RELAPSE.

Nearly 80% of patients with schizophrenia experience at least 1 relapse within 5 years of diagnosis.[1]

RELAPSE.

Patients with schizophrenia miss nearly one third of their oral antipsychotic doses every year.[2]

RETHINK.

Rx

Is it time we took another look at treatment for schizophrenia?

While no medication can guarantee a relapse will not occur, using long-acting therapies earlier can help you recognize the opportunity for missed doses and intervene when it matters most.

Janssen® is dedicated to finding innovative ways of helping patients with schizophrenia get the medication they need.

References: 1. Robinson D, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or Schizoaffective Disorder. *Arch Gen Psychiatry*. 1999;56:241-247. **2.** Mahmoud RA, Engelhart LM, Janagap CC, Oster G, Ollendorf D. Risperidone versus conventional antipsychotics for schizophrenia and schizoaffective disorder: Symptoms, quality of life and resource use under customary clinical care. *Clin Drug Invest*. 2004;24:275-286.

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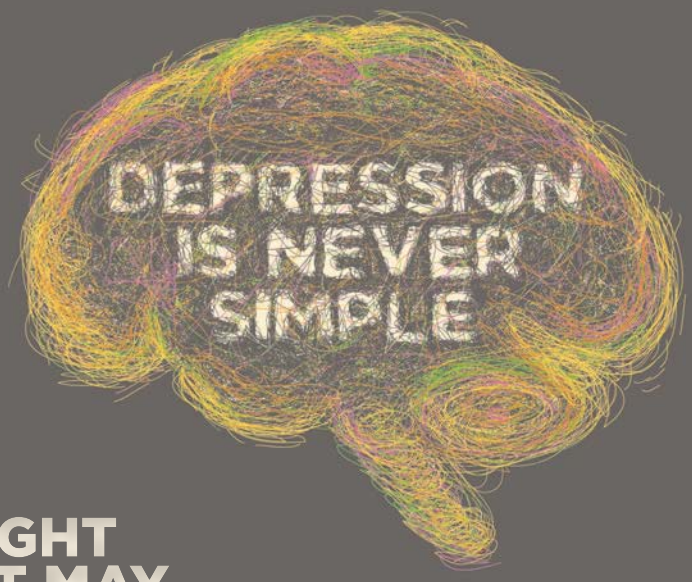
Venlafaxine Extended Release Tablets, a branded alternative for patients with Major Depressive Disorder (MDD)*



BUT THE RIGHT TREATMENT MAY MAKE A DIFFERENCE

Venlafaxine Extended Release Tablets: the first and only way to prescribe 225 mg of extended-release, once-daily venlafaxine HCl in a single tablet

- A single 225 mg Venlafaxine Extended Release Tablet vs a combination of venlafaxine HCl extended-release capsules may reduce pill burden for patients taking 225 mg for the treatment of MDD
- Patients with MDD should start treatment with 75 mg/day (in some patients, 37.5 mg/day for 4 to 7 days then increased to 75 mg/day); daily dose can be increased by 75 mg/day at intervals of ≥4 days (maximum 225 mg/day)

4 WORDS
1 TABLET
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Venlafaxine Extended Release Tablets (VENLAFAXINE HYDROCHLORIDE)
37.5 mg 75 mg 150 mg 225 mg

For more information, call 1.888.299.1053 or visit www.VERTablets.com

*Venlafaxine Extended Release Tablets are not indicated for the treatment of generalized anxiety disorder or panic disorder.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

WARNING: Suicidality and Antidepressants
See full Prescribing Information for complete boxed warning.

Increased risk of suicidal thinking and behavior has been reported in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Venlafaxine Extended Release Tablets are not approved for use in pediatric patients.

Venlafaxine Extended Release Tablets (venlafaxine hydrochloride) are indicated for the treatment of Major Depressive Disorder (MDD) and Social Anxiety Disorder (SAD). Efficacy of venlafaxine HCl was shown in both short-term trials and a longer-term trial in MDD, and in short-term SAD trials. Venlafaxine Extended Release Tablets are contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).

All patients should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose. Such monitoring should include daily observation by families and caregivers for emergence of agitation, irritability, unusual changes in behavior, or emergence of suicidality.

Venlafaxine Extended Release Tablets should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping Venlafaxine Extended Release Tablets before starting an MAOI.

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SSRIs and SNRIs (including Venlafaxine Extended Release Tablets) alone, but particularly if used concomitantly with serotonergic drugs (including triptans), MAO inhibitors, or with antipsychotics or other dopamine antagonists. Severe serotonin syndrome can resemble NMS, and patients should be monitored for symptoms of these disorders. If symptoms develop, Venlafaxine Extended Release Tablets and any serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately.

Treatment with venlafaxine hydrochloride is associated with sustained hypertension in some patients. Regular blood pressure monitoring is recommended. Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Dosing must be individualized according to the patient's hepatic and renal function status. Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms (generally self-limiting; serious symptoms possible). A gradual reduction in the dose rather than abrupt cessation is recommended.

After treatment with venlafaxine hydrochloride, insomnia and nervousness, activation of mania/hypomania, symptomatic hyponatremia, seizures, abnormal bleeding (most commonly ecchymosis), clinically relevant increases in serum cholesterol, interstitial lung disease and eosinophilic pneumonia have been reported. Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of seizures. Measurement of serum cholesterol should be considered during long-term treatment. Patients should be cautioned about the risk of bleeding associated with concomitant use of Venlafaxine Extended Release Tablets and NSAIDs, aspirin, or other drugs that affect coagulation.

Venlafaxine Extended Release Tablets should be used during pregnancy and nursing only if clearly needed due to the potential for serious adverse reactions.

Adverse reactions occurring in short-term studies of major depressive disorder* were abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, anorexia), CNS complaints (dizziness, somnolence, abnormal dreams) and sweating. Adverse reactions occurring in short-term studies of social anxiety disorder* were asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

*Occurring in at least 5% of patients receiving venlafaxine extended release capsules and at a rate at least twice that of placebo.

Please see brief summary of full Prescribing Information, including complete boxed warning, on adjacent pages.

TA1135-0409

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UPSTATE PHARMA, LLC

For:
Osmotica Pharmaceutical

Venlafaxine Extended Release Tablets (venlafaxine hydrochloride)

BRIEF SUMMARY. See package insert for full Prescribing Information. For further product information and current package insert, please visit www.VERTablets.com or call our medical communications department toll-free at 1-888-299-1053.

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 Venlafaxine Extended Release Tablets 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 or 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. Venlafaxine Extended Release Tablets are not approved for use in pediatric patients. [See *Warnings and Precautions and Patient Counseling Information* in the full Prescribing Information.]

