (24 hour) trials, the following were reported at an incidence ≥5% and greater than placebo, respectively: headache (12% vs 7%), nausea (9% vs 3%), dizziness (8% vs 5%), and somnolence (7% vs 4%).

ABILIFY for Schizophrenia:

- Rapid control of agitation*
- Early† and sustained positive and negative symptom control
- Low incidence of somnolence/sedation‡
- Low mean weight change in clinical trials
  - — In a 52-week schizophrenia trial, weight change averaged 1 kg for ABILIFY-treated patients (BMI <23, 2.6 kg; BMI 23 to 27, 1.4 kg; BMI >27, -1.2 kg). The percentage of ABILIFY-treated patients with ≥7% increase in baseline body weight was 30% for those with BMI <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27.
- Lipid profile comparable to placebo

*With ABILIFY Injection at primary endpoint (2 hours). ABILIFY Injection is indicated for the treatment of agitation associated with schizophrenia.
†As early as Week 1 through study endpoint (Week 4).
‡ABILIFY 10%, placebo 8%.

Physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Like other antipsychotics, ABILIFY may have the potential to **impair judgment, thinking, or motor skills.** Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

ABILIFY®
(aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

HELP ILLUMINATE THE PERSON WITHIN

Please see BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION, including **Boxed WARNING,** on adjacent pages.

Reference: 1. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizoaffective disorder. *Arch Gen Psychiatry.* 2003;60:681-690.

570US07AB09902 June 2007 AB07A-0027 Printed in USA Printed on recycled paper

ABILIFY® (aripiprazole) TABLETS
ABILIFY® (aripiprazole) ORAL SOLUTION
ABILIFY® DISCMELT™ (aripiprazole) Orally Disintegrating Tablets
ABILIFY® (aripiprazole) INJECTION FOR INTRAMUSCULAR USE ONLY

Rx only

BRIEF SUMMARY: PLEASE CONSULT PACKAGE INSERT FOR COMPLETE 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 seventeen placebo-controlled trials (modal 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS: Known hypersensitivity to aripiprazole

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. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

Neuroleptic Malignant Syndrome (NMS): Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including ABILIFY. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If signs and symptoms appear, immediate discontinuation is recommended (see **Full Prescribing Information for additional information on management of NMS).** Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia (TD): Potentially irreversible TD may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely. Antipsychotic treatment, itself, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possible mask the underlying process. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. The need for continued treatment should be reassessed periodically.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled clinical studies (two flexible-dose and one fixed-dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients. In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING**, **WARNINGS** and **PRECAUTIONS** in **Full Prescribing Information**)

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Patients diagnosed with diabetes who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control; patients with risk factors for diabetes should undergo baseline and periodic fasting blood glucose (FBG) testing. Any patient being treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia and those who develop symptoms of hyperglycemia should also undergo FBG testing.

PRECAUTIONS: General:

Orthostatic Hypotension: ABILIFY may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on oral ABILIFY included: orthostatic hypotension (1.9%), postural dizziness (0.8%), and syncope (0.6%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on oral ABILIFY included: orthostatic hypotension (0.7%), postural dizziness (0.5%), and syncope (0.3%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in agitation associated with schizophrenia or bipolar mania (n=501) on ABILIFY Injection included: orthostatic hypotension (0.6%), postural dizziness (0.2%), and syncope (0.4%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo in trials in patients with schizophrenia, bipolar mania, or agitation associated with schizophrenia or bipolar mania. ABILIFY should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY Injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension.

Seizures: In short-term trials, seizures/convulsions occurred in 0.1% (1/926) of oral aripiprazole-treated patients with schizophrenia, in 0.3% (2/597) of oral aripiprazole-treated patients with bipolar mania, and in 0.2% (1/501) of aripiprazole injection-treated patients with agitation associated with schizophrenia or bipolar mania. Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment: Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. In short-term trials, somnolence (including sedation) was reported in 10% of patients with schizophrenia on oral ABILIFY compared to 8% of patients on placebo; 14% of patients with bipolar mania on oral ABILIFY compared to 7% of patients on placebo; and in 9% of patients with agitation associated with schizophrenia or bipolar mania on ABILIFY Injection compared to 6% of patients on placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Use appropriate care when prescribing aripiprazole for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. ABILIFY and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management.

Use in Patients with Concomitant Illness: Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease.

In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were lethargy, somnolence (including sedation), incontinence (primarily, urinary incontinence), excessive salivation, and lightheadedness. ABILIFY is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration (See **Boxed WARNING**, **WARNINGS** and **CLINICAL PHARMACOLOGY: Special Populations** in **Full Prescribing Information**).

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY (aripiprazole) see full Prescribing Information for the complete information to discuss with patients taking aripiprazole:

Interference with Cognitive and Motor Performance: Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY.

Nursing: Patients should be advised not to breast-feed an infant if they are taking ABILIFY.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics: Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT orally disintegrating tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

Sugar Content: Patients should be advised that each mL of ABILIFY oral solution contains 400 mg of sucrose and 200 mg of fructose.

Drug Interactions: Use caution when ABILIFY is taken in combination with other centrally acting drugs and alcohol. ABILIFY may enhance the effect of certain antihypertensive agents. ABILIFY is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. *In vivo* studies using 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole.

Inducers of CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. When a **CYP3A4** inducer is added to ABILIFY, the dose of ABILIFY should be doubled. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from combination therapy, the ABILIFY dose should be reduced.

Carbamazepine: Coadministration of carbamazepine (200 mg BID) with ABILIFY (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of aripiprazole and its active metabolite, dehydro-aripiprazole.

Inhibitors of CYP3A4 (eg, ketoconazole) or **CYP2D6** (eg, quinidine, fluoxetine, or paroxetine) can inhibit the elimination of aripiprazole and cause increased blood levels. When a strong **CYP3A4** or **CYP2D6** inhibitor is added to ABILIFY, the dose of ABILIFY should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the ABILIFY dose should then be increased.

Ketoconazole: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of ABILIFY increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively.

Quinidine: Coadministration of a 10-mg single dose of ABILIFY with quinidine (166 mg/day for 13 days) increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%.

Alcohol: There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and at 10, 20, 40, 60 mg/kg/day (3 to 19 times the maximum recommended human dose [MRHD] based on mg/m^2) to SD rats and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the MRHD based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years. Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2). These findings are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 13-week dietary study in female mice at doses used in the carcinogenicity study. Serum prolactin was not increased in a 4- and 13-week dietary study in female rats. The relevance for human risk of prolactin-mediated endocrine tumors in rodents is unknown. **Mutagenesis:** Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice; however, the response was shown to be due to a mechanism not considered relevant to humans. **Impairment of Fertility:** Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD on an mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg. Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on an mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Aripiprazole should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Labor and Delivery: The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers: Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use: Safety and effectiveness in pediatric and adolescent patients have not been established.

Geriatric Use: Placebo-controlled studies of oral aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients. Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. (See also **Boxed WARNING, WARNINGS** and **PRECAUTIONS** in **Full Prescribing Information**)

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 8456 patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5635 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 2442 patients were treated with oral aripiprazole for at least 180 days and 1667 patients treated with oral aripiprazole had at least 1 year of exposure.

Adverse Events Associated with Discontinuation of Treatment: Overall, there was little difference in the incidence of discontinuation due to adverse events in placebo-controlled oral aripiprazole trials (aripiprazole vs placebo: schizophrenia, 7% vs 9%; bipolar mania, 11% vs vs 9%; or in placebo-controlled intramuscular aripiprazole injection trials (aripiprazole injection, 0.8%; placebo 0.5%). The types of adverse events that led to discontinuation were similar between the oral aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events: (≥5% incidence and at a rate at least twice the rate of placebo for ABILIFY vs placebo, respectively): In 4- to 6-week, placebo-controlled, schizophrenia trials (2 to 30 mg/day), the one commonly observed adverse event associated with the use of oral aripiprazole was: akathisia (8%, 4%). In 3-week, placebo-controlled, bipolar mania trials (15 or 30 mg/day), the most common adverse events associated with oral aripiprazole were: akathisia (15%, 3%), constipation (13%, 6%), sedation (8%, 3%), tremor (7%, 3%), restlessness (6%, 3%), extrapyramidal disorder (5%, 2%). In 24-hour placebo-controlled trials of intramuscular aripiprazole injection for agitation associated with schizophrenia or bipolar mania, nausea was the one adverse event observed (9%, 3%).

Adverse Events with an Incidence ≥2% in Oral Aripiprazole Trials: The following treatment-emergent

events were reported at an incidence of ≥2% with oral aripiprazole (doses ≥2 mg/d), and at a greater incidence with aripiprazole than with placebo in short-term placebo-controlled trials (aripiprazole N=1523, placebo N=849), respectively, were: headache (30%, 25%), anxiety (20%, 17%), insomnia (19%, 14%), nausea (16%, 12%), vomiting (12%, 6%), dizziness (11%, 8%), constipation (11%, 7%), dyspepsia (10%, 8%), akathisia (10%, 4%), sedation (7%, 4%), fatigue (6%, 5%), extrapyramidal disorder (6%, 4%), somnolence (5%, 4%), dry mouth (5%, 4%), arthralgia (5%, 4%), tremor (5%, 3%), restlessness (5%, 3%), pharyngolaryngeal pain (4%, 3%), pain in extremity (4%, 2%), cough (3%, 2%), nasal congestion (3%, 2%), abdominal discomfort (3%, 2%), stomach discomfort (3%, 2%), pain (3%, 2%), vision blurred (3%, 1%), salivary hypersecretion (2%, 1%), peripheral edema (2%, 1%), hypertension (including blood pressure increased) (2%, 1%). The following events were reported by patients treated with oral aripiprazole with an incidence equal to or less than placebo: diarrhea, toothache, upper abdominal pain, abdominal pain, musculoskeletal stiffness, back pain, myalgia, agitation, psychotic disorder, dysmenorrhea (percentage based on gender total), and rash.

Adverse Events with an Incidence ≥1% in Intramuscular Aripiprazole Injection Trials: The following treatment-emergent events were reported at an incidence ≥1% with intramuscular aripiprazole injection (doses ≥5.25 mg/day) and at incidence greater than placebo in 24-hour, placebo-controlled trials (aripiprazole injection N=501, placebo N=220) in agitated patients with schizophrenia or bipolar mania, respectively, include: headache (12%, 7%), nausea (9%, 3%), dizziness (8%, 5%), somnolence (7%, 4%), sedation (3%, 2%), vomiting (3%, 1%), fatigue (2%, 1%), tachycardia (2%, <1%), akathisia (2%, 0%), dyspepsia (1%, <1%), dry mouth (1%, <1%), blood pressure increased (1%, <1%), musculoskeletal stiffness (1%, <1%). The following events were reported by patients treated with aripiprazole injection with an incidence equal to or less than placebo: injection site pain, injection site burning, insomnia, agitation.

Dose-Related Adverse Events: Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. The one adverse event to have a possible dose response relationship was somnolence (including sedation) which was most prominent at the 30 mg/day dose (placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

Extrapyramidal Symptoms: In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia was (oral aripiprazole 13%, placebo 12%) and the incidence of akathisia-related events was (oral aripiprazole 8%, placebo 4%). In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events, excluding events related to akathisia was (oral aripiprazole 15%, placebo 8%) and the incidence of akathisia-related events was (oral aripiprazole 15%, placebo 4%). In the placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia was (aripiprazole injection 2%, placebo 2%) and the incidence of akathisia-related events was (aripiprazole injection 2%, placebo 0%).

Laboratory Test Abnormalities: A between group comparison for 3- to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

Weight Gain: In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%). In a 26-week schizophrenia trial, weight change, respectively, for ABILIFY (aripiprazole)- and placebo-treated patients was -0.5 kg and -0.5 kg for those with BMI <23, -1.3 kg and -0.6 kg for those with BMI 23 to 27, and -2.1 kg and -1.5 kg for those with BMI >27. The percentage of ABILIFY- and placebo-treated patients, respectively, with ≥7% increase in baseline body weight was 6.8% and 3.7% for those with BMI <23, 5.1% and 4.2% for those with BMI 23 to 27, and 5.7% and 4.1% for those with BMI >27. In a 52-week schizophrenia trial, weight change for ABILIFY-treated patients was 2.6 kg for those with BMI <23, 1.4 kg for those with BMI 23 to 27, and -1.2 kg for those with BMI >27. The percentage of ABILIFY-treated patients with ≥7% increase in baseline body weight was 30% for those with BMI <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27.

