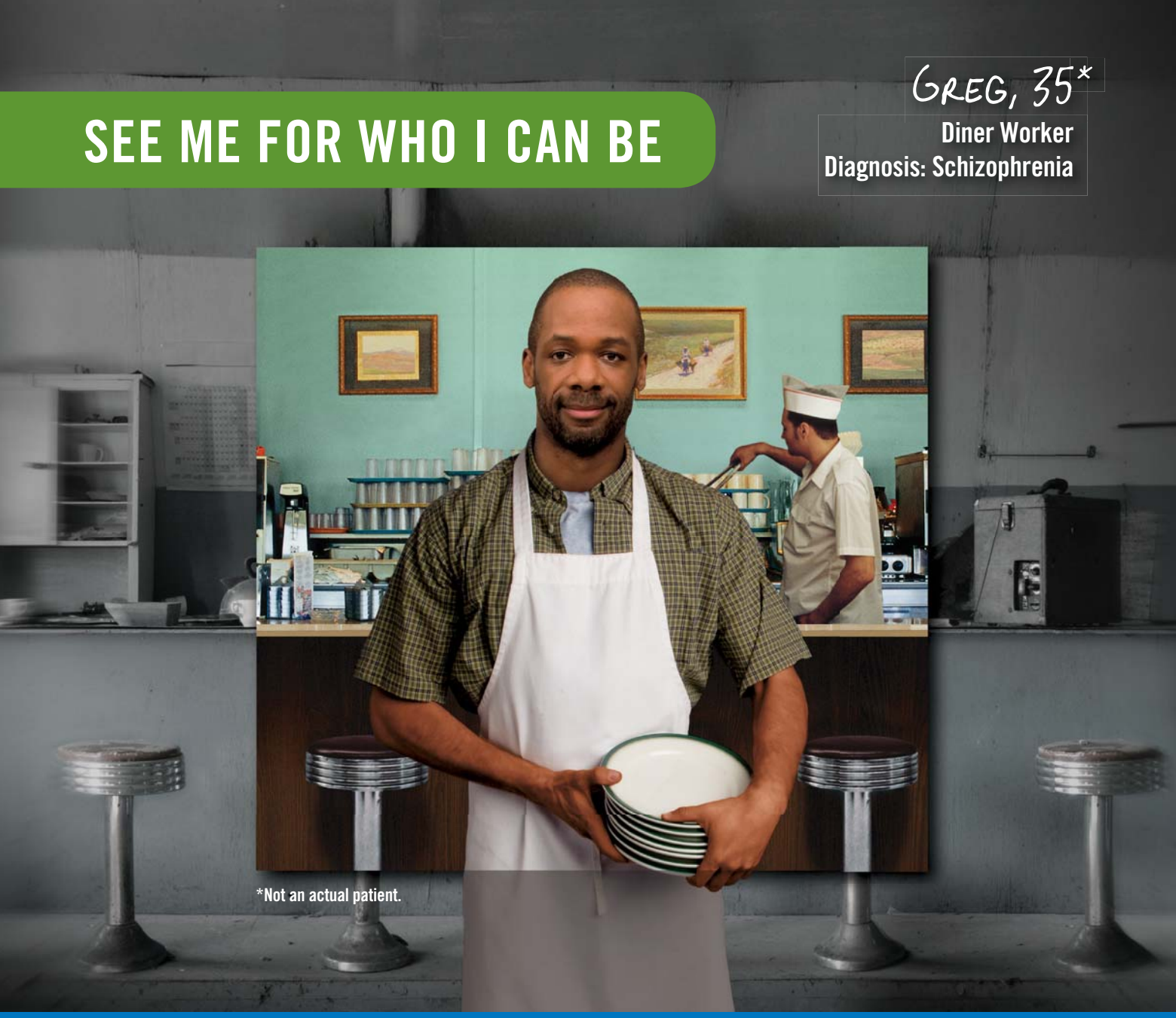
SEE ME FOR WHO I CAN BE

Greg, 35*
Diner Worker
Diagnosis: Schizophrenia



*Not an actual patient.

GEODON is indicated for schizophrenia. For full symptoms and diagnostic criteria, see the *DSM-IV-TR*® (2000).

Important Safety Information

Elderly patients with dementia-related psychosis treated with 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 certain 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. Hypokalemia may increase the risk of QT prolongation and arrhythmia.

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 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.

Please see brief summary of prescribing information on adjacent page.

For more information, please visit www.pfizerpro.com/GEODON

GEODON®
(ziprasidone HCl) Capsules

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 antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON® (ziprasidone HCl) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

INDICATIONS—GEODON Capsules are 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 antipsychotic drugs are at an increased risk of death. 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:*** **Leukopenia, Neutropenia and Agranulocytosis —** *Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia and agranulocytosis have been reported temporally related to antipsychotic agents. Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of GEODON should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue GEODON and have their WBC followed until recovery. 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 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 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/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. ***Dystonia:*** Prolonged abnormal contractions of muscle groups may occur in susceptible individuals during first few days of treatment. Dystonia may occur at any dose level but with greater frequency and severity with high potency and at higher doses of first generation antipsychotic drugs. Elevated risk is observed in males and younger age groups. ***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, 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. **Other Events Observed During Post-marketing Use:** Adverse event reports not listed above that have been received since market introduction include rare occurrences of the following (no causal relationship with ziprasidone has been established): *Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors - see **WARNINGS**); *Digestive System Disorders:* Swollen tongue; *Nervous System Disorders:* Facial droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Skin and subcutaneous Tissue Disorders:* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope. **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).

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IMPORTANT SAFETY INFORMATION

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking CHANTIX in the post-marketing experience.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

CHANTIX is indicated as an aid to smoking cessation treatment in adults 18 and over. Patients may benefit from behavioral modification and support during their quit attempt. Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.

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Please see brief summary of Prescribing Information on last pages of this advertisement.

THIS YEAR, HELP THEM KEEP THEIR RESOLUTION

CHANTIX® (varenicline) has been prescribed to more than 11 million patients worldwide*

CHANTIX® + GET QUIT® Plan

It's more than a prescription. It's a plan for quitting.

- **You put them on the quitting path. GETQUIT® is on call to help provide smoking cessation follow-up and support**

According to the US Public Health Service

Your involvement may improve your patients' chances of successfully quitting smoking[1]

CHANTIX® (varenicline) TABLETS

THE POWER TO HELP THEM QUIT

IMPORTANT SAFETY INFORMATION

Patients should be informed that there have been reports of serious skin reactions, such as Stevens Johnson Syndrome and Erythema Multiforme and of angioedema, with swelling of the face, mouth and neck that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms or at the first sign of rash with mucosal lesions or any other signs of hypersensitivity.

The most common adverse reactions include nausea (30%), sleep disturbance, constipation, flatulence, and vomiting. Patients should be informed that they may experience vivid, unusual, or strange dreams during treatment with CHANTIX. Patients should be advised to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

Safety and efficacy of CHANTIX in combination with other smoking cessation drug therapies have not been studied. Dosage adjustment with CHANTIX is recommended in patients with severe renal impairment or in patients undergoing hemodialysis.

Smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, such as theophylline, warfarin, and insulin. Dosage adjustment for these drugs may be necessary.