INDICATIONS AND USAGE: Venlafaxine Extended Release Tablets (venlafaxine hydrochloride) are indicated for the treatment of major depressive disorder (MDD) and Social Anxiety Disorder (SAD), also known as Social Phobia, as defined by DSM-IV. Efficacy of venlafaxine in MDD was shown in both short-term trials and a longer-term trial. Efficacy in SAD was established in short-term trials. **CONTRAINDICATIONS:** Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) [see Warnings and Precautions, Potential for interaction with Monoamine Oxidase inhibitors]. **WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk:** Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration (2.5) and Warnings and Precautions (5.7) in the full prescribing information for a description of the risks of discontinuation of Venlafaxine Extended-Release Tablets*]. **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Venlafaxine Extended Release Tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Potential for Interaction With Monoamine Oxidase Inhibitors: Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine hydrochloride, or who recently discontinued venlafaxine hydrochloride prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Venlafaxine Extended Release Tablets should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine hydrochloride before starting an MAOI.** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that Venlafaxine Extended Release Tablets are not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions:** The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with SSRIs and SNRIs alone, including Venlafaxine Extended Release Tablets, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (including MAOIs), with other antipsychotics, or with other dopamine antagonists [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms including mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms *[see Drug Interactions (7.10)]*. Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. The concomitant use of Venlafaxine Extended Release Tablets with MAOIs is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.2)]*. If concomitant treatment of Venlafaxine Extended Release Tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Venlafaxine Extended Release Tablets with serotonin precursors (such as tryptophan supplements) is not recommended *[see Drug Interactions (7.10)]*. Treatment with Venlafaxine Extended Release Tablets and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the patient develops any symptoms of serotonin syndrome or NMS, and supportive symptomatic treatment should be initiated. **Sustained Hypertension:** Venlafaxine hydrochloride is associated with sustained dose-related increases in blood pressure (BP) in some patients. Sustained BP increases could have adverse consequences. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by BP increases. Preexisting hypertension should be controlled before Venlafaxine Extended Release Tablets therapy is initiated. It is recommended that patients receiving Venlafaxine Extended Release Tablets have regular monitoring of BP. For patients experiencing sustained increase in BP, either dose reduction or discontinuation should be considered. **Elevations in Systolic and Diastolic Blood Pressure (SBP, DBP):** In placebo-controlled premarketing studies, there were changes in mean BP. In most indications, a dose-related increase in SBP and DBP was evident. Across all trials, 1.4% of patients receiving extended-release venlaxafine hydrochloride experienced a ≥15 mm Hg increase in supine DBP with BP ≥105 mm Hg, compared to 0.9% of patients in the placebo groups. One percent of patients receiving venlaxafine hydrochloride experienced a ≥20 mm Hg increase in supine SBP with BP ≥180 mm Hg compared to 0.3% of patients in the placebo groups. **Mydriasis:** Mydriasis has been reported in association with venlafaxine hydrochloride; patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma should be monitored. **Discontinuation of Treatment with Venlafaxine Extended Release Tablets:** Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials and retrospective surveys of trials in MDD and SAD. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been associated with the appearance of new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. During marketing of venlafaxine hydrochloride extended-release capsules, other SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment. 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) in full prescribing information*]. **Insomnia and Nervousness:** Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with venlafaxine hydrochloride extended-release capsules than with placebo in pooled analyses of short-term MDD and other clinical studies, as shown in *Table 5 in the full prescribing information*. **Changes in Weight:** In some placebo-controlled trials in MDD, 4% of the patients treated with venlafaxine hydrochloride extended-release capsules and 1% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 6 months of treatment. The safety and efficacy of venlafaxine therapy in combination with weight loss agents have not been established. Co-administration of Venlafaxine Extended Release Tablets and weight loss agents is not recommended. Venlafaxine Extended Release Tablets are not indicated for weight loss alone or in combination with other products. **Changes in Height:** Pediatric Patients: In the six-month, open-label MDD study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (<12 years old) than for adolescents (≥12 years old). **Changes in Appetite:** Adult Patients: Treatment-emergent anorexia was more commonly reported for patients treated with venlafaxine hydrochloride extended-release capsules than for placebo-treated patients in the pool of short-term, double-blind, placebo-controlled MDD (8% vs 4%) and SAD (20% vs 2%) studies. Pediatric Patients: In placebo-controlled trials in MDD and another disorder, 10% of patients aged 6-17 treated with venlafaxine hydrochloride extended-release capsules for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia. **Activation of Mania/Hypomania:** Mania or hypomania occurred during MDD studies in 0.3% of patients treated with extended release venlafaxine compared with 0% of placebo patients. With immediate release venlafaxine, the rate was 0.5% compared with 0% of placebo patients. No reports of mania or hypomania were reported in trials with SAD. As with all drugs effective in the treatment of MDD, Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of mania. **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Venlafaxine Extended Release Tablets. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Use in Specific Populations (8.5) in full prescribing information*]. Discontinuation of Venlafaxine Extended Release Tablets should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. **Seizures:** In all premarketing venlafaxine hydrochloride MDD trials, seizures were reported in 0.3% of venlafaxine hydrochloride-treated patients. Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures. **Abnormal Bleeding:** SSRIs and SNRIs, including Venlafaxine Extended Release Tablets, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Venlafaxine Extended Release Tablets and other drugs that affect coagulation. **Serum Cholesterol Elevation:** Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine hydrochloride-treated patients and 0.0% of patients receiving placebo for at least 3 months in trials. Measurement of serum cholesterol levels should be considered during long-term treatment. **Interstitial Lung Disease and Eosinophilic Pneumonia:** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine therapy have been rarely reported. The possibility of these adverse reactions should be considered in venlafaxine-treated patients who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo prompt medical evaluation, and discontinuation of venlafaxine therapy should be considered. **Use in Patients with Heart Disease:** Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Venlafaxine Extended Release Tablets to patients with diseases or conditions that could affect hemodynamic responses. Venlafaxine 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 systematically excluded from many clinical studies during venlafaxine's premarketing testing. As increases in heart rate (mean increase of 4 beats per minute in MDD trials and 5 beats per minute in SAD trials) were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction). **ADVERSE REACTIONS: Clinical Studies Experience: Short-Term, Placebo-Controlled Trials:** ***Adverse Events Leading to Discontinuation of Treatment:*** Approximately 11% of the 357 patients who received venlafaxine hydrochloride extended-release capsules in MDD trials discontinued treatment due to an adverse reaction (vs 6% of the 285 placebo-treated patients). Adverse reactions that led to treatment discontinuation in at least 2% of drug-treated patients were nausea, dizziness and somnolence. Approximately 17% of the 277 patients in SAD trials who received venlafaxine hydrochloride extended-release capsules discontinued treatment due to an adverse reaction (vs 5% of the 274 placebo-treated patients). Adverse reactions that led to treatment discontinuation in at least 2% of drug-treated patients were nausea, insomnia, impotence, headache, dizziness and somnolence. **Adverse Events Occurring at an Incidence of 5% or More:** Major Depressive Disorder: Note in particular the following adverse reactions that occurred in at least 5% of the patients receiving venlafaxine hydrochloride extended-release capsules and at a rate at least twice that of the placebo group for all placebo-controlled trials for the MDD indication (see Table 6): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional reactions occurred in at least 5% of patients treated with venlafaxine hydrochloride extended-release capsules (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning. Social Anxiety Disorder: Note in particular the following adverse reactions that occurred in at least 5% of the patients receiving venlafaxine hydrochloride extended-release capsules and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the SAD indication (see Table 7): Asthenia, gastrointestinal complaints (anorexia, constipation, dry mouth, nausea), CNS complaints (dizziness, insomnia, libido decreased, nervousness, somnolence), abnormalities of sexual function (abnormal ejaculation, impotence, libido decreased, orgasmic dysfunction), yawn, sweating, and abnormal vision. **Adverse Events Occurring at an Incidence of 2% or More:** MDD and SAD trials included patients receiving venlafaxine hydrochloride extended-release capsules in doses ranging from 75 mg to 225 mg/day for up to 12 weeks. The prescriber should be aware that the following adverse reactions figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to adverse reaction incidence rate in the population studied. [See **TABLE 6** in full Prescribing Information.] **TABLE 6: Treatment Emergent Adverse Reaction Incidence in Short-Term Placebo-Controlled Clinical Trials with Venlafaxine Hydrochloride Extended-Release Capsules in Patients with Major Depressive Disorder.** This table reports adverse events that occurred in 2%