ECG Changes: Pooled analysis of placebo-controlled trials in patients with schizophrenia or bipolar mania treated with oral aripiprazole or in patients with agitation associated with schizophrenia or bipolar mania treated with intramuscular aripiprazole injection, revealed no significant differences between aripiprazole and placebo of potentially important changes in ECG parameters. Oral aripiprazole was associated with a median increase in heart rate of 5 beats per minute compared to a 1 beat per minute increase among placebo patients.

Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse events reported in a 26-week, double-blind trial comparing oral ABILIFY and placebo in patients with schizophrenia or bipolar mania were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor (ABILIFY 8% vs placebo 2%).

Other Adverse Events Observed During the Premarketing Evaluation of Oral Aripiprazole

The following adverse events were reported with oral aripiprazole at multiple doses ≥2 mg/day in clinical trials (8456 patients, 5365 patient-years of exposure). This list may not include events previously listed elsewhere in the labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening. *Frequent events* are those occurring in at least 1/100 patients; *infrequent events* are those occurring in 1/100 to 1/1000 patients; *rare events* are those occurring in fewer than 1/1000 patients. ***Blood and Lymphatic System Disorders:*** *Infrequent* - anaemia, lymphadenopathy, leukopenia (including agranulocytosis, neutropenia); *Rare* - leukocytosis, thrombocytopenia, idiopathic thrombocytopenic purpura, thrombocythaemia. ***Cardiac Disorders:*** *Frequent* - tachycardia (including ventricular, supraventricular, sinus); *Infrequent* - bradycardia, palpitations, cardiac failure (including congestive and acute), myocardial infarction, cardiac arrest, atrial fibrillation, atrioventricular block (including first degree and complete), extrasystoles (including ventricular and supraventricular), angina pectoris, cyanosis, bundle branch block (including left, right), myocardial ischaemia; *Rare* - atrial flutter, cardiomegaly, cardiomyopathy, cardiopulmonary failure. ***Ear and Labyrinth Disorders:*** *Infrequent* - ear pain, vertigo, tinnitus; *Rare* - deafness. ***Endocrine Disorders:*** *Infrequent* - hypothyroidism; *Rare* - goitre, hyperparathyroidism, hyperthyroidism. ***Eye Disorders:*** *Frequent* - conjunctivitis; *Infrequent* - eye redness, eye irritation, dry eye, blepharospasm, visual disturbance, eye pain, eye discharge, blepharitis, cataract, lacrimation increased; *Rare* - eyelid function disorder, oculogyration, eyelid oedema, photophobia, diplopia, eyelid ptosis, eye haemorrhage. ***Gastrointestinal Disorders:*** *Frequent* - loose stools; *Infrequent* - flatulence, dysphagia, gastroesophageal reflux disease, gastritis, haemorrhoids, abdominal distension, faecal incontinence, haematochezia, gingival pain, rectal haemorrhage, abdominal pain lower, oral pain, retching, faecaloma, gastrointestinal haemorrhage, ulcer (including gastric, duodenal, peptic), tooth fracture, gingivitis, lip dry; *Rare* - abdominal tenderness, chapped lips, periodontitis, aptyalism, gastrointestinal pain, hypoaesthesia oral, inguinal hernia, swollen tongue, colitis, haematemesis, hyperchlorhydria, irritable bowel syndrome, oesophagitis, faeces hard, gingival bleeding, glossodynia, mouth ulceration, reflux oesophagitis, cheilitis, intestinal obstruction, pancreatitis, eructation, gastric ulcer haemorrhage, melaena, glossitis, stomatitis. ***General Disorders and Administration Site Conditions:*** *Frequent* - asthenia, pyrexia, chest pain, gait disturbance; *Infrequent* - malaise, oedema, influenza-like illness, chills, general physical health deterioration, feeling jittery, mobility decreased, thirst, feeling cold, difficulty in walking, facial pain, sluggishness, condition aggravated; *Rare* - inflammation localized, swelling, energy increased, inflammation, abasia, xerosis, feeling hot, hyperthermia, hypothermia. ***Hepatobiliary Disorders:*** *Infrequent* - cholecystitis (including acute and chronic); *Rare* - cholelithiasis, hepatitis. ***Immune System Disorders:*** *Infrequent* - hypersensitivity. ***Infections and Infestations:*** *Frequent* - respiratory tract infection (including upper and lower), pneumonia; *Infrequent* - cellulitis, dental caries, vaginitis, vaginal infection, cystitis, vaginal mycosis, eye infection, gastroenteritis, onychomycosis, vaginal candidiasis, otitis media, folliculitis, candidiasis, otitis externa, pyelonephritis, rash pustular; *Rare* - appendicitis, septic shock. ***Injury, Poisoning, and Procedural Complications:*** *Frequent* - fall, skin laceration, contusion, fracture; *Infrequent* - blister, scratch, joint sprain, burn, muscle strain, periorbital haematoma, arthropod bite/sting, head injury, sunburn; *Rare* - joint dislocation, alcohol poisoning, road traffic accident, self mutilation, eye penetration, injury asphyxiation, poisoning, heat exhaustion, heat stroke. ***Investigations:*** *Frequent* - weight decreased, blood creatine phosphokinase increased; *Infrequent* - blood glucose increased, heart rate increased, body temperature increased, alanine aminotransferase increased, blood cholesterol increased, white blood cell count increased, haemoglobin decreased, aspartame aminotransferase increased, blood urea increased, electrocardiogram ST segment abnormal (including depression, elevation), haematocrit decreased, hepatic enzyme increased, blood bilirubin increased, blood glucose decreased, blood creatinine increased, blood alkaline phosphatase increased, blood pressure decreased, blood potassium decreased, blood urine present, electrocardiogram QT corrected interval prolonged; *Rare* - transaminases increased, blood triglycerides increased, blood uric acid increased, cardiac murmur, eosinophil count increased, neutrophil count increased, platelet count increased, red blood cell count decreased, white blood cell count decreased, white blood cells urine positive, bacteria urine identified, blood lactate dehydrogenase increased, blood potassium increased, neutrophil count decreased, urine output decreased, blood creatine phosphokinase MB increased, ECG signs of myocardial ischemia, electrocardiogram T-wave inversion, heart rate decreased, tuberculin test positive, glucose urine present, glycosylated haemoglobin increased, glucose tolerance decreased, glycosylated haemoglobin decreased, muscle enzyme increased. ***Metabolism and Nutrition Disorders:*** *Frequent* - decreased appetite (including diet refusal, markedly reduced dietary intake), dehydration; *Infrequent* - anorexia, increased appetite, hypercholesterolaemia, hypokalaemia, hyperglycaemia, diabetes mellitus, hypoglycaemia, hyponatremia, diabetes mellitus non-insulin-dependent, hyperlipidaemia, obesity (including overweight), polydipsia; *Rare* - hypertriglyceridaemia, gout, hypernatraemia, weight fluctuation, diabetes mellitus inadequate control. ***Musculoskeletal and Connective Tissue Disorders:*** *Frequent* - musculoskeletal pain (including neck, jaw, chest wall, bone, buttock, groin, flank, musculoskeletal chest, pubic, and sacral), muscle rigidity, muscle cramp; *Infrequent* - muscle twitching, joint swelling, muscle spasms, muscle tightness, arthritis, osteoarthritis, muscular weakness, joint range of motion decreased, sensation of heaviness; *Rare* - tendonitis, osteoporosis, trismus, arthropathy, bursitis, exostosis, night cramps, coccydynia, joint contracture, localised osteoarthritis, osteopenia, rhabdomyolysis, costochondritis, rheumatoid arthritis, torticollis. ***Nervous System Disorders:*** *Frequent* - lethargy, dyskinesia; *Infrequent* - disturbance in attention, parkinsonism, dystonia, drooling, cogwheel rigidity, dysarthria, paraesthesia, hypoaesthesia, loss of consciousness (including depressed level of consciousness), hypersomnia, psychomotor hyperactivity, balance disorder, cerebrovascular accident, hypokinesia, tardive dyskinesia, memory impairment, amnesia, ataxia, dementia, hypotonia, burning sensation, dysgeusia, restless leg syndrome, hypertonia, Parkinson's disease, akinesia, dysphasia, transient ischaemic attack, facial palsy, hemiparesis, myoclonus, sciatica; *Rare* - bradykinesia, coordination abnormal, cognitive disorder, syncope vasovagal, carpal tunnel syndrome, hyporeflexia, intention tremor, muscle contractions involuntary, sleep apnea syndrome, dementia Alzheimer's type, epilepsy, hyperreflexia, mastication disorder, mental impairment, nerve compression, parkinsonian gait, tongue paralysis, aphasia, choreoathetosis, formication, masked facies, neuralgia, paresthesia oral, parkinsonian rest tremor, cerebral haemorrhage, dizziness exertional, hyperaesthesia, haemorrhage intracranial, ischaemic stroke, judgment impaired, subarachnoid haemorrhage. ***Psychiatric Disorders:*** *Frequent* - schizophrenia (including schizoaffective disorder), depression (including depressive symptom), hallucination (including auditory, visual, tactile, mixed, olfactory, and somatic), mood altered (including depressed, euphoric, elevated, and mood swings), paranoia, irritability, suicidal ideation, confusional state, aggression, mania, delusion (including persecutory, perception, somatic, and grandeur); *Infrequent* - tension, nervousness, nightmare, excitability, panic attack (including panic disorder, panic disorder with agoraphobia, and panic reaction), abnormal dreams, apathy, libido decreased, hostility, suicide attempt, bipolar disorder (including bipolar I), libido increased, anger, delirium, acute psychosis, disorientation, bruxism, hypomania, obsessive-compulsive disorder (including obsessive thoughts), mental status changes, crying, dysphoria, completed suicide, flat affect, impulsive behaviour; *Rare* - blunted affect, cognitive deterioration, logorrhea, psychomotor agitation, social avoidant behaviour, psychomotor retardation, suspiciousness, affect lability, anorgasmia, fear, homicidal ideation, tic, premature ejaculation, dysphemia, bradyphrenia, derealisation, depersonalisation. ***Renal and Urinary Disorders:*** *Infrequent* - pollakiuria, dysuria, haematuria, urinary retention, renal failure (including acute and chronic), urinary hesitation, enuresis, nephrolithiasis, micturition urgency, polyuria; *Rare* - nocturia, proteinuria, glycosuria, calculus urinary, azotaemia. ***Reproductive System and Breast Disorders:*** *Infrequent* - erectile dysfunction, vaginal discharge, amenorrhoea, vaginal haemorrhage, menstruation irregular, menorrhagia, premenstrual syndrome, testicular pain, genital pruritus female, ovarian cyst, benign prostatic hyperplasia, prostatitis; *Rare* - gynaecomastia, priapism (including spontaneous penile erection), breast pain, pelvic pain, epididymitis, galactorrhoea, uterine haemorrhage. ***Respiratory, Thoracic, and Mediastinal Disorders:*** *Frequent* - dyspnoea (including exertional); *Infrequent* - sinus congestion, rhinorrhoea, wheezing, epistaxis, asthma, hiccups, productive cough, chronic obstructive airways disease (including exacerbated), rhinitis allergic, pneumonia aspiration, pulmonary congestion, sinus pain, respiratory distress, dry throat, hoarseness; *Rare* - bronchopneumopathy, haemoptysis, respiratory arrest, sneezing, hypoxia, pulmonary embolism, pulmonary oedema (including acute), respiratory failure, brochospasm, nasal dryness, paranasal sinus hypersecretion, pharyngeal erythema, rhonchi, tonsillar hypertrophy, asphyxia, Mendelson's syndrome. ***Skin and Subcutaneous Tissue Disorders:*** *Infrequent* - hyperhydrosis, erythema, pruritis (including generalised), dry skin, decubitus ulcer, dermatitis (including allergic, seborrhoeic, acneiform, exfoliative, bullous, neurodermatitis), ecchymosis, skin ulcer, acne, eczema, hyperkeratosis, swelling face, skin discoloration, photosensitivity reaction, skin irritation, alopecia, rash maculopapular, cold sweat, scab, face oedema, dermal cyst, psoriasis, night sweats, rash erythematous; *Rare* - rash scaly, urticaria, rash maculopapular, rosacea, seborrhoea, periorbital oedema, rash vesicular. ***Vascular Disorders:*** *Frequent* - hypotension; *Infrequent* - hot flush (including flushing), haematoma, deep vein thrombosis, phlebitis; *Rare* - pallor, petechiae, varicose vein, circulatory collapse, haemorrhage, thrombophlebitis, shock.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole Injection

The following adverse events were reported with aripiprazole injection at doses ≥1 mg/day in clinical trials (749 patients). This list may not include events previously listed elsewhere in the labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening. *Frequent events* are those occurring in at least 1/100 patients; *Infrequent events* are those occurring in 1/100 to 1/1000 patients; *rare events* are those occurring in fewer than 1/1000 patients. ***Ear and Labyrinth Disorders:*** *Infrequent* - hyperacusis. ***General Disorders and Administration Site Conditions:*** *Infrequent* - injection site stinging, abnormal feeling, injection site pruritus, injection site swelling, venipuncture site bruise. ***Infections and Infestations:*** *Infrequent* - bacteruria, urinary tract infection, urosepsis. ***Investigations:*** *Infrequent* - blood pressure abnormal, heart rate irregular, electrocardiogram T-wave abnormal. ***Psychiatric Disorders:*** *Infrequent* - intentional self-injury. ***Respiratory, Thoracic, and Mediastinal Disorders:*** *Infrequent* - pharyngolaryngeal pain, nasal congestion. ***Vascular Disorders:*** *Infrequent* - blood pressure fluctuation.