*May 2006 through June 2009. IMS Health. 2009.

Reference: 1. Fiore MC, Jaén CR, Baker TB, et al. *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update.* Rockville, MD: US Dept of Health and Human Services, Public Health Service; 2008.

Brief summary of full Prescribing Information.

CHANTIX®
(varenicline) Tablets

WARNING:
Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking CHANTIX in the post-marketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

INDICATIONS AND USAGE
CHANTIX is indicated as an aid to smoking cessation treatment.

WARNINGS
Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX (See **Boxed Warning, PRECAUTIONS/ Information for patients, and ADVERSE REACTIONS/Post-Marketing Experience**). These post-marketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a health care provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Angioedema and Hypersensitivity Reactions.

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX (See **ADVERSE REACTIONS/Post-Marketing Experience**). Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

Serious Skin Reactions

There have been post-marketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using CHANTIX (See **ADVERSE REACTIONS/Post-Marketing Experience**) As these skin reactions can be life-threatening, patients should be instructed to stop taking CHANTIX and contact their healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

PRECAUTIONS
General Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

Accidental Injury There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Patients should be advised to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

Effect of smoking cessation. Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

Drug Interactions Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions (See **Full Prescribing Information, CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis. Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis. Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of fertility. There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

Pregnancy Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). **Nonteratogenic effects** Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, 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. **Labor and delivery** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. 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 responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSAGE AND ADMINISTRATION, Special Populations**).

Information for Patients:
- Patients should be instructed to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date.
- Patients should be advised that CHANTIX should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening.
- Patients should be advised that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that nausea and insomnia are side effects of CHANTIX and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
- Patients should be informed that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.
- Patients should be informed that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness. Furthermore, some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately.
- Patients should be encouraged to reveal any history of psychiatric illness prior to initiating treatment.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with CHANTIX.
- Patients should be advised to use caution driving or operating machinery until they know how quitting smoking with varenicline may affect them.
- Patients should be informed that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.
- Patients should be informed that serious skin reactions, such as Stevens Johnson Syndrome and Erythema Multiforme, were reported by some patients taking CHANTIX. They should be advised to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a health care provider immediately.

ADVERSE REACTIONS
During the premarketing development of CHANTIX, over 4500 individuals were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less. In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg BID was 12% for CHANTIX compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates for the most common adverse events in CHANTIX treated patients were as follows: nausea (3% vs. 0.5% for placebo), headache (0.6% vs. 0.9% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo). Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

The most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting. Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms.

The most common adverse event associated with CHANTIX treatment is nausea. For patients treated to the maximum recommended dose of 1 mg BID following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

Table 3 shows the adverse events for CHANTIX and placebo in the 12 week fixed dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5). MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg BID dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥ 1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1mg BID N=821	Placebo N=805
GASTROINTESTINAL			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain*	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
PSYCHIATRIC DISORDERS			
Sleep Disorders/Disturbances			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/THORACIC/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnoea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3,

though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with CHANTIX 1 mg BID in a one-year study, compared to 8% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS**. ***Infrequent***: Anemia, Lymphadenopathy. ***Rare***: Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS**. ***Infrequent***: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. ***Rare***: Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **EAR AND LABYRINTH DISORDERS**. ***Infrequent***: Tinnitus, Vertigo. ***Rare***: Deafness, Meniere's disease. **ENDOCRINE DISORDERS**. ***Infrequent***: Thyroid gland disorders. **EYE DISORDERS**. ***Infrequent***: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. ***Rare***: Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS. *Frequent***: Diarrhea, Gingivitis. ***Infrequent***: Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. ***Rare***: Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS**. ***Frequent***: Chest pain, Influenza like illness, Edema, Thirst. ***Infrequent***: Chest discomfort, Chills, Pyrexia. **HEPATOBILIARY DISORDERS. *Infrequent***: Gall bladder disorder. **IMMUNE SYSTEM DISORDERS**. ***Infrequent***: Hypersensitivity. ***Rare***: Drug hypersensitivity. **INVESTIGATIONS**. ***Frequent***: Liver function test abnormal, Weight increased. ***Infrequent***: Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal. **METABOLISM AND NUTRITION DISORDERS. *Infrequent***: Diabetes mellitus, Hyperlipidemia, Hypokalemia. ***Rare***: Hyperkalemia, Hypoglycemia. **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS**. ***Frequent***: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. ***Infrequent***: Arthritis, Osteoporosis. ***Rare***: Myositis. **NERVOUS SYSTEM DISORDERS**. ***Frequent***: Disturbance in attention, Dizziness, Sensory disturbance. ***Infrequent***: Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. ***Rare***: Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **PSYCHIATRIC DISORDERS**. ***Frequent***: Anxiety, Depression, Emotional disorder, Irritability, Restlessness. ***Infrequent***: Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. ***Rare***: Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS**. ***Frequent***: Polyuria. ***Infrequent***: Nephrolithiasis, Nocturia, Urine abnormality, Urethral syndrome. ***Rare***: Renal failure acute, Urinary retention. **REPRODUCTIVE SYSTEM AND BREAST DISORDERS**. ***Frequent***: Menstrual disorder. ***Infrequent***: Erectile dysfunction. ***Rare***: Sexual dysfunction. **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS**. ***Frequent***: Epistaxis, Respiratory disorders. ***Infrequent***: Asthma. ***Rare***: Pleurisy, Pulmonary embolism. **SKIN AND SUBCUTANEOUS TISSUE DISORDERS. *Frequent***: Hyperhidrosis. ***Infrequent***: Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. ***Rare***: Photosensitivity reaction. **VASCULAR DISORDERS**. ***Frequent***: Hot flush, Hypertension. ***Infrequent***: Hypotension, Peripheral ischemia, Thrombosis.

Post-Marketing Experience:

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX (See **Boxed Warning, WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients**). Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been reports of hypersensitivity reactions, including angioedema (See **WARNINGS** and **PRECAUTIONS**).

There have also been reports of serious skin reactions, including Stevens Johnson Syndrome and Erythema Multiforme in patients taking CHANTIX (See **WARNINGS** and **PRECAUTIONS**).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Varenicline is not a controlled substance. Humans: Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction. In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers. Animals: Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

OVERDOSAGE

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Patient Populations**), however, there is no experience in dialysis following overdose.

DOSAGE AND ADMINISTRATION

Usual Dosage for Adults Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt. The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date. CHANTIX should be taken after eating and with a full glass of water. The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1–3:	0.5 mg once daily
Days 4–7:	0.5 mg twice daily
Days 8–End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently. Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence. Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Special Populations

Patients with impaired renal function No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal impairment**).

Dosing in elderly patients and patients with impaired hepatic function No dosage adjustment is necessary for patients with hepatic impairment. 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 **PRECAUTIONS, Geriatric Use**).

Use in children Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Please see CHANTIX full Prescribing Information and patient Medication Guide at www.pfizerpro.com/chantix.

Rx only

July 2009, Version 4.0

Pfizer U.S. Pharmaceuticals

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IMPORTANT SAFETY INFORMATION FOR INVEGA®

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® (paliperidone) is not approved for the treatment of patients with dementia-related psychosis.

Hypersensitivity: Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone, which is a metabolite of risperidone, therefore paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA®.