or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules (n=357) was greater than the incidence for the respective placebo-treated patients (n=285). For each adverse reaction, the incidence of reactions in the drug-treated patients is listed before the incidence in placebo-treated patients. **Body as a Whole:** Asthenia (8% and 7%). **Cardiovascular System:** Vasodilation (4% and 2%); Hypertension (4% and 1%). **Digestive System:** Nausea (31% and 7%); Constipation (8% and 5%); Anorexia (8% and 4%); Vomiting (4% and 2%); Flatulence (4% and 3%). **Metabolic/Nutritional:** Weight Loss (3% and 0%). **Nervous System:** Dizziness (20% and 9%); Somnolence (17% and 8%) Insomnia (17% and 11%); Dry mouth (12% and 6%); Nervousness (10% and 5%); Abnormal Dreams (7% and 2%); Tremor (5% and 2%); Depression (3% and <1%); Paresthesia (3% and 1%); Libido Decreased (3% and <1%); Agitation (3% and 1%). **Respiratory System:** Pharyngitis (7% and 6%); Yawn (3% and 0%). **Skin:** Sweating (14% and 3%). **Special Senses:** Abnormal vision (4% and <1%). **Urogenital System:** Abnormal ejaculation (16% and <1%); Impotence (4% and <1%); Female anorgasmia (3% and <1%). [See **TABLE 7** in full Prescribing Information]. **TABLE 7: Treatment Emergent Adverse Reaction Incidence in Short-Term Placebo-Controlled Clinical Trials with Venlafaxine Hydrochloride Extended-Release Capsules in Patients with Social Anxiety Disorder.** This table reports adverse events that occurred in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules (n=277) was greater than the incidence for the respective placebo-treated patients (n=274). For each adverse reaction, the incidence of reactions in the drug-treated patients is listed before the incidence in placebo-treated patients. **Body as a Whole: Headache** (34% and 33%); Asthenia (17% and 8%); Flu Syndrome (6% and 5%); Accidental Injury (5% and 3%); Abdominal Pain (4% and 3%). **Cardiovascular System:** Hypertension (5% and 4%); Vasodilation (3% and 1%); Palpitation (3% and 1%). **Digestive System:** Nausea (29% and 9%); Anorexia (20% and 1%); Constipation (8% and 4%); Diarrhea (6% and 5%); Vomiting (3% and 2%); Eructation (2% and 0%). **Metabolic/Nutritional:** Weight Loss (4% and 0%). **Nervous System:** Insomnia (23% and 7%); Dry mouth (17% and 4%); Dizziness (16% and 8%); Somnolence (16% and 8%); Nervousness (11% and 3%); Libido Decreased (9% and <1%); Anxiety (5% and 3%); Agitation (4% and 1%); Tremor (4% and <1%); Abnormal Dreams (4% and <1%); Paresthesia (3% and <1%); Twitching (2% and 0%). **Respiratory System:** Yawn (5% and <1%); Sinusitis (2% and 1%) **Skin:** Sweating (13% and 2%). **Special Senses:** Abnormal vision (6% and 3%). **Urogenital System:** Abnormal ejaculation (16% and 1%); Impotence (10% and 1%); Female Orgasmic Dysfunction (8% and 0%). **Vital Sign Changes:** Venlafaxine hydrochloride was associated with a mean increase in pulse rate of 4 beats/min in SAD trials. In premarketing trials, the mean change from baseline heart rate for patients treated with extended-release venlafaxine hydrochloride in MDD and SAD trials was 4 beats-per-minute and 5 beats-per-minute, respectively. In a flexible-dose study with doses ranging from 200 mg to 375 mg/day, patients receiving extended-release venlafaxine hydrochloride had a mean increase in heart rate of 8.5 beats-per-minute [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information for effects on heart rate and blood pressure]. **Laboratory Changes:** Clinically relevant increases in serum cholesterol were noted in venlafaxine hydrochloride clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **ECG Changes:** In a flexible-dose MDD study with doses of venlafaxine hydrochloride immediate-release tablets in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo. [*See Warnings and Precautions (5.17)*]. **POSTMARKETING EXPERIENCE:** Voluntary reports of other adverse reactions temporally associated with the use of venlafaxine have been received since market introduction. Because these reactions have been reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports include the following reactions: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, impaired coordination and balance, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrolysis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic reactions (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly). **DRUG INTERACTIONS: Alcohol:** The effect of alcohol on plasma levels of Venlafaxine Extended Release Tablets is not known. **Cimetidine:** Use caution when administering venlafaxine hydrochloride with cimetidine to patients with preexisting hypertension or hepatic dysfunction, and the elderly. **Diazepam:** A single dose of diazepam did not appear to affect the PK of either venlafaxine hydrochloride (150 mg/day) or its major active metabolite, 0-desmethylvenlafaxine (ODV). Venlafaxine hydrochloride did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. **Haloperidol:** Venlafaxine hydrochloride (150 mg/day) decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination $t_{1/2}$ was unchanged. **Lithium:** A single dose of lithium (600 mg) did not appear to affect the PK of either venlafaxine hydrochloride (150 mg/day) or ODV. Venlafaxine hydrochloride had no effect on the PK of lithium. **Drugs Highly Bound to Plasma Proteins:** Venlafaxine hydrochloride is not highly bound to plasma proteins; coadministration of Venlafaxine Extended Release Tablets and a highly protein-bound drug should not cause increased free concentrations of the other drug. **Drugs That Inhibit Cytochrome P450 Isoenzymes:** CYP2D6 and CYP3A4 Inhibitors: Venlafaxine hydrochloride is metabolized to ODV by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine hydrochloride and decrease those of ODV. Because venlafaxine hydrochloride and ODV are approximately equiactive and equipotent, no dosage adjustment is required when venlafaxine hydrochloride is coadministered with a CYP2D6 inhibitor. Pharmacokinetic studies with ketoconazole in both poor and extensive metabolizers of CYP2D6 resulted in higher plasma concentrations and AUCs of both venlafaxine hydrochloride and ODV in most subjects following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors and venlafaxine hydrochloride may increase levels of both venlafaxine hydrochloride and ODV. Use caution if therapy includes venlafaxine hydrochloride and any CYP3A4 inhibitor. **Drugs Metabolized by Cytochrome P450 Isoenzymes:** Venlafaxine hydrochloride is a relatively weak inhibitor of CYP2D6 in vitro. Imipramine: Venlafaxine hydrochloride did not affect the PK of imipramine or 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine hydrochloride. The 2-OH-desipramine AUCs increased by 2.5 to 4.5 fold (with venlafaxine hydrochloride doses of up to 75 mg q 12h). The clinical significance of elevated 2-OH-desipramine is unknown. Imipramine did not affect the PK of venlafaxine hydrochloride and ODV. Metoprolol: Venlafaxine hydrochloride (50 mg q 8h for 5 days) appeared to reduce the blood-lowering effect of metoprolol (100 mg q 24h for 5 days) in one study. Caution