Postintroduction Reports: Reported since market introduction and temporally (not necessarily causally) related to aripiprazole therapy: allergic reaction (eg, anaphylactic reaction, angioedema, laryngospasm, oropharyngeal spasm, pruritis, or urticaria), grand mal seizure, and jaundice.

DRUG ABUSE AND DEPENDENCE: Aripiprazole is not a controlled substance.

Abuse and Dependence: Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Patients should be evaluated carefully for a history of drug abuse and closely observed for signs of ABILIFY (aripiprazole) misuse or abuse.

OVERDOSAGE: 76 cases of deliberate or accidental overdosage with oral ABILIFY alone or in combination with other substances were reported worldwide [44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal)]. Additionally, 10 of these cases were in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities. The largest known acute ingestion was 1080 mg of oral aripiprazole (36 times maximum recommended daily dose) in a patient who fully recovered. Common adverse events (reported in at least 5% of all overdose cases) were vomiting, somnolence, and tremor. **For more information on symptoms of overdose, see Full Prescribing Information.**

Management of Overdosage: No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers. ***Charcoal:*** In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%. ***Hemodialysis:*** Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Orally Disintegrating Tablets, Oral Solution and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
US Patent Nos: 5,006,528; 6,977,257; and 7,115,587

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Based on FPI Revised October 2006

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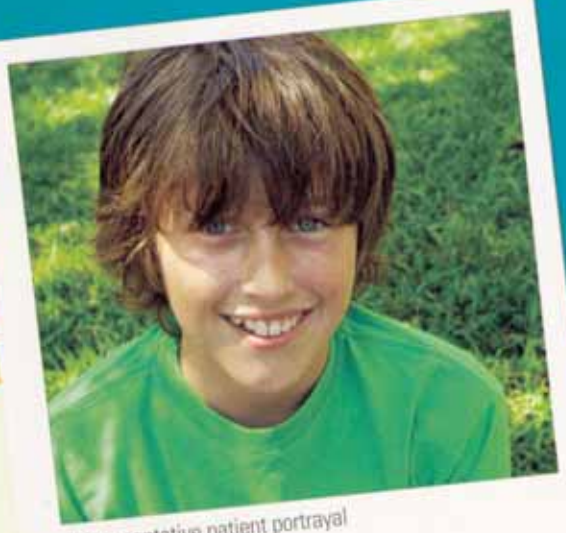
For the treatment of attention deficit hyperactivity disorder (ADHD)

CONCERTA® CAN MAKE A DIFFERENCE



Representative patient portrayal

Meet Matthew, age 12, who has ADHD Combined Type with comorbid ODD*

- Doesn't finish tests or schoolwork
- Forgets to do homework and chores
- Argues with teachers and parents

*ODD=Oppositional Defiant Disorder; CD=Conduct Disorder.

Consider CONCERTA® to give Matthew the help he needs

- Reduces ADHD symptoms in children with ADHD and ODD/CD* as well as in patients with ADHD alone[1]
- Improves academic performance and classroom behavior in children with ADHD[2]
- Significantly reduces ADHD symptoms and conflict with family members in adolescents with ADHD[3]

Important Safety Information

CONCERTA® is indicated for the treatment of ADHD in children and adolescents. CONCERTA® should not be taken by patients with: significant anxiety, tension, or agitation; allergies to methylphenidate or other ingredients in CONCERTA®; glaucoma; Tourette's syndrome, tics, or family history of Tourette's syndrome; current/recent use of monoamine oxidase inhibitors (MAOIs). Children under 6 years of age should not take CONCERTA®. Abuse of methylphenidate may lead to dependence.

Use with caution in patients with psychosis, bipolar disorder, history of seizures/EEG abnormalities, and hypertension. CONCERTA® should not be used in patients with pre-existing severe gastrointestinal narrowing, known structural cardiac abnormalities, or other serious heart problems. Stimulants may cause new psychotic or manic symptoms; discontinuation of treatment may be appropriate. Aggressive behavior or hostility should be monitored in patients beginning treatment. Methylphenidate may produce difficulties with accommodation and blurring of vision. Hematologic monitoring is advised during prolonged therapy.

The most common adverse events reported in children aged 6 to 12 years receiving up to 54 mg were headache (14%), upper respiratory tract infection (8%), and abdominal pain (7%). The most common adverse events reported in adolescents receiving up to 72 mg were headache (9%), accidental injury (6%), and insomnia (5%).

Please see brief summary of full prescribing information and references on next page.

For more information, call **1-888-440-7903** or visit **www.concerta.net**

ONCE-DAILY

CONCERTA®

methylphenidate HCl

Extended-release tablets: 18 mg, 27 mg, 36 mg, 54 mg

Delivering results that matter

CON07-034

Expires 6/08

CONCERTA® ℞

(methylphenidate HCl) Extended-release Tablets

BRIEF SUMMARY: Please see full prescribing information.

DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect.

CONTRAINDICATIONS

Agitation: CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate: CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma: CONCERTA® is contraindicated in patients with glaucoma.

Tics: CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors: CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) (see PRECAUTIONS, Drug Interactions).

WARNINGS

Serious Cardiovascular Events: Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults: Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other Cardiovascular Conditions: Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) (see Adverse Reactions-Hypertension), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications: Children, adolescents, or adults who are being considered for treatment with stimulant medications, should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events: Pre-Existing Psychosis: Administration of stimulants may exacerbate symptoms of behavior and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms: Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression: Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth: Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treated groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures: There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Potential for Gastrointestinal Obstruction: Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Use in Children Under Six Years of Age: CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients: Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions: CONCERTA® should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAO inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors). Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents. Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate. Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown. Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate. Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay. Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively.

Pregnancy: Teratogenic Effects: ***Pregnancy Category C:*** Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively. A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC. The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

Pediatric Use: The safety and efficacy of CONCERTA® in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS

The development program for CONCERTA® included exposures in a total of 2121 participants in clinical trials (1787 patients, 324 healthy adult subjects). These participants received CONCERTA® 18, 36, 54, and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with CONCERTA®: Adverse Events Associated with Discontinuation of Treatment: In the 4-week placebo-controlled, parallel-group trial in children (Study 3), one CONCERTA®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively). In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no CONCERTA®-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability). In the two open-label, long-term safety trials (Studies 5 and 6; one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with CONCERTA®), 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among CONCERTA®-Treated Patients: Table 1 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1
Incidence of Treatment-Emergent Events' in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA® in Children

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Table 2 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at CONCERTA® doses of 18, 36, 54 or 72 mg/day.

Table 2
Incidence of Treatment-Emergent Events' in a 2-Week Placebo-Controlled Clinical Trial of CONCERTA® in Adolescents

Body System	Preferred Term	CONCERTA® (n=87)	Placebo (n= 90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
	Headache	9 %	8 %
Digestive	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Tics: In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®. In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Hypertension: In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. (see WARNINGS)

Post-Marketing Experience with CONCERTA®: Post-marketing experiences with CONCERTA® have revealed spontaneous reports of the following adverse events: difficulties in visual accommodation, blurred vision, abnormal liver function test (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia.

Adverse Events with Other Methylphenidate HCl Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: hepatic coma; isolated cases of cerebral arteritis and/or occlusion; anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance: See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms: Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment: Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia. Efficacy of peritoneal dialysis or extracorp real hemodialysis for CONCERTA® overdosage has not been established. The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

Rx Only.

For more information call 1-888-440-7903 or visit www.concerta.net

Manufactured by ALZA Corporation, Mountain View, CA 94043. Distributed and marketed by McNeil Pediatrics, Division of McNeil-PPC, Inc., Fort Washington, PA 19034.

An ALZA OROS® Technology Product

Concerta® and OROS® are Registered Trademarks of ALZA Corporation.

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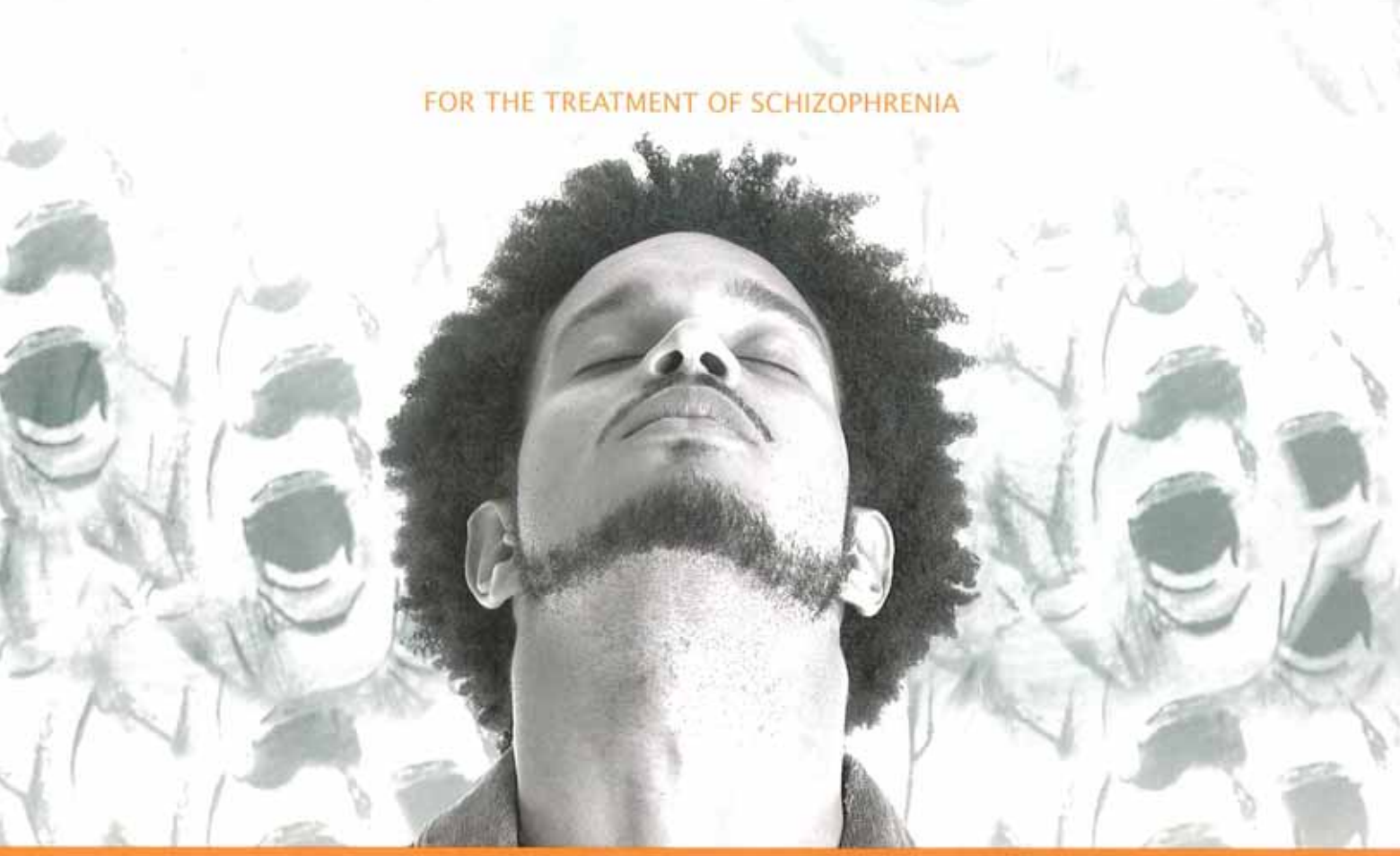
Edition: June 2006