Cerebrovascular Adverse Events (CAEs): CAEs, including fatalities and stroke, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. INVEGA® is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. 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 close medical monitoring, and treatment of any concomitant serious medical problems.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QT interval and in patients with risk factors for prolonged QT 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.

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, but can develop after relatively brief treatment at low doses. Elderly women patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD. Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Hyperglycemia and Diabetes: Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including INVEGA®. Patients starting treatment with APS who have or

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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. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, INVEGA® elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

Orthostatic Hypotension and Syncope: 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, cerebrovascular disease or conditions that would predispose patients to hypotension.

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including paliperidone. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a decline in WBC and in the absence of other causative factors, discontinuation of INVEGA® should be considered. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA®. INVEGA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® does not affect them adversely, and should use caution when operating machinery.

Seizures: INVEGA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold.

Suicide: The possibility of suicide attempt is inherent in schizophrenia. Close supervision of high-risk patients should accompany drug therapy.

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.

Commonly Observed Adverse Reactions: The most commonly observed adverse reactions in clinical trials occurring at an incidence of ≥5% and at least 2 times placebo were: schizophrenia—extrapyramidal symptoms, tachycardia, and akathisia; schizoaffective disorder—extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

Reference: 1. US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed September 24, 2009.

Please see brief summary of full Prescribing Information for INVEGA® on adjacent page.

Janssen
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

 December 2009 01JN090928

INVEGA®

(paliperidone) Extended-Release Tablets

Brief Summary

BEFORE PRESCRIBING INVEGA®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® (paliperidone) Extended-Release Tablets is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions]*

INVEGA® (paliperidone) Extended-Release Tablets are indicated for the acute and maintenance treatment of schizophrenia *[see Clinical Studies (14) in full PI*].

CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. INVEGA® (paliperidone) is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA®.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA® (paliperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

Cerebrovascular Adverse Reactions, 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 reactions (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 and Warnings and Precautions]*.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

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=50) 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 ng/mL 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 in subjects with schizophrenia, 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.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® despite the presence of the syndrome.

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. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA®. 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. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA® was not marketed at the time these studies were performed, it is not known if INVEGA® is associated with this increased risk.

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. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing

hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

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 considered in a patient with previously detected breast cancer. 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 Nonclinical Toxicology (13.1) in full PI]*. 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.

Potential for Gastrointestinal Obstruction: 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 Dosage and Administration (2.3) and Patient Counseling Information (17.8) in full PI]*.

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.

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 in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 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 (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: *Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including INVEGA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment: Somnolence was 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.

Seizures: During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. 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. Conditions that lower the seizure threshold may be more prevalent in patients 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 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. Prescriptions for INVEGA® should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Priapism: Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with INVEGA® during postmarketing surveillance. Severe priapism may require surgical intervention.

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Thrombotic Thrombocytopenic 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, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

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 (12.3) 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 Warnings and Precautions]*.

Monitoring: Laboratory Tests: No specific laboratory tests are recommended.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions]*
- QT prolongation *[see Warnings and Precautions]*
- Tardive dyskinesia *[see Warnings and Precautions]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions]*
- Hyperprolactinemia *[see Warnings and Precautions]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*
- Dysphagia *[see Warnings and Precautions]*
- Suicide *[see Warnings and Precautions]*
- Priapism *[see Warnings and Precautions]*
- Thrombotic thrombocytopenic purpura (TTP) *[see Warnings and Precautions]*
- Disruption of body temperature regulation *[see Warnings and Precautions]*
- Antiemetic effect *[see Warnings and Precautions]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions]*

The most common adverse reactions in clinical trials in subjects with schizophrenia (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate in any of the dose groups) were extrapyramidal symptoms, tachycardia, and akathisia. The most common adverse reactions in clinical trials in patients with schizoaffective disorder (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate) were extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

The most common adverse reactions that were associated with discontinuation from clinical trials in subjects with schizophrenia (causing discontinuation in 2% of INVEGA®-treated subjects) were nervous system disorders. The most common adverse reactions that were associated with discontinuation from clinical trials in subjects with schizoaffective disorder were gastrointestinal disorders, which resulted in discontinuation in 1% of INVEGA®-treated subjects. *[See Adverse Reactions]*.

The safety of INVEGA® was evaluated in 1205 adult subjects with schizophrenia who participated in three placebo-controlled, 6-week, double-blind trials, of whom 850 subjects received INVEGA® at fixed doses ranging from 3 mg to 12 mg once daily. The information presented in this section was derived from pooled data from these three trials. 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 mg to 15 mg (n=104), is also included.

The safety of INVEGA® was also evaluated in 622 adult subjects with schizoaffective disorder who participated in two placebo-controlled, 6-week, double-blind trials. In one of these trials, 206 subjects were assigned to one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg (n = 108) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. In the other study, 214

INVEGA® (paliperidone) Extended-Release Tablets

subjects received flexible doses of INVEGA® (3-12 mg once daily). Both studies included subjects who received INVEGA® either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. Adverse events during exposure to study treatment 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.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of INVEGA® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for INVEGA® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia: *Table 1* enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those 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.

Table 1. Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizophrenia in Three Short-Term, Fixed-Dose, Placebo-Controlled Clinical Trials *: Body System or Organ Class Dictionary-Derived Term followed by **Percent of Patients Reporting Event Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: **Total percentage of subjects with adverse reactions:** 37, 48, 47, 53, 59; **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; **Gastrointestinal disorders:** Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Salivary hypersecretion<10<114; **General disorders:** Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; **Nervous system disorders:** Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Extrapyramidal symptoms 8, 10, 7, 20, 18; Headache 12, 11, 12, 14, 14; Somnolence 7, 6, 9, 10, 11; **Vascular disorders:** Orthostatic hypotension 1, 2, 1, 2, 4.
* Table includes adverse reactions 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 study included once-daily INVEGA® doses of 3 mg and 9 mg, the second study included 6 mg, 9 mg, and 12 mg, and the third study included 6 mg and 12 mg *[see Clinical Studies (14) in full PI]*. Extrapyramidal symptoms includes the terms dyskinesia, dystonia, extrapyramidal disorder, hypertonia, muscle rigidity, oculogyration, parkinsonism, and tremor. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Adverse reactions for which the INVEGA® incidence was equal to or less than placebo are not listed in the table, but included the following: vomiting.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizoaffective Disorder: *Table 2* enumerates the pooled incidences of adverse reactions reported in the two placebo-controlled 6-week studies, listing those that occurred in 2% or more of subjects treated with INVEGA® and for which the incidence in INVEGA®-treated subjects was greater than the incidence in subjects treated with placebo.