should be exercised when these drugs are given together. Risperidone: Venlafaxine hydrochloride (150 mg/day) slightly inhibited metabolism of a single 1-mg dose of risperidone, resulting in an about 32% increase in risperidone AUC. Venlafaxine hydrochloride coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus its metabolite 9-hydroxyrisperidone). CYP3A4: Venlafaxine hydrochloride did not inhibit CYP3A4 in vitro or in vivo. Indinavir: In healthy volunteers, venlafaxine hydrochloride (150 mg/day) resulted in a 28% decrease in the AUC of a single dose of a single 800-mg dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine hydrochloride and ODV. CYP1A2: Venlafaxine hydrochloride did not inhibit CYP1A2 in vitro or in vivo. CYP2C9: Venlafaxine hydrochloride did not inhibit CYP2C9 in vitro. In vivo, venlafaxine hydrochloride 75 mg (75 mg q 12h) did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-OH-tolbutamide. CYP2C19: Venlafaxine hydrochloride did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see Diazepam above). **MAOIs:** [See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS in full Prescribing Information.] **Other CNS-Active Drugs:** Caution is advised if there is concomitant use of venlafaxine and other CNS-active drugs. Serotonergic Drugs and Triptans: Based on the mechanism of action of Venlafaxine Extended Release Tablets and the potential for serotonin syndrome, caution is advised when Venlafaxine Extended Release Tablets are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's Wort. If concomitant treatment of Venlafaxine Extended Release Tablets with these drugs is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of Venlafaxine Extended Release Tablets with tryptophan supplements is not recommended [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant use of Venlafaxine Hydrochloride Extended Release tablets with a triptan is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. **Drugs That Interfere With Hemostasis:** Interference with serotonin reuptake may affect platelet function and result in bleeding. Concurrent use of NSAIDs or aspirin may increase this risk. Increases in prothrombin time (PT), partial thromboplastin time (PTT), or INR have been reported when venlafaxine hydrochloride was given to patients on warfarin therapy. Patients on warfarin should be carefully monitored when Venlafaxine Extended Release Tablets are begun or discontinued. **Electroconvulsive Therapy:** There is no clinical data establishing the benefit of electroconvulsive therapy combined with Venlafaxine Hydrochloride Extended Release Tablets. **Postmarketing Spontaneous Drug Interaction Reports:** There have been reports of elevated clozapine levels temporally associated with adverse reactions, including seizures, following the addition of venlaxafine. There have been reports of increases in PT, PTT, or INR when venlafaxine was given to patients also receiving warfarin. **USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C:** There are no adequate and well-controlled studies of venlafaxine in pregnant women. Venlafaxine Extended Release Tablets should be used during pregnancy only if clearly needed. **Non-Teratogenic Effects:** Neonates exposed to venlafaxine hydrochloride late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, unstable temperature, feeding difficulty, vomiting, hypoglycemia, hypo- and hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a toxic effect of SSRIs or SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Venlafaxine Extended Release Tablets during the third trimester, carefully consider the potential risks and benefits of treatment. **Labor and Delivery:** The effect of venlafaxine hydrochloride on labor and delivery in humans is unknown. **Nursing Mothers:** Venlafaxine hydrochloride and ODV, its active metabolite, are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Venlafaxine Extended Release Tablets, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established [see **BOXED WARNING** and **Warnings and Precautions: Clinical Worsening and Suicide Risk**]. Anyone considering using Venlafaxine Extended Release Tablets in a child or adolescent must balance the potential risks with the clinical need. While no studies have adequately assessed the impact of venlafaxine hydrochloride on growth, development, and maturation of children and adolescents, studies suggest it may adversely affect weight and height [see **WARNINGS AND PRECAUTIONS: General: Changes in Height** and **Changes in Weight** in full Prescribing Information]. Should the decision be made to treat a pediatric patient with Venlafaxine Extended Release Tablets, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of venlafaxine hydrochloride in pediatric patients has not been assessed for treatment beyond 6 months. In patients aged 6-17, clinically relevant blood pressure and cholesterol increases were similar to those observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use:** While no overall differences in effectiveness or safety were observed between geriatric and younger patients, greater sensitivity of some older individuals cannot be ruled out. The elderly may be at greater risk for significant hyponatremia. No dose adjustment is recommended based on age alone. **Patients With Hepatic Impairment:** Decreased clearance was noted in patients with cirrhosis. A lower dose may be necessary in these patients; extra caution should be used in these patients. **Patients With Renal Impairment:** In patients with GFR = 10 to 70 mL/min, clearance of venlafaxine hydrochloride and its metabolites were decreased. It is recommended that total daily dose of Venlafaxine Extended Release Tablets be reduced by 25% to 50% in these patients. Individualization of dosage may be desirable in some patients. In hemodialysis patients, it is recommended that total daily dose be reduced by 50%. Venlafaxine Extended Release Tablets should be used with caution in such patients. **DRUG ABUSE AND DEPENDENCE:** Venlafaxine Extended Release Tablets are not a controlled substance. Carefully evaluate patients for history of drug abuse and observe such patients closely for signs of misuse or abuse of venlafaxine hydrochloride. Discontinuation effects have been reported in patients receiving venlafaxine hydrochloride [see **WARNINGS AND PRECAUTIONS;** and **DOSAGE AND ADMINISTRATION** in full Prescribing Information]. **OVERDOSAGE:** In postmarketing experience, overdosage has occurred predominately in combination with alcohol and/or other drugs. The most commonly reported reactions include tachycardia, changes in consciousness, mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine hydrochloride are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on treatment. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*® (PDR®). **DOSAGE AND ADMINISTRATION:** Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Venlafaxine Extended Release Tablets. At least 7 days should be allowed after stopping Venlafaxine Extended Release Tablets before starting an MAOI** [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information].