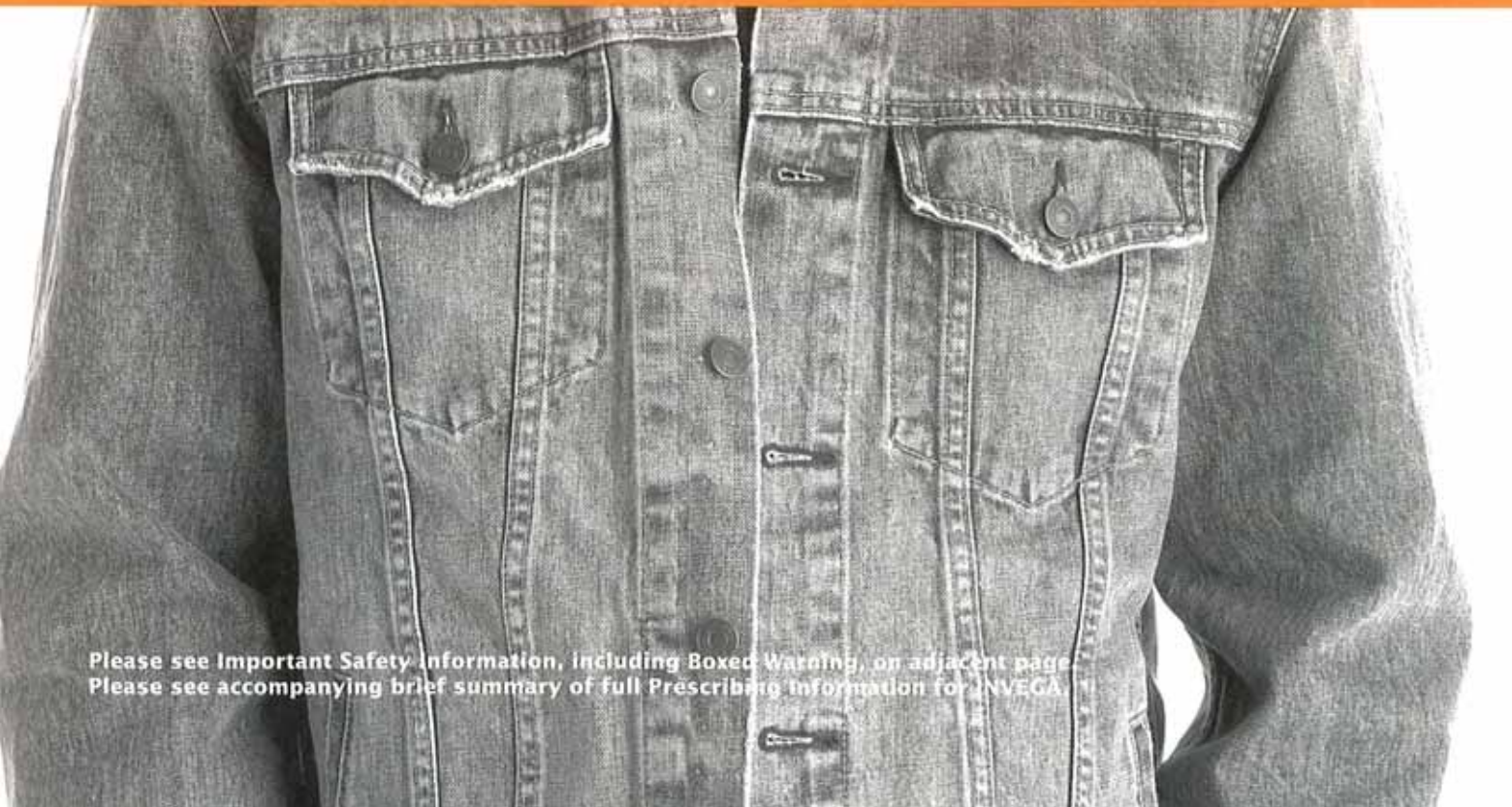
References: **1.** McBurnett K, Cooper KM. Effectiveness of OROS® methylphenidate in children with or without comorbid oppositional defiant disorder and conduct disorder. Poster presented at: American Academy of Child and Adolescent Psychiatry/Canadian Academy of Child and Adolescent Psychiatry Joint Annual Meeting; October 21, 2005; Toronto, Ontario, Canada. **2.** Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107(6). Available at: http://www.pediatrics.org/cgi/content/full/107/6/e105. **3.** Wilens TE, McBurnett K, Bukstein O, et al. Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med.* 2006;160:82-90.

McNEIL PEDIATRICS
DIVISION OF McNEIL-PPC, INC.

FOR THE TREATMENT OF SCHIZOPHRENIA



He Needs Powerful Efficacy for His Mind
But What Will It Do to His Body?



Please see Important Safety Information, including Boxed Warning, on adjacent page.
Please see accompanying brief summary of full Prescribing Information for INVEGA.

IN THE TREATMENT OF SCHIZOPHRENIA

Powerful Efficacy for the Mind

- Every dose proven to effectively control symptoms in every acute pivotal trial (6 weeks)[1]
- Demonstrated efficacy over the longer term by delaying time to relapse[2]
- The first antipsychotic to measure efficacy by improvements in personal and social performance[3]

EXPERIENCE THE

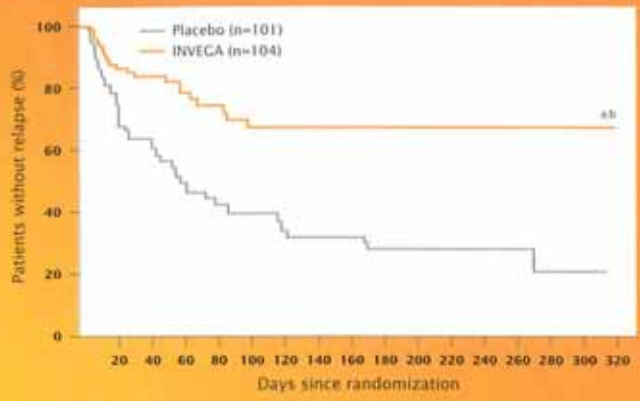
Proven Safety and Tolerability for the Body

- Weight gain comparable with placebo in 6-week clinical trials
- EPS rates comparable with placebo in 6-week trials with the recommended 6-mg dose*
- Adverse event type and severity in a longer-term trial were similar to those seen in 6-week pivotal trials

*Total EPS-related adverse events at the 9-mg and 12-mg doses were 25% and 26%, respectively, versus 11% for placebo.

Janssen L.P.

TIME TO RELAPSE[2]
(KAPLAN-MEIER PLOT OF TIME)



[a]$P<0.001$ vs placebo.
[b]Percentage of patients without recurrence at 11 months is projected.

From Kramer et al.[2]
Results from a placebo-controlled study that included a 14-week run-in and stabilization phase, during which patients received INVEGA (3 mg to 15 mg) once daily until they were deemed stable, followed by a double-blind phase in which patients were maintained on a stable dose of INVEGA or given placebo for up to 11 months. The average dose of INVEGA was 10.8 mg (average 24 weeks). The trial was ended at a predetermined interim analysis due to occurrence of a total number of relapses between the 2 groups (mean duration of therapy with INVEGA and placebo was 74 days and 56 days, respectively).[1,2]

BENEFITS OF INVEGA

WEIGHT CHANGE FROM BASELINE WITH INVEGA[1,2]

Short term (6 weeks)[c,d]

3-mg and 6-mg doses	1.3 lb
9-mg dose	2.2 lb
12-mg dose	2.4 lb
Placebo	−0.9 lb

Longer term (24 weeks)[d,e]

Data on file[1] and adapted from Kramer et al.[2]
[c]Pooled results from three 6-week pivotal trials.
[d]The proportion of patients gaining ≥7% of body weight with INVEGA was 7% (3 mg), 6% (6 mg), 9% (9 mg), and 9% (12 mg) versus 5% (placebo) in 6-week trials, and 20% (average 10.8 mg) versus 12% (placebo) in a longer-term, flexible-dose trial.
[e]Results from a longer-term trial of up to 11 months (average 24 weeks that includes a 14-week run-in and stabilization phase). The average dose of INVEGA was 10.8 mg.

Please see Important Safety Information, including Boxed Warning, on adjacent page.
Please see accompanying brief summary of full Prescribing Information for INVEGA.

INVEGA™
PALIPERIDONE
Extended-Release Tablets
STRENGTH FOR THE WHOLE PERSON

INVEGA™

(paliperidone)
Extended-Release Tablets

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY

Rx only

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 17 placebo-controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects 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. INVEGA™ (paliperidone) Extended-Release Tablets is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE: INVEGA™ (paliperidone) Extended-Release Tablets is indicated for the acute and maintenance treatment of schizophrenia.

CONTRAINDICATIONS: INVEGA™ (paliperidone) is contraindicated in patients with a known hypersensitivity to paliperidone, risperidone, or to any components in the INVEGA™ formulation.

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. INVEGA™ (paliperidone) Extended-Release Tablets is not approved for the treatment of dementia-related psychosis (see Boxed Warning). QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. 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. The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=44) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA™ ($C_{max\ ss}$ = 113 and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study. For the three fixed-dose efficacy studies, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA™ 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA™ had a QTcLD exceeding 500 msec at any time in any of these three studies. **Neuroleptic Malignant Syndrome:** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Other signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include: discontinuation of the antipsychotic and other drugs not essential to therapy; intensive symptomatic treatment and medical monitoring; and treatment of other serious medical problems. If a patient requires antipsychotic drugs after recovery from NMS, the reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. The risk of developing and likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. However, tardive dyskinesia can develop, after brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although it may remit, partially or completely, if the antipsychotic is withdrawn. Prescribing should be in a manner to minimize the occurrence. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms should appear drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. **Gastrointestinal:** Because the INVEGA™ tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA™ should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA™ should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients). A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis:** In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA™ was not marketed at the time these studies were performed. INVEGA™ is not approved for the treatment of patients with dementia-related psychosis (see also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).

PRECAUTIONS

General: Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA™ (3, 6, 9, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension. **Seizures:** Like other antipsychotic drugs, INVEGA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. **Hyperprolactinemia:** Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility). 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, but the available evidence is too limited to be conclusive. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA™ and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. **Potential for Cognitive and Motor Impairment:** Somnolence and sedation were reported in subjects treated with INVEGA™ (see ADVERSE REACTIONS). Antipsychotics, including INVEGA™, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them. **Priapism:** No cases of priapism have been reported in clinical trials with INVEGA™. **Thrombotic Thrombocytopenia Purpura (TTP):** No cases of TTP were observed during clinical studies with paliperidone. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown. **Body Temperature Regulation:** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA™ to patients who will be experiencing conditions which may contribute to an elevation in core body temperature. **Antiemetic Effect:** An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Use in Patients with Concomitant Illness:** Clinical experience with INVEGA™ in patients with certain concomitant illnesses is limited (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Hepatic Impairment and Renal Impairment in full PI). Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. INVEGA™ 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 trials. Because of the risk of orthostatic hypotension with INVEGA™, caution should be observed in patients with known cardiovascular disease (see PRECAUTIONS: General: Orthostatic Hypotension and Syncope). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA™. **Orthostatic Hypotension:** Patients should be advised that there is risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose. **Interference With Cognitive and Motor Performance:** As INVEGA™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA™ therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA™. **Nursing:** Patients should be advised not to breast-feed an infant if they are taking INVEGA™. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. **Alcohol:** Patients should be advised to avoid alcohol while taking INVEGA™. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Administration:** Patients should be informed that INVEGA™ should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool. **Drug Interactions: Potential for INVEGA™ to Affect Other Drugs** – Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties. At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein. Paliperidone is therefore not expected to inhibit P-glycoprotein-mediated transport of other drugs in a clinically relevant manner. Given the primary CNS effects of paliperidone (see ADVERSE REACTIONS), INVEGA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA™ is administered with other therapeutic agents that have this potential (see PRECAUTIONS: General: Orthostatic Hypotension and Syncope). **Potential for Other Drugs to Affect INVEGA™** – Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies of paliperidone have not been performed. Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum

INVEGA™ (paliperidone) extended-release tablets is indicated for the acute and maintenance treatment of schizophrenia.