Table 2. Adverse Drug Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials: Body System or Organ Class Dictionary-Derived Term followed by **Placebo (N=202)** first, **INVEGA® 3-6 mg once-daily fixed-dose range (N=108)** second, **INVEGA® 9-12 mg once-daily fixed-dose range (N=98)** third, **INVEGA® 3-12 mg once-daily flexible dose (N=214)** fourth: **Total percentage of subjects with adverse reactions:** 32, 48, 50, 43; **Cardiac disorders:** Tachycardia 2, 3, 1, 2; **Gastrointestinal disorders:** Abdominal discomfort/Abdominal pain upper 1, 1, 0, 3; Constipation 2, 4, 5, 4; Dyspepsia 2, 5, 6, 6; Nausea 6, 8, 8, 5; Stomach discomfort 1, 0, 1, 2; **General disorders:** Asthenia 1, 3, 4, <1; **Infections and Infestations:** Nasopharyngitis 1, 2, 5, 3; Rhinitis 0, 1, 3, 1; Upper respiratory tract infection 1, 2, 2, 2; **Investigations:** Weight increased 1, 5, 4, 4; **Metabolism and nutrition disorders:** Decreased appetite <1, 1, 0, 2; Increased appetite <1, 3, 2, 2; **Musculoskeletal and connective tissue disorders:** Back pain 1, 1, 1, 3; Myalgia <1, 2, 4, 1; **Nervous system disorders:** Akathisia 4, 4, 6, 6; Dysarthria 0, 1, 4, 2; Extrapyramidal symptoms 8, 20, 17, 12; Somnolence 5, 12, 12, 8; **Psychiatric disorders:** Sleep disorder <1, 2, 3, 0; **Respiratory, thoracic and mediastinal disorders:** Cough 1, 1, 3, 1; Pharyngolaryngeal pain <1, 0, 2, 1. * Table includes adverse reactions 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 two studies. One study included once-daily INVEGA® doses of 6 mg (with the option to reduce to 3 mg) and 12 mg (with the option to reduce to 9 mg). The second study included flexible once-daily doses of 3 to 12 mg. Among the 420 subjects treated with INVEGA®, 230 (55%) received INVEGA® as monotherapy and 190 (45%) received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. All EPS-related terms are grouped under "extrapyramidal symptoms".

Monotherapy versus Adjunctive Therapy: The designs of the two placebo-controlled, 6-week, double-blind trials in subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received INVEGA® as monotherapy and 190 (45%) subjects received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥ 3% difference) in subjects receiving INVEGA® as monotherapy.

Other Adverse Reactions Observed During Premarketing Evaluation of INVEGA®: The following additional adverse reactions occurred in < 2% of INVEGA®-treated subjects in the above schizophrenia and schizoaffective disorder clinical trial datasets.

Cardiac disorders: bradycardia, palpitations

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal pain, small intestinal obstruction, swollen tongue

General disorders: edema

Immune system disorders: anaphylactic reaction

Nervous system disorders: dizziness postural, grand mal convulsion, lethargy, syncope

Psychiatric disorders: nightmare

Reproductive system and breast disorders: amenorrhea, breast discharge, breast engorgement, breast pain, erectile dysfunction, galactorrhea, gynecomastia, menstruation irregular

Vascular disorders: hypotension, ischemia

Discontinuations Due to Adverse Reactions: Schizophrenia Trials:The percentages of subjects who discontinued due to adverse reactions in the three schizophrenia placebo-controlled, 6-week, fixed-dose studies were 3% and 1% in INVEGA®- and placebo-treated subjects, respectively. The most common reasons for discontinuation were nervous system disorders (2% and 0% in INVEGA®- and placebo-treated subjects, respectively).

Schizoaffective Disorder Trials: The percentages of subjects who discontinued due to adverse reactions in the two schizoaffective disorder placebo-controlled 6-week studies were 1% and <1% in INVEGA®- and placebo-treated subjects, respectively. The most common reasons for discontinuation were gastrointestinal disorders (1% and 0% in INVEGA®- and placebo-treated subjects, respectively).

Dose-Related Adverse Reactions: Schizophrenia Trials: Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

Schizoaffective Disorder Trials: In a placebo-controlled, 6-week, high- and low-dose study in subjects with schizoaffective disorder, akathisia, dystonia, dysarthria, myalgia, nasopharyngitis, rhinitis, cough, and pharyngolaryngeal pain occurred more frequently (i.e., a difference of at least 2%) in subjects who received higher doses of INVEGA® compared with subjects who received lower doses.

Demographic Differences: An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia and in the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder did not reveal any evidence of clinically relevant differences in safety on the basis of gender or race alone; there was also no difference on the basis of age *[see Use in Specific Populations]*.

Extrapyramidal Symptoms (EPS): Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia 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 *(Table 3)*, and (4) incidence of spontaneous reports of EPS *(Table 4)*. 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.

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies: EPS Group followed by **Percentage of Patients Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: 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

Table 4. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizophrenia Studies: EPS Group followed by **Percentage of Patients Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: Overall percentage of patients with EPS-related AE 11, 13, 10, 25, 26; Dyskinesia 3, 5, 3, 8, 9; Dystonia 1, 1, 1, 5, 5; Hyperkinesia 4, 4, 3, 8, 10; Parkinsonism 2, 3, 3, 7, 6; Tremor 3, 3, 3, 4, 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

Compared to data from the studies in schizophrenia, pooled data from the two placebo-controlled 6-week studies in subjects with schizoaffective disorder showed similar types and frequencies of EPS as measured by rating scales, anticholinergic medication use, and spontaneous reports of EPS-related adverse events. For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

Table 5 shows the EPS data from the pooled schizoaffective disorder trials.

Table 5. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies: EPS Group followed by **Percentage of Patients Placebo (N=202)** first, **INVEGA® 3-6 mg once-daily fixed-dose range (N=108)** second, **9-12 mg once-daily fixed-dose range (N=98)** third, **3-12 mg once-daily flexible dose (N=214):** Overall percentage of patients with EPS-related AE 11, 23, 22, 17; Dyskinesia 1, 3, 1, 1; Dystonia 1, 2, 3, 2; Hyperkinesia 5, 5, 8, 7; Parkinsonism 3, 14, 7, 7; Tremor 3, 12, 11, 5.

Dyskinesia group includes: Dyskinesia, muscle twitching

Dystonia group includes: Dystonia, muscle spasms, oculogyration

Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness

Parkinsonism group includes: Bradykinesia, drooling, hypertonia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonian gait, parkinsonism

Tremor group includes: Tremor

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia and from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, between-group comparisons revealed no medically important differences between INVEGA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® was associated with increases in serum prolactin *[see Warnings and Precautions].*

Weight Gain: Schizophrenia Trials: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, the proportions of subjects meeting a weight gain criterion of ≥7% of body weight were compared, revealing a similar incidence of weight gain for INVEGA® 3 mg and 6 mg (7% and 6%, respectively) compared with placebo (5%), and a higher incidence of weight gain for INVEGA® 9 mg and 12 mg (9% and 9%, respectively).

Schizoaffective Disorder Trials: In the pooled data from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, a higher percentage of INVEGA®-treated subjects (5%) had an increase in body weight of ≥ 7% compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of ≥ 7% was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

Other Findings Observed During Clinical Trials: 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 Studies (14) in full PI].* In general, adverse reaction 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 reactions 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.

Postmarketing Experience: The following adverse reaction has been identified during postapproval use of INVEGA®; because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency: priapism.

Adverse Reactions Reported With Risperidone: Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

DRUG INTERACTIONS

Potential for INVEGA® to Affect Other Drugs: 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 Warnings and Precautions].*

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.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

In a clinical study, subjects on a stable dose of valproate showed comparable valproate average plasma concentrations when 3-15 mg of INVEGA® was added to their existing valproate treatment.