To report SUSPECTED ADVERSE REACTIONS, contact Upstate Pharma, LLC Pharmaceutical Corp. at 1-888-299-1053 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

This brief summary is based on Venlafaxine Extended Release Tablets Prescribing Information, January 2009. Osmotica Pharmaceutical Corp.

Marketed by Upstate Pharma, LLC, Rochester, NY 14623 for Osmotica Pharmaceutical, Wilmington, NC 28405.

 2E-01/2009

SEE ME FOR WHO I CAN BE

GREG, 35*
Diner Worker
Diagnosis: Schizophrenia

*Not an actual patient.

Do you see your patients' full potential?

GEODON is indicated for the treatment of schizophrenia.

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) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

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

CONTRAINDICATIONS — *QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS — *Increased Mortality in Elderly Patients with Dementia-Related Psychosis:*** **Elderly patients with dementia-related psychosis treated with 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:*** 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/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS — *Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash, and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***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, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole — headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular — postural hypotension, hypertension, bradycardia, vasodilation. Digestive — nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous — dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory — rhinitis. Skin and Appendages — furunculosis, sweating. Urogenital — dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE — *Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE** — In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

Revised August 2008

NOW APPROVED FOR THE MAINTENANCE TREATMENT OF BIPOLAR I DISORDER EITHER AS MONOTHERAPY OR AS ADJUNCTIVE THERAPY TO LITHIUM OR VALPROATE

As monotherapy or as adjunctive therapy when oral medications* may not be enough to help maintain stability†

WHY WAIT TO PRESCRIBE RISPERDAL® CONSTA®?

- RISPERDAL® CONSTA® significantly delayed time to relapse when used alone‡ or as adjunctive therapy§ to lithium or valproate‖[1]
- Proven efficacy with guaranteed medication coverage when administered every 2 weeks[1]
- Flexibility in administration sites, with deltoid and gluteal options to match your patient's preference¶[1]

***Lithium or valproate.**

†Patients judged to be stable for at least 4 weeks (in adjunctive therapy trial) or at least 8 weeks (in monotherapy trial) were randomized in the double-blind phase.

‡Up to 104 weeks in a multicenter, randomized, double-blind, placebo-controlled study in 303 patients with Bipolar I Disorder.

§52-week, multicenter, randomized, double-blind, placebo-controlled study in 124 patients with Bipolar I Disorder.

‖Adjunctive treatment consisted of mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. All other antipsychotics were discontinued after the first 3 weeks of the initial injection.

¶Deltoid administration is only appropriate for patients with adequate muscle mass.

Reference: 1. RISPERDAL® CONSTA® Prescribing Information. Ortho-McNeil-Janssen Pharmaceuticals, Inc, Titusville, NJ.

Risperdal® CONSTA®
risperidone Long-Acting Injection

RISPERDAL® CONSTA® (risperidone) long-acting injection is indicated for the maintenance treatment of Bipolar I Disorder, either as monotherapy or as adjunctive therapy to lithium or valproate.

IMPORTANT SAFETY INFORMATION FOR RISPERDAL® CONSTA®

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. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Events (CAEs): CAEs, including fatalities, 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. RISPERDAL® CONSTA® 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 RISPERDAL® CONSTA®. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

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

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

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, RISPERDAL® CONSTA® elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Orthostatic Hypotension: RISPERDAL® CONSTA® 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. RISPERDAL® CONSTA® should be used with caution in patients with known cardiovascular disease, and conditions that would predispose patients to hypotension.

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including risperidone. Patients with a pre-existing low white blood cell count (WBC) or a history of 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 RISPERDAL® CONSTA® should be considered.

Potential for Cognitive and Motor Impairment: RISPERDAL® CONSTA® 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 RISPERDAL® CONSTA® does not affect them adversely.

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

Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia.

Priapism has been reported. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported.

Administration: RISPERDAL® CONSTA® should be injected into the deltoid or gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel.

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

Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies has been reported. Manifestations and features are consistent with NMS.

Use RISPERDAL® CONSTA® with caution in patients with conditions and medical conditions that could affect metabolism or hemodynamic responses (e.g. recent myocardial infarction or unstable cardiac disease).

Maintenance Treatment: Patients should be periodically reassessed to determine the need for continued treatment.

Commonly Observed Adverse Reactions for RISPERDAL® CONSTA®: The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increased (5% in monotherapy trial) and tremor and Parkinsonism (≥10% in adjunctive therapy trial).

Please see accompanying brief summary of full Prescribing Information for RISPERDAL® CONSTA®.

Visit our Web site at www.risperdalconsta.com.

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

RISPERDAL® CONSTA®
(risperidone) LONG-ACTING INJECTION

Brief Summary

BEFORE PRESCRIBING RISPERDAL® CONSTA®, 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. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions]*

RISPERDAL® CONSTA® (risperidone) is indicated for the treatment of schizophrenia *[see Clinical Studies (14.1) in full PI]*.

RISPERDAL® CONSTA® is indicated as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder *[see Clinical Studies (14.2, 14.3) in full PI]*.

CONTRAINDICATIONS: RISPERDAL® CONSTA® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