IMPORTANT SAFETY INFORMATION FOR INVEGA

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 17 placebo-controlled trials (modal 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. INVEGA™ (paliperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

Commonly observed adverse events: The most commonly observed adverse events, occurring at an incidence of ≥5% and at least 2 times placebo, were akathisia and extrapyramidal disorder.

QT Prolongation: INVEGA causes a modest increase in the corrected QT (QTc) interval. INVEGA should be avoided in combination with other drugs that are known to prolong the QTc interval, in patients with congenital long QT syndrome or a history of cardiac arrhythmias. Certain circumstances may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including INVEGA. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose. Elderly patients appeared to be at increased risk for TD. Prescribing should be consistent with the need to minimize the risk of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Hyperglycemia and Diabetes: Hyperglycemia, some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Gastrointestinal: INVEGA should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing. Rare instances of obstructive symptoms have been reported in patients with known strictures taking nondeformable formulations. INVEGA should only be used in patients who are able to swallow the tablet whole.

Cerebrovascular Adverse Events (CAEs): CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking atypical antipsychotics in clinical trials. INVEGA is not approved for treating these patients.

Seizures: INVEGA should be used cautiously in patients with a history of seizures.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, INVEGA elevates prolactin levels and the elevation persists during chronic administration.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses and close supervision of high-risk patients should accompany drug therapy.

Orthostatic Hypotension: INVEGA may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. INVEGA should be used with caution in patients with known cardiovascular disease, and conditions that would predispose patients to hypotension.

Potential for Cognitive and Motor Impairment: INVEGA has the potential to impair judgment, thinking, or motor skills. Caregivers and patients should use caution until they are reasonably certain that INVEGA does not affect them adversely.

Maintenance Treatment: Physicians who elect to use INVEGA for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

References: 1. Data on file. Janssen, L.P., Titusville, NJ. **2.** Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol.* 2007;27(1):6-14. **3.** Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res.* 2007;90:147-161.

Please see accompanying brief summary of full Prescribing Information for INVEGA.

recommended human dose of risperidone on a mg/m^2 basis (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see PRECAUTIONS: General: Hyperprolactinemia). **Mutagenesis:** No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test. **Impairment of Fertility:** In a study of fertility, the percentage of treated female rats that became pregnant was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose on a mg/m^2 basis. The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31-5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued). **Pregnancy: Pregnancy Category C:** In studies in rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are 8 times the maximum recommended human dose on a mg/m^2 basis). In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see risperidone package insert). Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms. There are no adequate and well controlled studies of INVEGA™ in pregnant women. INVEGA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of INVEGA™ on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA™ should not breast-feed infants. **Pediatric Use:** Safety and effectiveness of INVEGA™ in patients < 18 years of age have not been established. **Geriatric Use:** The safety, tolerability, and efficacy of INVEGA™ were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA™ (3 to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA™ (3 to 15 mg once daily, see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). Overall, of the total number of subjects in clinical studies of INVEGA™ (n = 1796), including those who received INVEGA™ or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Renal Impairment in full PI), who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION: Dosing in Special Populations in full PI).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for INVEGA™ consisting of 2720 patients and/or normal subjects exposed to one or more doses of INVEGA™ for the treatment of schizophrenia. Of these 2720 patients, 2054 were patients who received INVEGA™ while participating in multiple dose, effectiveness trials. The conditions and duration of treatment with INVEGA™ varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure. Adverse events were assessed by collecting adverse events and performing physical examinations, vital signs, weights, laboratory analyses and ECGs. Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology. The stated frequencies of adverse events represent the proportions of individuals who experienced a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The information presented in these sections was derived from pooled data from the three placebo-controlled, 6-week, fixed-dose studies based on subjects with schizophrenia who received INVEGA™ at daily doses within the recommended range of 3 to 12 mg (n = 850). Additional safety information from the placebo-controlled phase of the long-term maintenance study, in which subjects received INVEGA™ at daily doses within the range of 3 to 15 mg (n = 104), is also included. **Adverse Events Observed in Short-Term, Placebo-Controlled Trials of Subjects with Schizophrenia** The information presented in these sections were derived from pooled data from the three placebo-controlled, 6-week, fixed-dose studies based on subjects with schizophrenia who received INVEGA™ at daily doses within the recommended range of 3 to 12 mg (n = 850). Adverse Events Occurring at an Incidence of 2% or More Among INVEGA™-Treated Patients with Schizophrenia and More Frequent on Drug than Placebo Table 1 enumerates the pooled incidences of treatment-emergent adverse events that were spontaneously reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those events that occurred in 2% or more of subjects treated with INVEGA™ in any of the dose groups, and for which the incidence in INVEGA™-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo. **Treatment-Emergent Adverse Events in Short-Term, Fixed-Dose, Placebo-Controlled Trials in Adult Subjects with Schizophrenia.* Body System or Organ Class** (Dictionary-derived Term) Percentage of Patients Reporting Event INVEGA™ Placebo (N=355) first, INVEGA™ dosage once daily 3 mg (N=127) second, 6 mg N=235) third, 9 mg (N=246) fourth, 12 mg (N=242) fifth, **Percentage of subjects with adverse events** 66, 72, 66, 70, 76; **Cardiac disorders:** Atrioventricular block first degree 1, 2, 0, 2, 1; Bundle branch block 2, 3, 1, 3, <1; Sinus arrhythmia 0, 2, 1, 1, <1; Tachycardia 7, 14, 12, 12, 14; **Eye disorders:** Vision blurred 1, 1, <1, 0, 2; **Gastrointestinal disorders:** Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Dyspepsia 4, 2, 3, 2, 5; Nausea 5, 6, 4, 4, 4; Salivary hypersecretion <1, 0, <1, 1, 4; **General disorders**: Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; Pyrexia 1, 1, <1, 2, 2; **Investigations:** Blood insulin increased 1, 2, 1, 1, <1; Blood pressure increased 1, 2, <1, <1, 1; Electrocardiogram QT corrected interval prolonged 3, 3, 4, 3, 5; Electrocardiogram T wave abnormal 1, 2, 1, 2, 1; **Musculoskeletal and connective tissue disorders**: Back pain 1, 1, 1, 1, 2; Pain in extremity 1, 0, 1, 0, 2; **Nervous system disorders**: Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Dystonia 1, 1, 1, 5, 4; Extrapyramidal disorder 2, 5, 2, 7, 7; Headache 12, 11, 12, 14, 14; Hypertonia 1, 2, 1, 4, 3; Parkinsonism 0, 0, <1, 2, 1; Somnolence 7, 6, 9, 10, 11; Tremor 3, 3, 3, 4, 3; **Psychiatric disorders**: Anxiety 8, 9, 7, 6, 5; **Respiratory, thoracic and mediastinal disorders**: Cough 1, 3, 2, 3, 2; **Vascular disorders**: Orthostatic hypotension 1, 2, 1, 2, 4; *Table includes adverse events that were reported in 2% or more of subjects in any of the INVEGA™ dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies; one included once-daily INVEGA™ doses of 3 and 9 mg, the second study included 6, 9, and 12 mg, and the third study included 6 and 12 mg (see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). Events for which the INVEGA™ incidence was equal to or less than placebo are not listed in the table, but included the following: constipation, diarrhea, vomiting, nasopharyngitis, agitation, and insomnia. **Dose-Related Adverse Events in Clinical Trials:** Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, adverse events that occurred with a greater than 2% incidence in the subjects treated with INVEGA™, the incidences of the following adverse events increased with dose: somnolence, orthostatic hypotension, salivary hypersecretion, akathisia, dystonia, extrapyramidal disorder, hypertonia and Parkinsonism. For most of these, the increased incidence was seen primarily at the 12 mg, and in some cases the 9 mg dose. **Common and Drug-Related Adverse Events in Clinical Trials** In the pooled data from three placebo-controlled, 6-week, fixed-dose studies, adverse events reported in 5% or more of subjects treated with INVEGA™ and at least twice the placebo rate for at least one dose included: akathisia and extrapyramidal disorder. **Extrapyramidal Symptoms (EPS) in Clinical Trials:** Pooled data from the three placebo-controlled, 6-week, fixed-dose studies provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, and (4) incidence of spontaneous reports of EPS. For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA™ 3 mg and 6 mg doses for any of these EPS measures. **Percentage of Patients INVEGA™** Placebo (N=355) first, INVEGA™ dosage once daily 3 mg (N=127) second, 6 mg N=235) third, 9 mg (N=246) fourth, 12 mg (N=242) fifth, **EPS Group:** Parkinsonism [a] 9, 11, 3, 15, 14; Akathisia [b] 6, 6, 4, 7, 9; Use of anticholinergic medications [c] 10, 10, 9, 22, 22; [a]: For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items). [b]: For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2. [c]: Percent of patients who received anticholinergic medications to treat emergent EPS. **Percentage of Patients INVEGA™** Placebo (N=355) first, INVEGA™ dosage once daily 3 mg (N=127) second, 6 mg N=235) third, 9 mg (N=246) fourth, 12 mg (N=242) fifth, **EPS Group**: Overall percentage of patients with EPS-related AE 11.0, 12.6, 10.2, 25.2, 26.0; Dyskinesia 3.4, 4.7, 2.6, 7.7, 8.7; Dystonia 1.1, 0.8, 1.3, 5.3, 4.5; Hyperkinesia 3.9, 3.9, 3.0, 8.1, 9.9; Parkinsonism 2.3, 3.1, 2.6, 7.3, 6.2; Tremor 3.4, 3.1, 2.6, 4.5, 3.3: Dyskinesia group includes: Dyskinesia, Extrapyramidal disorder, Muscle twitching, Tardive dyskinesia Dystonia group includes: Dystonia, Muscle spasms, Oculogyration, Trismus. Hyperkinesia group includes: Akathisia, Hyperkinesia. Parkinsonism group includes: Bradykinesia, Cogwheel rigidity, Drooling, Hypertonia, Hypokinesia, Muscle rigidity, Musculoskeletal stiffness, Parkinsonism. Tremor group includes: Tremor. **Adverse Events Associated with Discontinuation of Treatment in Controlled Clinical Studies:** Based on the pooled data from the three placebo-controlled, 6-week, fixed dose studies, there was no difference in the incidence of discontinuation due to adverse events between INVEGA™-treated (5%) and placebo-treated (5%) subjects. The types of adverse events that led to discontinuation were similar for the INVEGA™-and placebo-treated subjects, except for Nervous System Disorders events which were more common among INVEGA™-treated subjects than placebo-treated subjects (2% and 0%, respectively), and Psychiatric Disorders events which were more common among placebo-treated subjects than INVEGA™-treated subjects (3% and 1%, respectively). **Demographic Differences in Adverse Reactions in Clinical Trials:** An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race (see PRECAUTIONS: Geriatric Use). **Laboratory Test Abnormalities in Clinical Trials:** In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, between-group comparisons revealed no medically important differences between INVEGA™ and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. Similarly, there were no differences between INVEGA™ and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry. However, INVEGA™ was associated with increases in serum prolactin (see PRECAUTIONS: General: Hyperprolactinemia). **Weight Gain in Clinical Trials:** In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, the proportions of subjects having a weight gain of ≥ 7% of body weight were similar for INVEGA™ 3 mg and 6 mg (7% and 6%, respectively) and placebo (5%), but there was a higher incidence of weight gain for INVEGA™ 9 mg and 12 mg (9% and 9%, respectively). **Other Events Observed During the Premarketing Evaluation of INVEGA™:** The following list contains all serious and non-serious treatment-emergent adverse events reported at any time by individuals taking INVEGA™ during any phase of a trial within the premarketing database (n = 2720), except (1) those listed in Table 1 above or elsewhere in labeling, (2) those for which a causal relationship to INVEGA™ use was considered remote, and (3) those occurring in only one subject treated with INVEGA™ and that were not acutely life-threatening. Events are classified within body system categories using the following definitions: *very frequent* adverse events are defined as those occurring on one or more occasions in at least 1/10 subjects, *frequent* adverse events are defined as those occurring on one or more occasions in at least 1/100 subjects, *infrequent* adverse events are those occurring on one or more occasions in 1/100 to 1/1000 subjects, and *rare* events are those occurring on one or more occasions in less than 1/1000 subjects. **Blood and Lymphatic System Disorders:** *rare*: thrombocytopenia; **Cardiac Disorders:** *frequent*: palpitations; *infrequent*: bradycardia; **Gastrointestinal Disorders:** *frequent:* abdominal pain; *infrequent*: swollen tongue; **General Disorders:** *infrequent*: edema; **Immune Disorder:** *rare*: anaphylactic reaction; **Nervous System Disorders:** *rare*: coordination abnormal; **Psychiatric Disorders:** *infrequent*: confusional state; **Respiratory, Thoracic and Mediastinal Disorders:** *frequent*: dyspnea; *rare*: pulmonary embolus; **Vascular Disorders:** *rare*: ischemia, venous thrombosis; The safety of INVEGA™ was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA™ in adults with schizophrenia (see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). In general, adverse event types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse events reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase. **Adverse Events Reported With Risperidone**; Paliperidone is the major active metabolite of risperidone. Adverse events reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: INVEGA™ (paliperidone) is not a controlled substance.