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. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of INVEGA® 6 mg once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA® should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology (12.3) in full PI].* In an interaction study in healthy subjects in which a single 3 mg dose of INVEGA® was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

Co-administration of a single dose of INVEGA® 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Dosage reduction for INVEGA® should be considered when INVEGA® is co-administered with valproate after clinical assessment.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.: 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.

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.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated during the period of organogenesis with up to 8 times the maximum recommended human dose of paliperidone (on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, there were increases in pup deaths 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).

Nursing Mothers: Paliperidone is 9-hydroxyrisperidone, the active metabolite of risperidone. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Caution should be exercised when INVEGA® is administered to a nursing woman. The known benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone.

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 mg 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 mg to 15 mg once daily) *[see Clinical Studies (14) in full PI].* There were no subjects ≥ 65 years of age in the schizoaffective disorder studies.

Overall, of the total number of subjects in schizophrenia 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 (12.3) 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 (2.5) in full PI]*.

Renal Impairment: Dosing must be individualized according to the patient's renal function status *[see Dosage and Administration (2.5) in full PI]*.

Hepatic Impairment: No dosage adjustment is required in patients with mild to moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

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

Abuse: Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of INVEGA® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Dependence: Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

OVERDOSAGE

Human Experience: While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA® was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

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New York, NY 10036
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THE CHILD AND ADOLESCENT PSYCHIATRY RECERT COURSE
Audrey Walker, MD, Andrea J. Weiss, MD and David Myland Kaufman, MD

This intensive one-day course designed for child and adolescent psychiatrists reviews material likely to be on the recertification examination and provides an update on the diagnosis and treatment of children and adolescents with psychiatric disorders. Presentations are given in a mixed format, with both lecture and question-and-answers utilizing an audience response system. Faculty discuss responses to questions and from there review the content.

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IMPORTANT SAFETY INFORMATION

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking CHANTIX in the post-marketing experience.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

www.pfizerpro.com/chantix

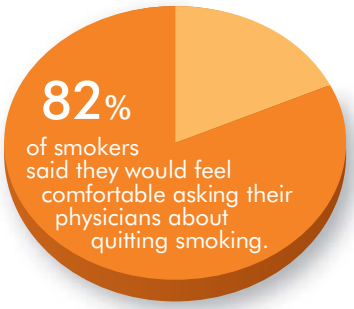
Please see accompanying brief summary of Prescribing Information.

WHEN IT COMES TO QUITTING SMOKING, WHAT ARE YOUR PATIENTS *NOT* TELLING YOU?

With smoking bans and cigarette taxes on the rise, smoking is becoming more of a burden each year, and smokers are feeling the effects.[1,2] Of the **45 million people that still smoke today, 70% want to quit**. Unfortunately, many don't know how to talk about it.[3]

Over 50% of patients who want to quit aren't talking to you about it.[4]

Even if your patients are thinking about quitting, some may not know how to bring it up. In a recent survey, 82% of smokers said they would feel comfortable asking their physicians about quitting smoking.[4] Yet **of those smokers who were thinking about quitting, more than half never asked their physicians for help**.



You can help make a difference in minutes.

As a physician, you are in a unique position to help encourage your patients to quit smoking. Research shows that a brief discussion can go a long way. Even **a smoking cessation conversation of 3 minutes has been shown to increase quit rates**.[3]

Two questions may help start the quit conversation.

You can initiate the conversation by assessing how ready your patient is to quit. Start by asking these questions:

1. On a scale of 1 to 10 how important is it for you to stop smoking? (Importance Score)
2. On a scale of 1 to 10 how confident are you in your ability to quit? (Confidence Score)

Chances are, your patients will have a higher Importance Score. Ask them why. It's a simple way to gauge their reasons for quitting. Then, ask your patients why they didn't have a lower Confidence Score. For example, if your patient chooses a 5, ask why they didn't choose a 3 or 4. It's a good way to begin the dialogue about quitting, and it can help patients realize how ready they may be to quit.[3]

The US Department of Health and Human Services recognizes the need for behavioral support.

Even with treatment, quitting smoking can be a challenge.[5] Giving your patients the support they need once they leave your office may help them stay motivated to achieve their goal. The PHS guidelines state that medication combined with support is more effective in quitting smoking than either alone.[3]

Give your patients a plan with their prescription.

The GETQUIT® Plan is one type of behavioral support, and it's available for free to your CHANTIX® (varenicline) patients. CHANTIX helps reduce the urge to smoke[6] and GETQUIT helps your patients overcome behavioral challenges by providing a plan for quitting. It's a two-part approach to quitting.

GETQUIT is on call to help provide smoking cessation follow-up and support.

The GETQUIT Plan is a full year of free, 24/7 online and phone support designed to help you support your patients as they quit smoking. GETQUIT includes:

Trained, professional support.

If your patients are having an urge, and you're not available, they can call a GETQUIT Coach for professional, empathetic support.

Patient follow-up.

GETQUIT tracks your patients' progress and answers questions they may have forgotten to ask during your visit.

Customizable support.

To help your patients stay motivated, GETQUIT lets them choose their level of participation and the type of support they prefer to receive — online or by phone.

References: 1. Centers for Disease Control and Prevention. Higher Cost of Tobacco Products, Cigarettes Increases Quit Attempts. Updated April 2009. http://www.cdc.gov/tobacco/tax_increase/. Accessed May 5, 2009. **2.** Centers for Disease Control and Prevention. State Smoke Free Indoor Air Fact Sheet. State Tobacco Activities Tracking & Evaluation. http://apps.nccd.cdc.gov/statesystem/publications/STATESystemFactSheetSmokefree.pdf. Accessed May 14, 2009. **3.** Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008. http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf. Accessed August 4, 2008. **4.** American Cancer Society. Guide to Quitting Smoking. Revised October 27, 2006. http://www.cancer.org/docroot/PED/content/PED_10_13X_Guide_for_Quitting_Smoking.asp?sit. Accessed May 8, 2007. **5.** American Legacy Foundation, Pfizer, and Harris Interactive. Survey: Smokers' Perceptions of Healthcare Providers. January 2009. **6.** Pfizer. CHANTIX Prescribing Information. June 30, 2009. **7.** Pfizer. GETQUIT Program Evaluation Study Report. Conducted by ORC Guideline. June 15, 2009.

Brief summary of full Prescribing Information.

CHANTIX®
(varenicline) Tablets

WARNING:
Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking CHANTIX in the post-marketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

INDICATIONS AND USAGE
CHANTIX is indicated as an aid to smoking cessation treatment.

WARNINGS
Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX (See **Boxed Warning, PRECAUTIONS/ Information for patients, and ADVERSE REACTIONS/Post-Marketing Experience**). These post-marketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a health care provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Angioedema and Hypersensitivity Reactions.

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX (See **ADVERSE REACTIONS/Post-Marketing Experience**). Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

Serious Skin Reactions

There have been post-marketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using CHANTIX (See **ADVERSE REACTIONS/Post-Marketing Experience**) As these skin reactions can be life-threatening, patients should be instructed to stop taking CHANTIX and contact their healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

PRECAUTIONS
General Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

Accidental Injury There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Patients should be advised to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

Effect of smoking cessation: Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

Drug Interactions Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions (See **Full Prescribing Information, CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis. Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis. Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of fertility. There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

Pregnancy Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). **Nonteratogenic effects** Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, 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. **Labor and delivery** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. 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 responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSAGE AND ADMINISTRATION, Special Populations**).