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. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral risperidone compared to patients treated with placebo. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis *[See also Boxed Warning and Warnings and Precautions]* **Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. 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 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:** 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 rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to 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 are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, RISPERDAL® CONSTA® 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: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. 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 RISPERDAL® CONSTA®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® CONSTA® 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 atypical antipsychotics including RISPERDAL®. 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. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. 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:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin 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 contemplated in a patient with previously detected breast cancer. An increase in 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]*. 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. **Orthostatic Hypotension:** RISPERDAL® CONSTA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period with oral risperidone, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with RISPERDAL® CONSTA® in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). RISPERDAL® CONSTA® should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL® and antihypertensive medication. **Leukopenia, Neutropenia, and Agranulocytosis:** *Class Effect:* In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis (including fatal cases) has also been reported. Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and a history of drug induced leukopenia/neutropenia. Patients with a preexisting low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® CONSTA® should be considered at the first sign of a decline in WBC in the absence of other causative factors. Patients with 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 RISPERDAL® CONSTA® and have their WBC followed until recovery. **Potential for Cognitive and Motor Impairment:** Somnolence was reported by 5% of patients treated with RISPERDAL® CONSTA® in multiple-dose trials. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL® CONSTA® does not affect them adversely. **Seizures:** During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL® CONSTA®. Therefore, RISPERDAL® CONSTA® should be used cautiously in patients with a history of seizures. **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. RISPERDAL® CONSTA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. *[See also Boxed Warning and Warnings and Precautions]* **Priapism:** Priapism has been reported during postmarketing surveillance *[see Adverse Reactions (6.9) in full PI]*. Severe priapism may require surgical intervention. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® or RISPERDAL® CONSTA® use. Caution is advised when prescribing RISPERDAL® CONSTA® for patients who will be exposed to temperature extremes. **Administration:** RISPERDAL® CONSTA® should be injected into the deltoid or gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel. *[See Dosage and Administration (2) and Adverse Reactions (6.8) in full PI]* **Antiemetic Effect:** Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Suicide:** There is an increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. RISPERDAL® CONSTA® is to be administered by a health care professional *[see Dosage and Administration (2) in full PI];* therefore, suicide due to an overdose is unlikely. **Use in Patients with Concomitant Illness:** Clinical experience with RISPERDAL® CONSTA® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL® CONSTA®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. Caution is advisable when using RISPERDAL® CONSTA® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® CONSTA® 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 clinical studies during the product's premarket testing. Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2) treated with oral RISPERDAL®; an increase in the free fraction of risperidone is also seen in patients with severe hepatic impairment. Patients with renal or hepatic impairment should be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL® CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with renal or hepatic impairment *[see Dosage and Administration]*. **Osteodystrophy and Tumors in Animals:** RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks. RISPERDAL® CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL® CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. (Cellular proliferation was not measured at the low dose or in females in either study.) The effect dose for osteodystrophy and the tumor findings is 8 times the IM maximum recommended human dose (MRHD) (50 mg) on a mg/m^2 basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the IM MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the IM MRHD on a mg/m^2 basis). Plasma exposure (AUC) at the no-effect dose was one third the expected plasma exposure (AUC) at the IM MRHD. **Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone.** Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study. The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail in Section 13.1 (Carcinogenicity, Mutagenesis, Impairment of Fertility). The relevance of these findings to human risk is unknown. **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 • Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis • euroleptic malignant syndrome • Tardive dyskinesia • Hyperglycemia and diabetes mellitus • Hyperprolactinemia • Orthostatic hypotension • Leukopenia/Neutropenia and Agranulocytosis • Potential for cognitive and motor impairment • Seizures • Dysphagia • Priapism • Thrombotic Thrombocytopenic Purpura (TTP) • Disruption of body temperature regulation • Avoidance of inadvertent injection into a blood vessel • Antiemetic effect • Suicide • Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies • Diseases or conditions that could affect metabolism or hemodynamic responses • Osteodystrophy and tumors in animals The most common adverse reactions in clinical trials in patients with schizophrenia (≥ 5%) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions in the double-blind, placebo-controlled periods of the bipolar disorder trials were weight increased (5% in the monotherapy trial) and tremor and parkinsonism (≥ 10% in the adjunctive treatment trial). The most common adverse reactions that were associated with discontinuation from the 12-week double-blind, placebo-controlled trial in patients with schizophrenia (causing discontinuation in ≥1% of patients) were agitation, depression, anxiety, and akathisia. Adverse reactions that were associated with discontinuation from the double-blind, placebo-controlled periods of the bipolar disorder trials were hyperglycemia (one patient in the monotherapy trial) and hypokinesia and tardive dyskinesia (one patient each in the adjunctive treatment trial). The data described in this section are derived from a clinical trial database consisting of 2392 patients exposed to one or more doses of RISPERDAL® CONSTA® for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received RISPERDAL® CONSTA® while participating in a 12-week double-blind, placebo-controlled trial. Two hundred two (202) of the 332 were schizophrenia patients who received 25 mg or 50 mg RISPERDAL® CONSTA®. The conditions and duration of treatment with RISPERDAL® CONSTA® in the other clinical trials varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs. In addition to the studies in patients with schizophrenia, safety data are presented from a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder. The subjects in this multi-center, double-blind, placebo-controlled study were adult patients who met DSM-IV criteria for Bipolar Disorder Type I and who were stable on risperidone (oral or long-acting injection), were stable on other antipsychotics or mood stabilizers, or were experiencing an acute episode. After a 3-week period of treatment with open-label oral risperidone (n=440), subjects who demonstrated an initial response to oral risperidone in this period and those who were stable on risperidone (oral or long-acting injection) at study entry entered into a 26-week stabilization period of open-label RISPERDAL® CONSTA® (n=501). Subjects who demonstrated a maintained response during this period were then randomized into a 24-month double-blind, placebo-controlled period in which they received RISPERDAL® CONSTA® (n=154) or placebo (n=149) as monotherapy. Subjects who relapsed or who completed the double-blind period could choose to enter an 8-week open-label RISPERDAL®CONSTA® extension period (n=160). Safety data are also presented from a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar disorder. The subjects in this multi-center, double-blind, placebo-controlled study were adult patients who met DSM-IV criteria for Bipolar Disorder Type I or Type II and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12 months, including at least 2 episodes in the 6 months prior to the start of the study. At the start of this study, all patients (n = 275) entered into a 16-week open-label treatment phase in which they received RISPERDAL® CONSTA® in addition to continuing their treatment as usual, which consisted of various mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. Patients who reached remission at the end of this 16-week open-label treatment phase (n = 139) were then randomized into a 52-week double-blind, placebo-controlled phase in which they received RISPERDAL® CONSTA® (n = 72) or placebo (n = 67) as adjunctive treatment in addition to continuing their treatment as usual. Patients who did not reach remission at the end of the 16-week open-label treatment phase could choose to continue to receive RISPERDAL®CONSTA® as adjunctive therapy in an open-label manner, in addition to continuing their treatment as usual, for up to an additional 36 weeks as clinically indicated for a total period of up to 52 weeks; these patients (n = 70) were also included in the evaluation of safety. 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 RISPERDAL® CONSTA® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for RISPERDAL® CONSTA® 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. The majority of all adverse reactions were mild to moderate in severity. **Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia:** Table 1 lists the adverse reactions reported in 2% or more of RISPERDAL® CONSTA®-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial. **Table 1.** Adverse Reactions in ≥ 2% of RISPERDAL® CONSTA®-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial, **System/Organ Class, Percentage of Patients Reporting Event RISPERDAL® CONSTA® 25 mg (N=99)** first, **50 mg (N=103)** second, **Placebo (N=98)** third, Adverse Reaction, **Eye disorders**: Vision blurred 2, 3, 0; **Gastrointestinal disorders:** Constipation 5, 7, 1; Dry mouth 0, 7, 1; Dyspepsia 6, 6, 0; Nausea 3, 4, 5; Toothache 1, 3, 0; Salivary hypersecretion 4, 1, 0; **General disorders and administration site conditions:** Fatigue* 3, 9, 0; Edema peripheral 2, 3, 1; Pain 4, 1, 0; Pyrexia 2, 1, 0; **Infections and infestations:** Upper respiratory tract infection 2, 0, 1; **Investigations**: Weight increased 5, 4, 2; Weight decreased 4, 1, 1; **Musculoskeletal and connective tissue disorders:** Pain in extremity 6, 2, 1; **Nervous system disorders:** Headache 15, 21, 12; Parkinsonism* 8, 15, 9; Dizziness 7, 11, 6; Akathisia* 4, 11, 6; Sedation* 5, 6, 3; Tremor 0, 3, 0; Syncope 2, 1, 0; Hypoesthesia 2, 0, 0; **Respiratory, thoracic and mediastinal disorders:** Cough 4, 2, 3; Sinus congestion 2, 0, 0; **Skin and subcutaneous tissue disorders:** Acne 2, 2, 0; Dry skin 2, 0, 0. * Fatigue includes fatigue and asthenia. Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restlessness. Sedation includes sedation and somnolence. **Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Disorder:** Table 2 lists the treatment-emergent adverse reactions reported in 2% or more of RISPERDAL® CONSTA®-treated patients in the 24-month double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with Bipolar I Disorder. **Table 2.** Adverse Reactions in ≥2% of Patients with Bipolar I Disorder Treated with RISPERDAL® CONSTA® as Monotherapy in a 24-Month Double-Blind, Placebo-Controlled Trial, **System/Organ Class, Percentage of Patients Reporting Event, RISPERDAL® CONSTA® (N=154)** first,