For more information on symptoms and treatment of overdosage, see full Prescribing Information.

10105901B Issued: April 2007

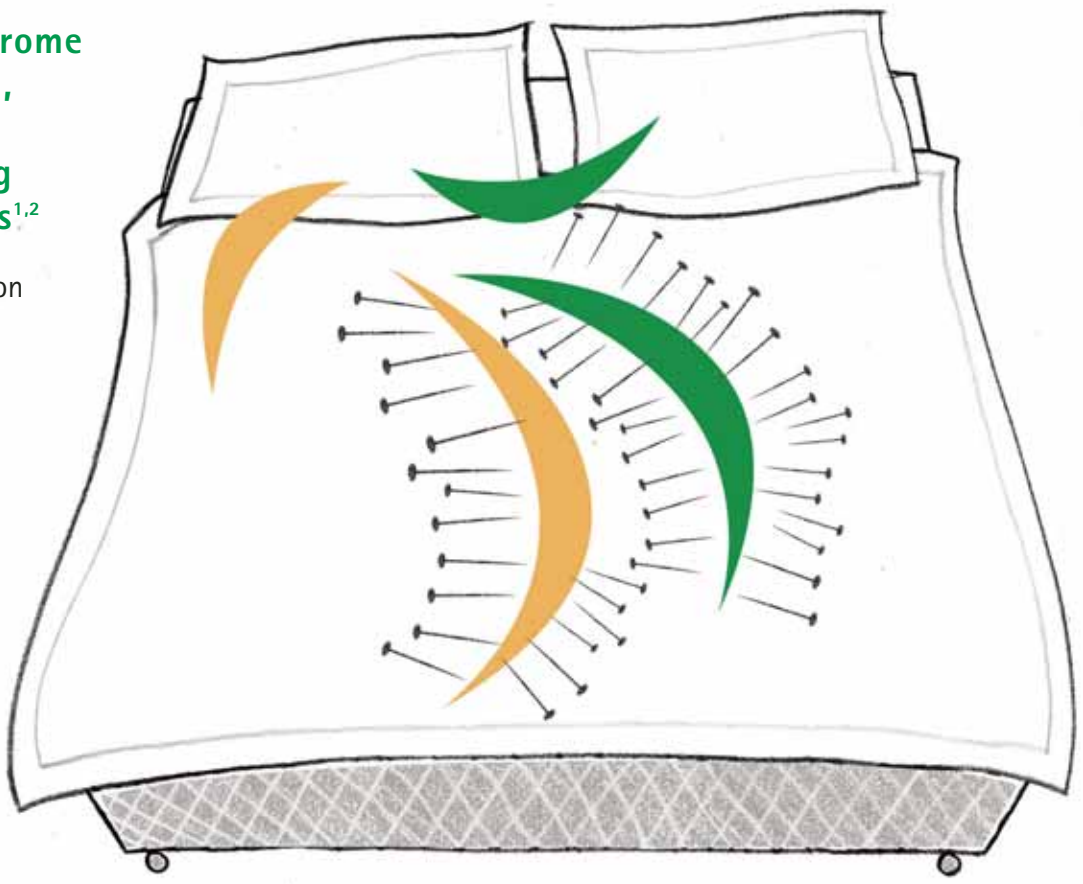
Janssen

01JN396B

Are your patients' restless legs to

Restless Legs Syndrome (RLS) is a common, underdiagnosed condition affecting a range of patients[1,2]

- Approximately 12 million Americans suffer from moderate to severe primary RLS[1,3,4]
- A differential diagnosis can help rule out other health conditions that can cause problems with sleeping, including insomnia/sleep disorders, depression, or RLS[1]



These essential criteria can help confirm RLS[5,6]

1. Urge to move legs—usually accompanied by uncomfortable leg sensations
2. Symptoms begin or worsen during rest such as when lying or sitting
3. Symptoms are partially or totally relieved by movement
4. Symptoms are worse in the evening or night

The only FDA-approved medications for the treatment of RLS are within the dopamine agonist (DA) class

blame for their sleepless nights?

Restless Legs Syndrome...Simplified

MIRAPEX offers effective, long-term relief from the symptoms of moderate to severe primary RLS[7]

- Well-established safety and tolerability profile
- No predicted P450 interactions
- Not a controlled substance
- Convenient dosing and titration
  - 75% of patients on the 0.25 mg dose of MIRAPEX responded to therapy*
  - MIRAPEX Starter Kit offers simple single-step titration†

IMPORTANT SAFETY INFORMATION ABOUT MIRAPEX: **Patients have reported falling asleep without perceived warning signs during activities of daily living, including operation of a motor vehicle.** Hallucinations and postural (orthostatic) hypotension may occur. The most commonly reported adverse events in RLS clinical trials for MIRAPEX vs placebo were nausea (16% vs 5%), headache (16% vs 15%), fatigue (9% vs 7%), and somnolence (6% vs 3%).

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines, including pramipexole, to treat Parkinson's disease and RLS.

Please see accompanying Brief Summary of Prescribing Information.

* Results of a 12-week, placebo-controlled, randomized, double-blind, fixed-dose–treatment trial to assess the efficacy and safety of MIRAPEX vs placebo in the treatment of moderate to severe primary RLS.
Responders defined as patients with symptoms rated as "much improved" or "very much improved," as measured on the CGI-I.

† Provides samples of the first 2 dosage strengths. Additional titration steps may be needed to achieve symptom relief.

References: 1. Hening W, Walters AS, Allen RP, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* 2004;5:237-246. **2.** Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol.* 2001;18:128-147. **3.** National Heart, Lung, and Blood Institute Working Group on Restless Legs Syndrome. Restless legs syndrome: detection and management in primary care. *Am Fam Physician.* 2000;62:108-114. **4.** US Census Bureau. Table 1: Population Age 18 or Over: July 1, 2003. http://www.census.gov/PressRelease/www/releases/CB04-38TABLE1.pdf. Accessed April 12, 2005. **5.** Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med.* 2003;4:101-119. **6.** National Institute of Neurological Disorders and Stroke. Restless legs syndrome fact sheet. http://www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm. Accessed May 26, 2006. **7.** Trenkwalder C, Stiasny-Kolster K, Kupsch A, et al. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome. *Mov Disord.* 2006;21:1404-1410.

Mirapex®
pramipexole dihydrochloride tablets

Boehringer Ingelheim

Printed in U.S.A. (08/07) MRLS47332A

www.mirapex.com

Mirapex® (pramipexole dihydrochloride) **Brief Summary of Prescribing Information**
0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg tablets

INDICATIONS AND USAGE

Parkinson's Disease: MIRAPEX tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

Restless Legs Syndrome: MIRAPEX tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

CONTRAINDICATIONS: MIRAPEX tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS: Falling Asleep During Activities of Daily Living

Patients treated with Mirapex® (pramipexole dihydrochloride) have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on MIRAPEX tablets, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving MIRAPEX tablets at doses above 1.5 mg/day (0.5 mg TID) for Parkinson's disease. In controlled clinical trials in RLS, patients treated with MIRAPEX tablets at doses of 0.25-0.75 mg once a day, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients (see ADVERSE EVENTS). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with MIRAPEX tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX tablets such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine – see PRECAUTIONS, Drug Interactions). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX tablets, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Symptomatic Hypotension: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, both Parkinson's disease patients and RLS patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see **PRECAUTIONS, Information for Patients**).

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to Mirapex® (pramipexole dihydrochloride) tablets than among those assigned to placebo. This result, especially with the higher doses used in Parkinson's disease, is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.

While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded. Also, clinical trials in patients with RLS did not incorporate orthostatic challenges with intensive blood pressure monitoring done in close temporal proximity to dosing.

Hallucinations: In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving MIRAPEX tablets, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received MIRAPEX tablets and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving MIRAPEX tablets compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% of the advanced Parkinson's disease patients compared with about 0.4% of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to pramipexole. In the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.

In the RLS clinical program, one pramipexole-treated patient (of 889) reported hallucinations; this patient discontinued treatment and the symptoms resolved.

PRECAUTIONS

Rhabdomyolysis: A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication. **Renal:** Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing Mirapex® (pramipexole dihydrochloride) tablets to patients with renal insufficiency (see **DOSAGE AND ADMINISTRATION** in full Prescribing Information). **Dyskinesia:** MIRAPEX tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect. **Retinal Pathology in Albino Rats:** Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved (see **ANIMAL TOXICOLOGY**).

Events Reported with Dopaminergic Therapy: Although the events enumerated below may not have been reported in association with the use of pramipexole in its development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date. ***Withdrawal-Emergent Hyperpyrexia and Confusion:*** Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. ***Fibrotic Complications:*** Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis in the post-marketing experience for Mirapex® (pramipexole dihydrochloride) tablets. While the evidence is not sufficient to establish a causal relationship between MIRAPEX tablets and these fibrotic complications, a contribution of MIRAPEX tablets cannot be completely ruled out in rare cases. ***Melanoma:*** Some epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. MIRAPEX tablets are one of the dopamine agonists used to treat Parkinson's disease. Although MIRAPEX tablets have not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients using MIRAPEX tablets for any indication should be made aware of these results and should undergo periodic dermatologic screening.

Impulse Control/Compulsive Behaviors: Cases of pathological gambling, hypersexuality, and compulsive eating (including binge eating) have been reported in patients treated with dopamine agonist therapy, including pramipexole therapy. As described in the literature, such behaviors are generally reversible upon dose reduction or treatment discontinuation.

Rebound and Augmentation in RLS: Reports in the literature indicate treatment of RLS with dopaminergic medications can result in a shifting of symptoms to the early morning hours, referred to as rebound. Rebound was not reported in the clinical trials of MIRAPEX tablets but the trials were generally not of sufficient duration to capture this phenomenon. Augmentation has also been described during therapy for RLS. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. In a controlled trial of MIRAPEX tablets for RLS, approximately 20% of both the Mirapex- and placebo-treated patients reported at least a 2-hour earlier onset of symptoms during the day by the end of 3 months of treatment. The frequency and severity of augmentation and/or rebound after longer-term use of MIRAPEX tablets and the appropriate management of these events have not been adequately evaluated in controlled clinical trials.

Information for Patients (also see Patient Package Insert): Patients should be instructed to take MIRAPEX tablets only as prescribed.

Patients should be alerted to the potential sedating effects associated with MIRAPEX tablets, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with Mirapex® (pramipexole dihydrochloride) tablets to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX tablets and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine).

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease. In clinical trials, patients with RLS treated with pramipexole rarely reported hallucinations.

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines to treat Parkinson's disease or RLS, including MIRAPEX tablets. These include pathological gambling, hypersexuality, and compulsive eating (including binge eating). If such behaviors are observed with MIRAPEX tablets, dose reduction or treatment discontinuation should be considered.

Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with MIRAPEX tablets.

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see **PRECAUTIONS, Pregnancy**).

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking MIRAPEX tablets with food may reduce the occurrence of nausea.

Laboratory Tests: During the development of MIRAPEX tablets, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

Drug Interactions: *Carbidopa/levodopa:* Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5 to 0.5 hours. *Selegiline:* In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole. *Amantadine:* Population pharmacokinetic analyses suggest that amantadine may slightly decrease the oral clearance of pramipexole. *Cimetidine:* Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12). *Probenecid:* Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12). *Other drugs eliminated via renal secretion:* Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole. *CYP interactions:* Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 µM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day (1.5 mg TID). *Dopamine antagonists:* Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Mirapex® (pramipexole dihydrochloride) tablets.

Drug/Laboratory Test Interactions: There are no known interactions between MIRAPEX tablets and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day [0.3, 2.2, and 11 times the Maximum Recommended Human Dose (MRHD) (MRHD of 1.5 mg TID on a mg/m^2 basis)]. Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs were 0.3, 2.5, and 12.5 times the AUC in humans at the MRHD). No significant increases in tumors occurred in either species.

Pramipexole was not mutagenic or clastogenic in a battery of assays, including the in vitro Ames assay, V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus assay.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m^2 basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pregnancy: Teratogenic Effect: Pregnancy Category C: When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m^2 basis). Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats at this dose was 4 times the AUC in humans at the MRHD. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans at the MRHD). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the MRHD on a mg/m^2 basis) or greater during the latter part of pregnancy and throughout lactation.

There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of Mirapex® (pramipexole dihydrochloride) tablets in pediatric patients has not been established.

Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies with Parkinson's disease patients, 38.7% of patients were older than 65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of MIRAPEX tablets was increased in the elderly. In clinical studies with RLS patients, 22% of patients were at least 65 years old. There were no apparent differences in efficacy or safety between older and younger patients.

ADVERSE EVENTS

Parkinson's Disease: During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.

Early Parkinson's Disease: In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX tablets who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX tablets vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX tablets vs 1% on placebo]; somnolence [1.6% on MIRAPEX tablets vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX tablets vs 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on Mirapex® (pramipexole dihydrochloride) tablets vs 0% on placebo]); and gastrointestinal system (nausea [2.1% on MIRAPEX tablets vs 0.4% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Early Parkinson's Disease: This section lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=388) vs placebo (N=235), respectively. ***Body as a whole:*** asthenia (14% vs 12%), general edema (5% vs 3%), malaise (2% vs 1%), reaction unevaluable (2% vs 1%), fever (1% vs 0%). ***Digestive system:*** nausea (28% vs 18%), constipation (14% vs 6%), anorexia (4% vs 2%), dysphagia (2% vs 0%). ***Metabolic and nutritional system:*** peripheral edema (5% vs 4%), decreased weight (2% vs 0%). ***Nervous system:*** dizziness (25% vs 24%), somnolence (22% vs 9%), insomnia (17% vs 12%), hallucinations (9% vs 3%), confusion (4% vs 1%), amnesia (4% vs 2%), hypesthesia (3% vs 1%), dystonia (2% vs 1%), akathisia (2% vs 0%), thinking abnormalities (2% vs 0%), decreased libido (1% vs 0%), myoclonus (1% vs 0%). ***Special senses:*** vision abnormalities (3% vs 0%). ***Urogenital system:*** impotence (2% vs 1%).

Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

In a fixed-dose study in early Parkinson's disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

Advanced Parkinson's Disease: In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.

Approximately 12% of 260 patients with advanced Parkinson's disease who received Mirapex® (pramipexole dihydrochloride) tablets and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX tablets vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX tablets vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX tablets vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX tablets vs 1.5% on placebo]; confusion [1.2% on MIRAPEX tablets vs 2.3% on placebo]); and cardiovascular system (postural [orthostatic] hypotension [2.3% on MIRAPEX tablets vs 1.1% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Advanced Parkinson's Disease: This section lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, MIRAPEX tablets or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=260) vs placebo (N=264), respectively. ***Body as a whole:*** accidental injury (17% vs 15%), asthenia (10% vs 8%), general edema (4% vs 3%), chest pain (3% vs 2%), malaise (3% vs 2%). ***Cardiovascular system:*** postural hypotension (53% vs 48%). ***Digestive system:*** constipation (10% vs 9%), dry mouth (7% vs 3%). ***Metabolic and nutritional system:*** peripheral edema (2% vs 1%), increased creatine PK (1% vs 0%). ***Musculoskeletal system:*** arthritis (3% vs 1%), twitching (2% vs 0%), bursitis (2% vs 0%), myasthenia (1% vs 0%). ***Nervous system:*** dyskinesia (47% vs 31%), extrapyramidal syndrome (28% vs 26%), insomnia (27% vs 22%), dizziness (26% vs 25%), hallucinations (17% vs 4%), dream abnormalities (11% vs 10%), confusion (10% vs 7%), somnolence (9% vs 6%), dystonia (8% vs 7%), gait abnormalities (7% vs 5%), hypertonia (7% vs 6%), amnesia (6% vs 4%), akathisia (3% vs 2%), thinking abnormalities (3% vs 2%), paranoid reaction (2% vs 0%), delusions (1% vs 0%), sleep disorders (1% vs 0%). ***Respiratory system:*** dyspnea (4% vs 3%), rhinitis (3% vs 1%), pneumonia (2% vs 0%). ***Skin and appendages:*** skin disorders (2% vs 1%). ***Special senses:*** accommodation abnormalities (4% vs 2%), vision abnormalities (3% vs 1%), diplopia (1% vs 0%). ***Urogenital system:*** urinary frequency (6% vs 3%), urinary tract infection (4% vs 3%), urinary incontinence (2% vs 1%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

Restless Legs Syndrome: MIRAPEX tablets for treatment of RLS have been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year.

The overall safety assessment focuses on the results of three double-blind, placebo-controlled trials, in which 575 patients with RLS were treated with MIRAPEX tablets for up to 12 weeks. The most commonly observed adverse events with MIRAPEX tablets in the treatment of RLS (observed in >5% of pramipexole-treated patients and at a rate at least twice that observed in placebo-treated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and transient.

Approximately 7% of 575 patients treated with MIRAPEX tablets during the double-blind periods of three placebo-controlled trials discontinued treatment due to adverse events compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of treatment was nausea (1%).

This section lists treatment-emergent events that occurred in three double-blind, placebo-controlled studies in RLS patients that were reported by 2% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=575) vs placebo (N=223), respectively. ***Gastrointestinal disorders:*** nausea (16% vs 5%), constipation (4% vs 1%), diarrhea (3% vs 1%), dry mouth (3% vs 1%). ***General disorders and administration site conditions:*** fatigue (9% vs 7%). ***Infections and infestations:*** influenza (3% vs 1%). ***Nervous system disorders:*** headache (16% vs 15%), somnolence (6% vs 3%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

This section summarizes data for adverse events that appeared to be dose related in the 12-week fixed dose study. Dose related adverse events in a 12-week, double-blind, placebo-controlled, fixed dose study in Restless Legs Syndrome (occurring in 5% or more of all patients in the treatment phase) are listed by body system in order of decreasing incidence for MIRAPEX (0.25 mg [N=88]; 0.5 mg [N=80]; 0.75 mg [N=90]) vs placebo (n=86), respectively. ***Gastrointestinal disorders:*** nausea (11%; 19%; 27% vs 5%), diarrhea (3%; 1%; 7% vs 0%), dyspepsia (3%; 1%; 4% vs 7%). ***Infections and infestations:*** influenza (1%; 4%; 7% vs 1%). ***General disorders and administration site conditions:*** fatigue (3%; 5%; 7% vs 5%). ***Psychiatric disorders:*** insomnia (9%; 9%; 13% vs 9%), abnormal dreams (2%; 1%; 8% vs 2%). ***Respiratory, thoracic and mediastinal disorders:*** nasal congestion (0%; 3%; 6% vs 1%). ***Musculoskeletal and connective tissue disorders:*** pain in extremity (3%; 3%; 7% vs 1%).

Other events reported by 2% or more of RLS patients treated with Mirapex® (pramipexole dihydrochloride) tablets but equally or more frequently in the placebo group, were: vomiting, nasopharyngitis, back pain, pain in extremity, dizziness, and insomnia.

General

Adverse Events; Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX tablets, hallucination appeared to exhibit a positive relationship to age in patients with Parkinson's disease. Although no gender-related differences were observed in Parkinson's disease patients, nausea and fatigue, both generally transient, were more frequently reported by female than male RLS patients. Less than 4% of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During Phase 2 and 3 Clinical Trials: MIRAPEX tablets have been administered to 1620 Parkinson's disease patients and to 889 RLS patients in Phase 2 and 3 clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing; similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. Adverse events which are not listed above but occurred on at least two occasions (one occasion if the event was serious) in the 2509 individuals exposed to MIRAPEX tablets are listed below. The reported events below are included without regard to determination of a causal relationship to MIRAPEX tablets.

Blood and lymphatic system disorders: anemia, iron deficiency anemia, leukocytosis, leukopenia, lymphadenitis, lymphadenopathy, thrombocythaemia, thrombocytopenia. *Cardiac disorders:* angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block first degree, atrioventricular block second degree, bradycardia, bundle branch block, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomegaly, coronary artery occlusion, cyanosis, extrasystoles, left ventricular failure, myocardial infarction, nodal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular fibrillation, ventricular extrasystoles, ventricular hypertrophy. *Congenital, familial and genetic disorders:* atrial septal defect, congenital foot malformation, spine malformation. *Ear and labyrinth disorders:* deafness, ear pain, hearing impaired, hypoacusis, motion sickness, vestibular ataxia. *Endocrine disorders:* goiter, hyperthyroidism, hypothyroidism. *Eye disorders:* amaurosis fugax, blepharitis, blepharospasm, cataract, dacryostenosis acquired, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema, eyelid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment, retinal vascular disorder, scotoma, vision blurred, visual acuity reduced, vitreous floaters. *Gastrointestinal disorders:* abdominal discomfort, abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis ulcerative, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, esophageal spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia. *General disorders:* chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, feeling hot, feeling jittery, gait disturbance, impaired healing, influenza-like illness, irritability, localized edema, edema, pitting edema, thirst. *Hepatobiliary disorders:* biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis. *Immune system disorders:* drug hypersensitivity. *Infections and infestations:* abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis, bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, furuncle, gangrene, gastroenteritis, gingival infection, herpes simplex, herpes zoster, hordeolum, intervertebral discitis, laryngitis, lobar pneumonia, nail infection, onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia, pyelonephritis, pyoderma, sepsis, skin infection, tonsillitis, tooth abscess, tooth infection, upper respiratory tract infection, urethritis, vaginal candidiasis, vaginal infection, viral infection, wound infection. *Injury, poisoning and procedural complications:* accidental falls, drug toxicity epicondylitis, road traffic accident, sunburn, tendon rupture. *Metabolism and nutrition disorders:* cachexia, decreased appetite, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased appetite, metabolic alkalosis. *Musculoskeletal and connective tissue disorders:* bone pain, fasciitis, flank pain, intervertebral disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monarthritis, muscle rigidity, muscle spasms, musculoskeletal stiffness, myopathy, myositis, nuchal rigidity, osteoarthritis, osteonecrosis, osteoporosis, polymyalgia, rheumatoid arthritis, shoulder pain, spinal osteoarthritis, tendonitis, tenosynovitis. *Neoplasms benign, malignant and unspecified:* abdominal neoplasm, adenocarcinoma, adenoma benign, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer, gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lip and/or oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma, melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benign, neoplasm, neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer, prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilloma, squamous cell carcinoma, thyroid neoplasm, uterine leiomyoma. *Nervous system disorders:* ageusia, akinesia, anticholinergic syndrome, aphasia, balance disorder, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, coordination abnormal, dementia, depressed level of consciousness, disturbance in attention, dizziness postural, dysarthria, dysgraphia, facial palsy, grand mal convulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance, sleep talking, stupor, syncope vasovagal, tension headache. *Psychiatric disorders:* affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, delusional disorder persecutory type, disorientation, dissociation, emotional distress, euphoric mood, hallucination auditory, hallucination visual, initial insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, obsessive thoughts, obsessive-compulsive disorder, panic reaction, parasomnia, personality disorder, psychotic disorder, restlessness, sleep walking, suicidal ideation. *Renal and urinary disorders:* chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolithiasis, neurogenic bladder, nocturia, oliguria, pollakiuria, proteinuria, renal artery stenosis, renal colic, renal cyst, renal failure, renal impairment, urinary retention. *Reproductive system and breast disorders:* amenorrhea, breast pain, dysmenorrhea, epididymitis, gynaecomastia, menopausal symptoms, menorrhagia, metrorrhagia, ovarian cyst, priapism, prostatitis, sexual dysfunction, uterine hemorrhage, vaginal discharge, vaginal hemorrhage. *Respiratory, thoracic and mediastinal disorders:* apnea, aspiration, asthma, choking, chronic obstructive pulmonary disease, dry throat, dysphonia, dyspnea exertional, epistaxis, haemoptysis, hiccups, hyperventilation, increased bronchial secretion, laryngospasm, nasal dryness, nasal polyps, obstructive airways disorder, pharyngolaryngeal pain, pleurisy, pneumonia aspiration, pneumothorax, postnasal drip, productive cough, pulmonary embolism, pulmonary edema, respiratory alkalosis, respiratory distress, respiratory failure, respiratory tract congestion, rhinitis allergic, rhinorrhea, sinus congestion, sleep apnoea syndrome, sneezing, snoring, tachypnea, wheezing. *Skin and subcutaneous tissue disorders:* acne, alopecia, cold sweat, dermal cyst, dermatitis, dermatitis bullous, dermatitis contact, dry skin, ecchymosis, eczema, erythema, hyperkeratosis, livedo reticularis, night sweats, periorbital edema, petechiae, photosensitivity allergic reaction, psoriasis, purpura, rash erythematous, rash maculo-papular, rash papular, rosacea, seborrhea, seborrheic dermatitis, skin burning sensation, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer, urticaria. *Vascular disorders:* aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose vein.