Information for Patients:
- Patients should be instructed to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date.
- Patients should be advised that CHANTIX should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening.
- Patients should be advised that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that nausea and insomnia are side effects of CHANTIX and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
- Patients should be informed that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.
- Patients should be informed that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness. Furthermore, some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately.
- Patients should be encouraged to reveal any history of psychiatric illness prior to initiating treatment.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with CHANTIX.
- Patients should be advised to use caution driving or operating machinery until they know how quitting smoking with varenicline may affect them.
- Patients should be informed that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.
- Patients should be informed that serious skin reactions, such as Stevens Johnson Syndrome and Erythema Multiforme, were reported by some patients taking CHANTIX. They should be advised to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a health care provider immediately.

ADVERSE REACTIONS
During the premarketing development of CHANTIX, over 4500 individuals were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less. In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg BID was 12% for CHANTIX compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates for the most common adverse events in CHANTIX treated patients were as follows: nausea (3% vs. 0.5% for placebo), headache (0.6% vs. 0.9% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo). Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

The most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting. Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms.

The most common adverse event associated with CHANTIX treatment is nausea. For patients treated to the maximum recommended dose of 1 mg BID following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

Table 3 shows the adverse events for CHANTIX and placebo in the 12 week fixed dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5). MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg BID dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥ 1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1mg BID N=821	Placebo N=805
GASTROINTESTINAL			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain*	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
PSYCHIATRIC DISORDERS			
Sleep Disorders/Disturbances			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/THORACIC/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnoea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3,

though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with CHANTIX 1 mg BID in a one-year study, compared to 8% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all c linical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS.** ***Infrequent***: Anemia, Lymphadenopathy. ***Rare***: Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS.** ***Infrequent***: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. ***Rare***: Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **EAR AND LABYRINTH DISORDERS.** ***Infrequent***: Tinnitus, Vertigo. ***Rare***: Deafness, Meniere's disease. **ENDOCRINE DISORDERS.** ***Infrequent***: Thyroid gland disorders. **EYE DISORDERS.** ***Infrequent***: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. ***Rare***: Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS.** ***Frequent***: Diarrhea, Gingivitis. ***Infrequent***: Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. ***Rare***: Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS.** ***Frequent***: Chest pain, Influenza like illness, Edema, Thirst. ***Infrequent***: Chest discomfort, Chills, Pyrexia. **HEPATOBILIARY DISORDERS.** ***Infrequent***: Gall bladder disorder. **IMMUNE SYSTEM DISORDERS.** ***Infrequent***: Hypersensitivity. ***Rare***: Drug hypersensitivity. **INVESTIGATIONS.** ***Frequent***: Liver function test abnormal, Weight increased. ***Infrequent***: Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal. **METABOLISM AND NUTRITION DISORDERS.** ***Infrequent***: Diabetes mellitus, Hyperlipidemia, Hypokalemia. ***Rare***: Hyperkalemia, Hypoglycemia. **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS.** ***Frequent***: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. ***Infrequent***: Arthritis, Osteoporosis. ***Rare***: Myositis. **NERVOUS SYSTEM DISORDERS.** ***Frequent***: Disturbance in attention, Dizziness, Sensory disturbance. ***Infrequent***: Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. ***Rare***: Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **PSYCHIATRIC DISORDERS.** ***Frequent***: Anxiety, Depression, Emotional disorder, Irritability, Restlessness. ***Infrequent***: Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. ***Rare***: Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS.** ***Frequent***: Polyuria. ***Infrequent***: Nephrolithiasis, Nocturia, Urine abnormality, Urethral syndrome. ***Rare***: Renal failure acute, Urinary retention. **REPRODUCTIVE SYSTEM AND BREAST DISORDERS.** ***Frequent***: Menstrual disorder. ***Infrequent***: Erectile dysfunction. ***Rare***: Sexual dysfunction. **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS.** ***Frequent***: Epistaxis, Respiratory disorders. ***Infrequent***: Asthma. ***Rare***: Pleurisy, Pulmonary embolism. **SKIN AND SUBCUTANEOUS TISSUE DISORDERS.** ***Frequent***: Hyperhidrosis. ***Infrequent***: Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. ***Rare***: Photosensitivity reaction. **VASCULAR DISORDERS.** ***Frequent***: Hot flush, Hypertension. ***Infrequent***: Hypotension, Peripheral ischemia, Thrombosis.

Post-Marketing Experience:

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX (See **Boxed Warning, WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients**). Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been reports of hypersensitivity reactions, including angioedema (See **WARNINGS** and **PRECAUTIONS**).

There have also been reports of serious skin reactions, including Stevens Johnson Syndrome and Erythema Multiforme in patients taking CHANTIX (See **WARNINGS** and **PRECAUTIONS**).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Varenicline is not a controlled substance. Humans: Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction. In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects , especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers. Animals: Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

OVERDOSAGE

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Patient Populations**), however, there is no experience in dialysis following overdose.

DOSAGE AND ADMINISTRATION

Usual Dosage for Adults Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt. The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date. CHANTIX should be taken after eating and with a full glass of water. The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1–3:	0.5 mg once daily
Days 4–7:	0.5 mg twice daily
Days 8–End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently. Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence. Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Special Populations

Patients with impaired renal function No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal impairment**).

Dosing in elderly patients and patients with impaired hepatic function No dosage adjustment is necessary for patients with hepatic impairment. 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 **PRECAUTIONS, Geriatric Use**).

Use in children Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Please see CHANTIX full Prescribing Information and patient Medication Guide at www.pfizerpro.com/chantix.

Rx only

July 2009, Version 4.0

Pfizer U.S. Pharmaceuticals

County of Santa Cruz
Employment Opportunity

PSYCHIATRIST

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Santa Cruz County is seeking staff Psychiatrists to join their Mental Health and Substance Abuse Services (MHSAS) division to ensure new community resources and opportunities for recovery and resiliency in this small coastal community in Northern California. MHSAS is part of a large Health Services Agency that provides a broad range of services for mental health care. The County is known for having many innovative programs and a strong history of effective collaboration.

For job details and/or to apply, please visit www.santacruzcountyjobs.com and click on the Psychiatrist job title. For any questions and/or to learn more about this position contact Dr. Charles Lewis Johnson, M.D. by calling (831) 454-5468.

SAM-certified Internist or Psychiatrist

Coatesville Veterans Affairs Medical Center, an affiliate with Drexel University School of Medicine, seeks a full-time SAM-certified internist or psychiatrist to oversee substance abuse services in the medical center. The incumbent will provide direct patient care and have administrative and supervisory responsibilities for the following substance abuse services; inpatient detox, substance abuse rehabilitation, residential program, outpatient buprenorphine program, and the development of an outpatient detox program. Applicants must possess USA citizenship and be board-certified in internal medicine or psychiatry. Coatesville VAMC offers excellent federal benefits, competitive salaries and a faculty appointment. Incentive pay will be considered. Coatesville VAMC is located in a scenic environment in close proximity to Philadelphia.