Placebo (N=149) second, Adverse Reaction, **Investigations:** Weight increased 5, 1; **Nervous system disorders:** Dizziness 3, 1; **Vascular disorders:** Hypertension 3, 1. Table 3 lists the treatment-emergent adverse reactions reported in 4% or more of patients in the 52-week double-blind, placebo-controlled treatment phase of a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar disorder. **Table 3.** Adverse Reactions in ≥ 4% of Patients with Bipolar Disorder Treated with RISPERDAL® CONSTA® as Adjunctive Therapy in a 52-Week Double-Blind, Placebo-Controlled Trial, **System/Organ Class, Percentage of Patients Reporting Event, RISPERDAL® CONSTA® + Treatment as Usual[a] (N=72)** first, **Placebo + Treatment as Usual[a] (N=67)** second, Adverse Reaction, **General disorders and administration site conditions:** Gait abnormal 4, 0; **Infections and infestations:** Upper respiratory tract infection 6, 3; **Investigations:** Weight increased 7, 1; **Metabolism and nutrition disorders:** Decreased appetite 6, 1; Increased appetite 4, 0; **Musculoskeletal and connective tissue disorders:** Arthralgia 4, 3; **Nervous system disorders:** Tremor 24, 16; Parkinsonism[b] 15, 6; Dyskinesia[b] 6, 3; Sedation[c] 7, 1; Disturbance in attention 4, 0; **Reproductive system and breast disorders:** Amenorrhea 4, 1; **Respiratory, thoracic and mediastinal disorders:** Cough 4, 1. [a] Patients received double-blind RISPERDAL® CONSTA® or placebo in addition to continuing their treatment as usual, which included mood stabilizers, antidepressants, and/or anxiolytics. [b] Parkinsonism includes muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia. Dyskinesia includes muscle twitching and dyskinesia. [c] Sedation includes sedation and somnolence. **Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL® CONSTA®:** The following additional adverse reactions occurred in < 2% of the RISPERDAL® CONSTA®-treated patients in the above schizophrenia double-blind, placebo-controlled trial dataset, in < 2% of the RISPERDAL® CONSTA®-treated patients in the above double-blind, placebo-controlled period of the monotherapy bipolar disorder trial dataset, or in < 4% of the RISPERDAL® CONSTA®-treated patients in the above double-blind, placebo-controlled period of the adjunctive treatment bipolar disorder trial dataset. The following also includes additional adverse reactions reported at any frequency in RISPERDAL® CONSTA®-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia, and in the open-label phases of the bipolar disorder studies. **Blood and lymphatic system disorders:** anemia, neutropenia **Cardiac disorders:** tachycardia, atrioventricular block first degree, palpitations, sinus bradycardia, bundle branch block left, bradycardia, sinus tachycardia, bundle branch block right **Ear and labyrinth disorders:** ear pain, vertigo **Endocrine disorders:** hyperprolactinemia **Eye disorders:** conjunctivitis, visual acuity reduced **Gastrointestinal disorders:** diarrhea, vomiting, abdominal pain, stomach discomfort, gastritis **General disorders and administration site conditions:** injection site pain, chest discomfort, chest pain, influenza like illness, sluggishness, malaise, induration, injection site induration, injection site swelling, injection site reaction, face edema **Immune system disorders:** hypersensitivity **Infections and infestations:** nasopharyngitis, influenza, bronchitis, urinary tract infection, rhinitis, ear infection, pneumonia, lower respiratory tract infection, pharyngitis, sinusitis, viral infection, infection, localized infection, cystitis, gastroenteritis, subcutaneous abscess **Injury and poisoning:** fall, procedural pain **Investigations:** blood prolactin increased, alanine aminotransferase increased, electrocardiogram abnormal, gamma-glutamyl transferase increased, blood glucose increased, hepatic enzyme increased, aspartate aminotransferase increased, electrocardiogram QT prolonged **Metabolism and nutritional disorders:** anorexia, hyperglycemia **Musculoskeletal, connective tissue and bone disorders:** posture abnormal, myalgia, back pain, buttock pain, muscular weakness, neck pain, musculoskeletal chest pain **Nervous system disorders:** coordination abnormal, dystonia, tardive dyskinesia, drooling, paresthesia, dizziness postural, convulsion, akinesia, hypokinesia, dysarthria **Psychiatric disorders:** insomnia, agitation, anxiety, sleep disorder, depression, libido decreased, nervousness **Renal and urinary disorders:** urinary incontinence **Reproductive system and breast disorders:** oligomenorrhea, erectile dysfunction, galactorrhea, sexual dysfunction, ejaculation disorder, gynecomastia, breast discomfort, menstruation irregular, menstruation delayed, menstrual disorder **Respiratory, thoracic and mediastinal disorders:** nasal congestion, pharyngolaryngeal pain, dyspnea, rhinorrhea **Skin and subcutaneous tissue disorders:** rash, eczema, pruritus **Vascular disorders:** hypotension, orthostatic hypotension **Discontinuations Due to Adverse Reactions:** Schizophrenia Approximately 11% (22/202) of RISPERDAL® CONSTA®-treated patients in the 12-week double-blind, placebo-controlled schizophrenia trial discontinued treatment due to an adverse event, compared with 13% (13/98) who received placebo. The adverse reactions associated with discontinuation in two or more RISPERDAL® CONSTA®-treated patients were: agitation (3%), depression (2%), anxiety (1%), and akathisia (1%). Bipolar Disorder In the 24-month double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 1 (0.6%) of 154 RISPERDAL® CONSTA®-treated patients discontinued due to an adverse reaction (hyperglycemia). In the 52-week double-blind phase of the placebo-controlled trial in which RISPERDAL® CONSTA® was administered as adjunctive therapy to patients with bipolar disorder in addition to continuing with their treatment as usual, approximately 4% (3/72) of RISPERDAL® CONSTA®-treated patients discontinued treatment due to an adverse event, compared with 1.5% (1/67) of placebo-treated patients. Adverse reactions associated with discontinuation in RISPERDAL® CONSTA®-treated patients were: hypokinesia (one patient) and tardive dyskinesia (one patient). **Dose Dependency of Adverse Reactions in Clinical Trials:** Extrapyramidal Symptoms: Two methods were used to measure extrapyramidal symptoms (EPS) in the 12-week double-blind, placebo-controlled trial comparing three doses of RISPERDAL® CONSTA® (25 mg, 50 mg, and 75 mg) with placebo in patients with schizophrenia, including: (1) the incidence of spontaneous reports of EPS symptoms; and (2) the change from baseline to endpoint on the total score (sum of the subscale scores for parkinsonism, dystonia, and dyskinesia) of the Extrapyramidal Symptom Rating Scale (ESRS). As shown in Table 1, the overall incidence of EPS-related adverse reactions (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL® CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse reactions was higher in patients treated with 50 mg RISPERDAL® CONSTA®. The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with RISPERDAL® CONSTA® compared with patients treated with placebo: 0 (placebo group); -1 (25-mg group, significantly less than the placebo group); and 0 (50-mg group). 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. **Changes in Body Weight:** In the 12-week double-blind, placebo-controlled trial in patients with schizophrenia, 9% of patients treated with RISPERDAL® CONSTA®, compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint. In the 24-month double-blind, placebo-controlled treatment period of a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 11.6% of patients treated with RISPERDAL® CONSTA® compared with 2.8% of patients treated with placebo experienced a weight gain of >7% of body weight at endpoint. In the 52-week double-blind, placebo-controlled trial in patients with bipolar disorder, 26.8% of patients treated with RISPERDAL® CONSTA® as adjunctive treatment in addition to continuing their treatment as usual, compared with 27.3% of patients treated with placebo in addition to continuing their treatment as usual, experienced a weight gain of >7% of body weight at endpoint. **Changes in ECG:** The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® and 98 schizophrenic patients treated with placebo in the 12-week double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL® CONSTA®. The electrocardiograms of 227 patients with Bipolar I Disorder were evaluated in the 24-month double-blind, placebo-controlled period. There were no clinically relevant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL® CONSTA® compared to placebo. The electrocardiograms of 85 patients with bipolar disorder were evaluated in the 52-week double-blind, placebo-controlled trial. There were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL® CONSTA® 25 mg, 37.5 mg, or 50 mg when administered as adjunctive treatment in addition to continuing treatment as usual compared to placebo. **Pain Assessment and Local Injection Site Reactions:** The mean intensity of injection pain reported by patients with schizophrenia using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® experienced redness, swelling, or induration at the injection site. In a separate study to observe local-site tolerability in which RISPERDAL® CONSTA® was administered into the deltoid muscle every 2 weeks over a period of 8 weeks, no patient discontinued treatment due to local injection site pain or reaction. Clinician ratings indicated that only mild redness, swelling, or induration at the injection site was observed in subjects treated with 37.5 mg or 50 mg RISPERDAL® CONSTA® at 2 hours after deltoid injection. All ratings returned to baseline at the predose assessment of the next injection 2 weeks later. No moderate or severe reactions were observed in any subject. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of risperidone; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrial fibrillation, diabetic ketoacidosis in patients with impaired glucose metabolism, inappropriate antidiuretic hormone secretion, hypothermia, intestinal obstruction, jaundice, mania, pancreatitis, priapism, QT prolongation, sleep apnea syndrome, thrombocytopenia, and water intoxication. In addition, the following adverse reactions have been observed during postapproval use of RISPERDAL® CONSTA®: cerebrovascular disorders, including cerebrovascular accidents, and diabetes mellitus aggravated. Retinal artery occlusion after injection of RISPERDAL® CONSTA® has been reported during postmarketing surveillance. This has been reported in the presence of abnormal arteriovenous anastomosis. Serious injection site reactions including abscess, cellulitis, cyst, hematoma, necrosis, nodule, and ulcer have been reported with RISPERDAL® CONSTA® during postmarketing surveillance. Isolated cases required surgical intervention.