Falling Asleep During Activities of Daily Living: Patients treated with Mirapex® (pramipexole dihydrochloride) tablets have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see bolded **WARNING**).

Post-Marketing Experience: In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of MIRAPEX tablets, primarily in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to pramipexole tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA dictionary: abnormal behavior, abnormal dreams, accidents (including fall), blackouts, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating , compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, syncope, and weight increase.

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance. Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipexole for 2 days in a clinical trial to evaluate the effect of pramipexole in schizophrenic patients. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg TID). In a similar study of pigmented rats with 2 years' exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on a mg/m^2 basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2 and 11 times the highest clinical dose on a mg/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m^2 basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice: An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

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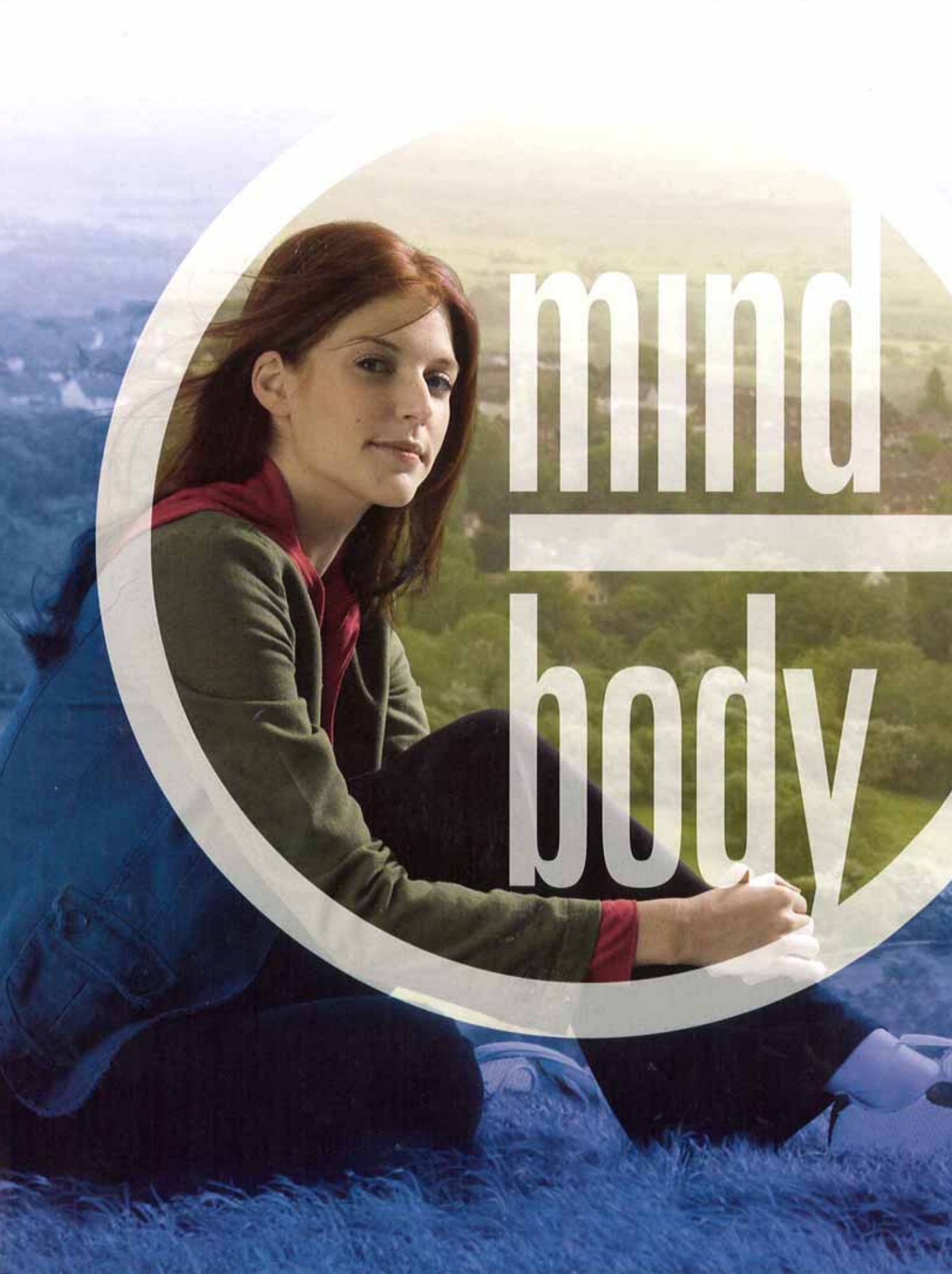
Rx only

OT1317D
MRLS-BS

Boehringer Ingelheim

Mirapex®
pramipexole dihydrochloride tablets

Because she does not like to compromise...

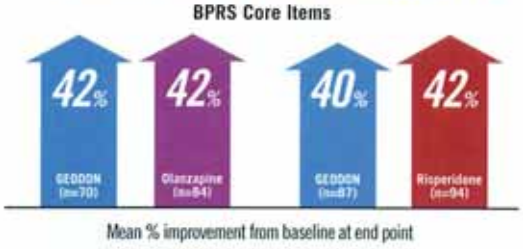

mind
body

IN SCHIZOPHRENIA

Treat With the Body in Mind

CHOOSE COMPARABLE POWER...

Consistent results in acute head-to-head studies[1-3]

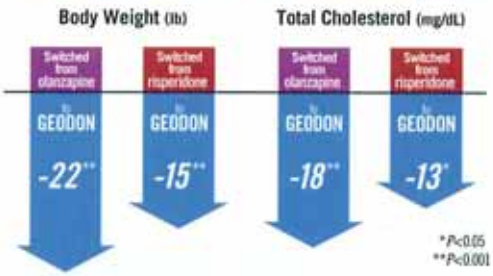


A 6-week, double-blind, randomized study of GEODON vs olanzapine and an 8-week, double-blind, randomized study of GEODON vs risperidone.

- BPRS core items include hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness
- Comparable efficacy was maintained in double-blind extension studies
  —up to 1 year vs risperidone[1]
  —up to 6 months vs olanzapine[4]

...WITHOUT COMPROMISING METABOLIC PARAMETERS

Significant results in switch studies after 1 year[1,5]



Two 1-year open-label extensions of 6-week, open-label switch studies in patients suboptimally controlled due to partial response or poor tolerability.

- Patients switching to GEODON from olanzapine and risperidone also experienced reductions in triglycerides[5]

In the acute head-to-head studies...

- In the GEODON vs olanzapine study, olanzapine significantly increased body weight (8 lb vs 2 lb for GEODON, $P<0.0001$)[1,2]
- In the GEODON vs risperidone study, risperidone increased body weight (2 lb vs 0 lb for GEODON, $P<0.01$)[1,3]

CHOOSE GEODON® (ziprasidone HCl) Oral Capsules

GEODON is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder and for the treatment of schizophrenia.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_C interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

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 GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

In short-term schizophrenia trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence and respiratory tract infection.

In short-term schizophrenia clinical trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo.

Pfizer

Please see brief summary of prescribing information, including boxed warning, on adjacent page.

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 seventeen placebo controlled trials (modal 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® (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, probucol, 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_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c 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 QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c 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 QT_c 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/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c 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/QT_c 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 QT_c 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 QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c 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 QT_c 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 QT_c 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 QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c 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 QT_c 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, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c 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 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 GEODON 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 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 D_2 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 QT, 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 QT- 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 bid 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 benztropine, 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 contraceptive, 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 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. 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 ≥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, hypesthesia, 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, hypertonia, 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 ≥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" 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:*** GEODON is associated with an increase in the QT_c 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 1/100 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, 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, phlebitis, pulmonary embolus, 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, polycythemia, thrombocythemia. 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, hyperlipemia, hypocholesterolemia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypopotenemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System—*Frequent*: myalgia; *Infrequent*: tenosynovitis; *Rare*: myopathy. Nervous System—*Frequent*: agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, bucoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent*: paralysis; *Rare*: myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, 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*: gynecomastia, 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 (≥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 (26%). **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 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, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, 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 overdosage 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).

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161:1837-1847. **3.** Addington DEN, Pantelis C, Dineen M, Benattia I, Romano SJ. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry*. 2004;65:1624-1633. **4.** Simpson GM, Weiden P, Pigott T, Murray S, Siu CO, Romano SJ. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *Am J Psychiatry*. 2005;162:1535-1538. **5.** Weiden PJ, Loebel A, Yang R, Lebovitz H. Course of weight & metabolic benefits 1 year after switching to ziprasidone. Presented at: American Psychiatric Association Annual Meeting; May 1-6, 2004; New York, NY.

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ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. Antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1 of the full prescribing information. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder**: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represents such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Serotonin Syndrome**—The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **Mydriasis**—Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS**: **General**—***Discontinuation of Treatment with Effexor XR.*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. ***Changes in Weight***: ***Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; *P*<0.001) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; *P*<0.001). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Height***: ***Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); *P*=0.041. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Appetite***: ***Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Interstitial Lung Disease and Eosinophilic Pneumonia***: These have been rarely reported. Consider the possibility of these events in venlafaxine patients who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation and should consider discontinuation of venlafaxine. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide called *"Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions"* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk**: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**— ***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome)**: Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy**—***Teratogenic Effects***—***Pregnancy Category C***. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***: Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and

effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C027, revised May 2007.

Wyeth® 206299-01

Take a closer look at

Dialogues

Time to Talk™

Dialogues
is a unique patient support and education program that is designed to help you foster successful therapy

Dialogues
offers patients access to a call center to speak with a health care provider for patient support and education to reinforce your efforts

Dialogues
supplies feedback and updates about these patient calls to you, their physician

Encourage your **EFFEXOR XR** patients to enroll in ***Dialogues*** by calling **866-313-3737** — and you can visit **mddpatientsupport.com**

- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® *EXTENDED RELEASE CAPSULES*

The change they deserve.

Please see brief summary of Prescribing Information on adjacent pages.

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Still depressed?

- ☑ *Anxiety, insomnia, low energy*
- ☑ *Currently on an SSRI**
- ☑ *Still suffering*

It may be time to make a change

Break the Cycle with EFFEXOR XR

* Patients currently on an SSRI should be evaluated following an adequate trial.

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients.

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).**
- Adult and pediatric patients taking antidepressants can experience worsening of their depression and/or the emergence of suicidality. **All patients should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.
- The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually.

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