Please contact:

Theresa Englerth
Human Resources Specialist
Coatesville VAMC
610-384-7711 x-4680
Theresa.Englerth@va.gov

Adult Psychiatrist

Saint Louis University, a Catholic, Jesuit institution dedicated to student learning, research, health care, and service is seeking applicants for a tenure-track and non-tenure track appointments in the newly formed Department of Neurology & Psychiatry beginning immediately. The position is offered at open rank, appointment level commensurate with academic accomplishment.

This clinically–oriented, full time position emphasizes inpatient psychiatry services and offers the opportunity to see adult patients on an outpatient basis. This position will also have the opportunity to work offsite performing psychiatry services to our community-based contract partners. Based at the Health Sciences Center campus, all faculty have ample opportunity to be involved in teaching medical students and psychiatric residents. Support for research is available. Applicant must be BC/BE. Generous benefits, including excellent retirement package and tuition remission at SLU.

Demonstrated academic record of excellence in patient care, teaching and research is desirable. Must be legally authorized to work in the USA. Position requires a background check for the successful candidate.

Interested candidates must submit a cover letter, application, and current curriculum vitae to http://jobs.slu.edu.

Please send Curriculum Vitae, representative publications, description of research plans, statement of teaching and philosophy, and letters of reference to:

Henry Kaminski, M.D.
Chair, Department of Neurology & Psychiatry
1438 South Grand Blvd.
St. Louis, MO 63104
hkaminsk@slu.edu

SAINT LOUIS UNIVERSITY

Department of Veterans Affairs

Director of Residency Training

Harvard South Shore Psychiatry Residency Training Program
Department of Psychiatry Harvard Medical School
&
The VA Boston Healthcare System

Harvard Medical School and the VA Boston Healthcare System are recruiting a Training Director for the Harvard South Shore Psychiatry Residency Training Program (HSS). The Harvard Department of Psychiatry at the VA Boston Healthcare System has undergone a major expansion of teaching, research, and academic clinical programming over the past two years. The current Training Director is assuming the duties of Departmental Chair for Academic Development, which will include ongoing support to HSS including teaching, supervision, and consultative support to the incoming Training Director.

HSS is a consortium program affiliated with Harvard Medical School and sponsored by the VA Boston Healthcare System. Residents rotate among three Boston VA campuses, other Harvard-affiliated training hospitals, and Massachusetts Department of Mental Health facilities. HSS receives stable funding for 32 PGY I-IV resident positions plus ample administrative support, not dependent on GME pass-through funding. Major foci of program excellence include biopsychosocial assessment and interviewing skills, academic development in research, teaching and leadership, evidence-based pharmacotherapy, and manual-guided psychotherapies. Comprehensive program description can be found at **www.harvardsouthshorepsychiatry.org.**

The competitive Training Director candidate will have strong academic credentials, residency administration experience at the site or program level, and demonstrated scholarly ability in a relevant field. The applicant must be board-certified in psychiatry with a minimum of 5 years of post-residency experience, and is expected to qualify for a Harvard Medical School appointment at the Assistant or Associate Professor level.

This position offers a highly competitive federal salary and benefits. VA Boston is an Affirmative Action / Equal Opportunity Employer, and women and individuals from health-underserved minority populations are encouraged to apply.

To apply, candidates should send a letter of interest, CV, and the names of three persons to contact for references to:

Drs. Mark Bauer & Gary Kaplan, Search Committee Co-Chairs
940 Belmont Street, Brockton, MA 02301; or email materials to:
Eugene.Francois@va.gov with a copy to vhabhsjobs@med.va.gov

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McLeod Health Behavioral Health Psychiatric Center is located in the beautiful southern town of Darlington, SC- a quick 45 minute drive to our state capital, Columbia, SC, and a 2 Hour drive to Charleston, SC and Charlotte, NC. We are looking for two BC/BE Psychiatrists with an innovative approach to medicine. Duties will include inpatient, outpatient, and Consult Services. Depending on the Physician's strengths, the Physician will perform any combination of these duties. Other features of the position include:

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McLeod is a leader in the healthcare industry. We are committed to developing patient-centered, evidence-based, physician-led, quality health care in a not-for-profit hospital system that values each individual patient.

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Atascadero State Hospital

BE/BC Psychiatrist

Atascadero State Hospital now pays board certified psychiatrists starting at $223,464 and advancing stepwise to $255,732. Atascadero is the nation's premier center for the treatment of forensically committed mentally ill patients. Our hospital is a teaching site affiliated with the University of California, accredited by JCAHO, and recipient of the prestigious Codman Award. All of our psychiatrists are board eligible and most are board certified. Many of our psychiatrists have forensic subspecialty boards.

We are located midway between San Francisco and Los Angeles on the scenic central California Coast, south of Big Sur. We offer a spectacularly beautiful environment in San Luis Obispo County with temperate climate, beaches, world class wineries, cultural activities, golfing, sailing, riding, clean air, and excellent schools through the University level.

Our benefit package is valued at an additional 30%, which includes retirement plans (including safety retirement), health plans, professional liability coverage, paid holidays, educational leave, and generous annual leave. On-call duty is compensated hour for hour over and above the base salary. Applicants must hold a current California license, or have pending application with the Medical Board of California.

For a prompt and confidential review, send CV to:

Jeanne Garcia, M.D.
P. O. Box 7001
Atascadero, CA 93423-7001
(805) 468-2005 or fax (805) 468-2138
or e-mail us: jeanne.garcia@ash.dmh.ca.gov

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Postdoctoral Research Fellowship Program

The San Francisco VAMC is recruiting for the two-year MIRECC Postdoctoral Research Fellowship Program in PTSD and Dementia affiliated with the University of California, San Francisco. This interdisciplinary program aims to train physicians with an interest in mental health research and residency training from a broad range of specialties (e.g., psychiatry, neurology, geriatrics, internal medicine) to become outstanding translational and clinical researchers in high priority areas of mental health. Individualized, mentored research and clinical training is combined with a state-of-the-art curriculum that emphasizes research methods, statistics, epidemiology, mental health systems, quality improvement methods, education, and service delivery. Nationally, over 20 fellowship sites are linked electronically for didactic, academic, and research efforts. Fellows devote 75% of their time to research and education activities and 25% to clinical training. In collaboration with their mentors, Fellows will develop and implement a research project, publish and present findings, participate in grant writing, and utilize the latest technology for educational activities and clinical service delivery. Fellows may conduct research in the areas of PTSD, dementia, or both. Fellowships will begin between July 1 and September 30, 2010.

Applicants must have completed ACGME accredited residency training, be board eligible or board certified, and have an active, unrestricted license to practice in California. International medical graduates must also have a current visa and an ECFMG certificate that is valid indefinitely. Applicants on a J-1 visa must have current ECFMG sponsorship as well. The VA funds Fellows' stipends in amounts based on previously completed ACGME accredited residency training. To apply for this fellowship, contact the Psychiatry Fellowship Program Director, Kristine Yaffe, M.D. at kristine.yaffe@ucsf.edu.

VA is an Equal Opportunity/Affirmative Action Employer. All qualified applicants are encouraged to apply, including minorities and women. VA seeks candidates whose experience, teaching, research, or community service has prepared them to contribute to our commitment to diversity and excellence.