DRUG INTERACTIONS: The interactions of RISPERDAL® CONSTA® with coadministration of other drugs have not been systematically evaluated. The drug interaction data provided in this section is based on studies with oral RISPERDAL®. **Centrally-Acting Drugs and Alcohol:** Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® CONSTA® is administered in combination with other centrally-acting drugs or alcohol. **Drugs with Hypotensive Effects:** Because of its potential for inducing hypotension, RISPERDAL® CONSTA® may enhance the hypotensive effects of other therapeutic agents with this potential. **Levodopa and Dopamine Agonists:** RISPERDAL® CONSTA® may antagonize the effects of levodopa and dopamine agonists. **Amitriptyline:** Amitriptyline did not affect the pharmacokinetics of risperidone or of risperidone and 9-hydroxyrisperidone combined following concomitant administration with oral RISPERDAL®. **Cimetidine and Ranitidine:** Cimetidine and ranitidine increased the bioavailability of oral risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and 9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%. **Clozapine:** Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Lithium:** Repeated doses of oral RISPERDAL® (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated doses of oral RISPERDAL® (4 mg once daily) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate

(1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of oral RISPERDAL®. **Digoxin:** Oral RISPERDAL® (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Topiramate:** Oral RISPERDAL® administered at doses from 1-6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone Cmax and a 33% decrease in risperidone $AUC_{0\text{-}12\ hour}$ at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral RISPERDAL® on the pharmacokinetics of topiramate. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs *[see Clinical Pharmacology (12.3) in full PI]*. Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≅70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. Fluoxetine and Paroxetine: Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily), CYP 2D6 inhibitors, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of RISPERDAL® CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg RISPERDAL® CONSTA®, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. When RISPERDAL® CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[See also DOSAGE AND ADMINISTRATION (2.5) in full PI]*. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied. Erythromycin: There were no significant interactions between oral RISPERDAL® and erythromycin. **Carbamazepine and Other CYP 3A4 Enzyme Inducers:** Carbamazepine co-administration with oral RISPERDAL® decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known CYP 3A4 enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of RISPERDAL® CONSTA® treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4–8 weeks, since the dose of RISPERDAL® CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of RISPERDAL® CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 enzyme inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL® CONSTA® and discontinuing from carbamazepine or other CYP 3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[See also DOSAGE AND ADMINSTRATION (2.5) in full PI]* **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® CONSTA® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral RISPERDAL® did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C.: The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the oral MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m^2 basis. No studies were conducted with RISPERDAL® CONSTA®. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® CONSTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® CONSTA® on labor and delivery in humans is unknown. **Nursing Mothers:** Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with RISPERDAL® CONSTA® and for at least 12 weeks after the last injection. **Pediatric Use:** RISPERDAL® CONSTA® has not been studied in children younger than 18 years old. **Geriatric Use:** In an open-label study, 57 clinically stable, elderly patients (≥ 65 years old) with schizophrenia or schizoaffective disorder received RISPERDAL® CONSTA® every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL® CONSTA® were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern *[see Warnings and Precautions (5.7) in full PI]*. Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with oral placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of oral risperidone regardless of concomitant use with furosemide. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis. *[See Boxed Warning and Warnings and Precautions]*

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL® CONSTA®. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension and instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position) *[see Warnings and Precautions]*. **Interference with Cognitive and Motor Performance:** Because RISPERDAL® CONSTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL® CONSTA® does not affect them adversely *[see Warnings and Precautions]*. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® *[see Use in Specific Populations]*. **Nursing:** Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® *[see Use in Specific Populations]*. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions]*. **Alcohol:** Patients should be advised to avoid alcohol during treatment with RISPERDAL® CONSTA® *[see Drug Interactions]*.

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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* – Liver function test abnormal, blood prolactin increased. *Nervous system disorders* – Convulsion, syncope, extrapyramidal disorder. *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). **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. No adjustment in starting dosage is necessary for patients with hepatic impairment.

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 W10529C004, revised February 2009.

Wyeth®

For the treatment of adults with major depressive disorder

The start is just the beginning

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

Pristiq® desvenlafaxine 50 mg

think beyond start™

IMPORTANT TREATMENT CONSIDERATIONS

PRISTIQ 50-mg Extended-Release Tablets are 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 sustained 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 (by giving 50 mg of PRISTIQ less frequently) rather than abrupt cessation is recommended whenever possible.
- Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or end-stage renal disease (ESRD). 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 twice 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.

Pristiq® desvenlafaxine EXTENDED-RELEASE TABLETS

Wyeth®