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dose-dependent increase in the proportion of patients who developed sustained hypertension. **Abnormal Bleeding-** SSRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma-**Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania-**During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease-**Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1)*]. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation-** Dose-related elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [*see Adverse Reactions (6.1)*]. **Discontinuation of Treatment with Pristiq-** Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in major depressive disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [*see Dosage and Administration (2.4) and Adverse Reactions (6.1) in full prescribing information*]. **Renal Impairment-**In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [*see Clinical Pharmacology (12.6) in full prescribing information*]. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [*see Dosage and Administration (2.2) in full prescribing information*]. **Seizure-**Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hyponatremia-** Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6) in full prescribing information*]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine-** Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia-** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

ADVERSE REACTIONS: Clinical Studies Experience: The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥5% and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Adverse reactions reported as reasons for discontinuation of treatment- The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). Common adverse reactions in placebo-controlled MDD studies- Table 3 in full PI shows the incidence of common adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. Cardiac disorders: Palpitations, Tachycardia, Blood pressure increased; Gastrointestinal disorders: Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; General disorders and administration site conditions: Fatigue, Chills, Feeling jittery, Asthenia; Metabolism and nutrition disorders: Decreased appetite, weight decreased; Nervous system disorders: Dizziness, Somnolence, Headache, Tremor, Paraesthesia, Disturbance in attention; Psychiatric Disorders: Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; Renal and urinary disorders: Urinary hesitation; Respiratory, thoracic, and mediastinal disorders: Yawning; Skin and subcutaneous tissue disorders: Hyperhidrosis, Rash; Special Senses: Vision blurred; Mydriasis, Tinnitus, Dysgeusia; Vascular Disorders: Hot flush. Sexual function adverse reactions-Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). Men Only: Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; Women Only: Anorgasmia; Other adverse reactions observed in premarketing clinical studies: Other infrequent adverse reactions occurring at an incidence of <2% in MDD patients treated with Pristiq were: *Immune system disorders* – Hypersensitivity. *Investigations* – Weight increased, liver function test abnormal, blood prolactin increased. *Nervous system disorders* – Convulsion, syncope, extrapyramidal disorder. *Musculoskeletal and connective tissue disorders* – Musculoskeletal stiffness. *Psychiatric disorders* – Depersonalization, hypomania. *Respiratory, thoracic and mediastinal disorders* – Epistaxis. *Vascular disorders* – Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [*see Warnings and Precautions (5.7)*]. Discontinuation events-Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥5% include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information*]. Laboratory, ECG and vital sign changes observed in MDD clinical studies-The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. *Lipids*-Elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [*see Warnings and Precautions (5.8)*]. *Proteinuria*-Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. *ECG changes*-Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. *Vital sign changes*-Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. *Orthostatic hypotension*- In the short-term, placebo-controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease ≥30 mm Hg from supine to standing position) occurred more frequently in patients ≥65 years of age receiving Pristiq (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients <65 years of age receiving Pristiq (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218). **Adverse Reactions Identified During Post-Approval Use-** The following adverse reaction has been identified during post-approval use of Pristiq. Because post-approval 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: *Skin and subcutaneous tissue disorders* – Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*]. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*]. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)-** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-** There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects– Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects-Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-** Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [*see Adverse Reactions (6)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.12)*]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-** The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [*see Clinical Pharmacology (12.6)*].

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. 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), sinus and 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. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also 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. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

This brief summary is based on Pristiq Prescribing Information W10529C009, revised September 2009.

261838-01

December 2009

FOR MAJOR DEPRESSIVE DISORDER

Help your patients on a path forward with proven SNRI therapy

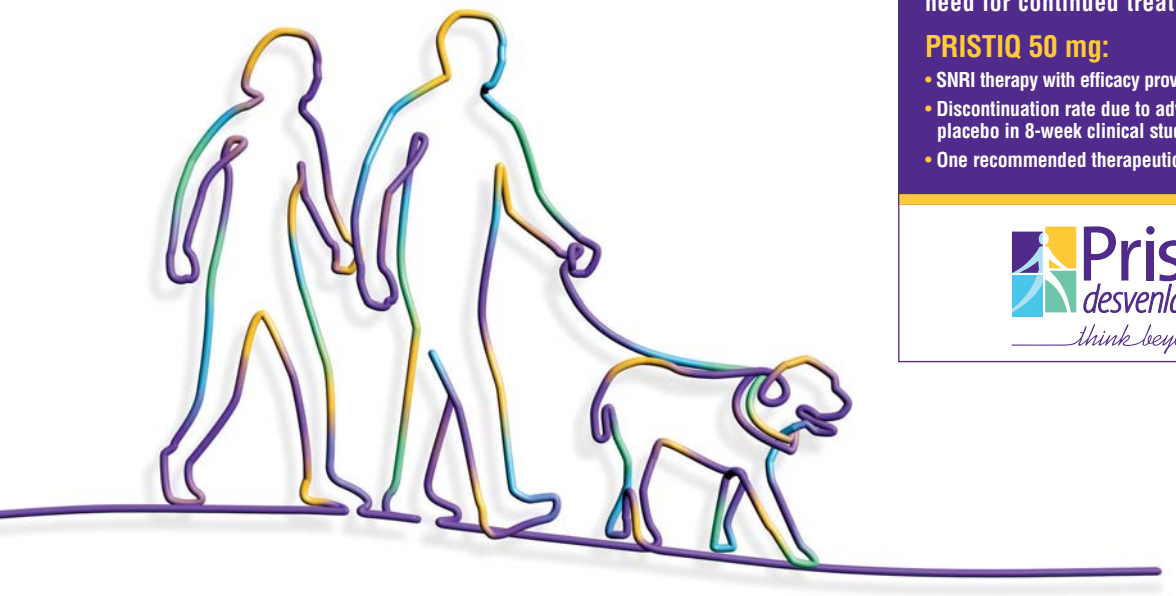
It's not just about starting your adult patients with MDD on therapy; it's about helping them toward their treatment goals. Patients should be periodically reassessed to determine the need for continued treatment.[1]

PRISTIQ 50 mg:

- **SNRI therapy with efficacy proven in 8-week clinical studies**
- **Discontinuation rate due to adverse events comparable to placebo in 8-week clinical studies**
- **One recommended therapeutic dose from the start[1]**

Pristiq® desvenlafaxine 50 mg

think beyond start™



Important Treatment Considerations for PRISTIQ

PRISTIQ is indicated for the treatment of major depressive disorder in adults.

WARNING: 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 PRISTIQ 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. PRISTIQ is not approved for use in pediatric patients.

Contraindications

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

Warnings and Precautions

- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.**
- Development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions have been reported with SNRIs and SSRIs alone, including PRISTIQ treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs that impair the metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. If concomitant use with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.
- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose rather than abrupt cessation is recommended whenever possible.
- The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.
- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence ≥5% and ≥2x the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

Reference: 1. Pristiq® (desvenlafaxine) Prescribing Information, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent pages.

For more information on PRISTIQ, please visit **www.PristiqHCP.com**.

Pristiq®
EXTENDED-RELEASE TABLETS

Pfizer