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.

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™

- 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.

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

Pristiq® desvenlafaxine EXTENDED-RELEASE TABLETS

Wyeth®

Pristiq® desvenlafaxine Extended-Release Tablets

BRIEF SUMMARY. See package insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

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 [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1 in the full prescribing information)*].

INDICATIONS AND USAGE: Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD).

CONTRAINDICATIONS: Hypersensitivity-Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. **Monoamine Oxidase Inhibitors-**Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI [*see Dosage and Administration (2.5) in the full prescribing information*].

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk-Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. 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 studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (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 studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1 of the full prescribing information. No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, 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, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies 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 major depressive disorder 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 Warnings and Precautions (5.9) and Dosage and Administration (2.3) in the full prescribing information for a description of the risks of discontinuation of Pristiq*]. Families and caregivers of patients being treated with antidepressants for major depressive disorder 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 Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Screening patients for bipolar disorder- A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) 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; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Pristiq is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions-** The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-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 metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Serotonin syndrome in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Pristiq with MAOIs intended to treat depression is contraindicated [*see Contraindications (4.2)*]. If concomitant treatment of Pristiq 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 Pristiq with serotonin precursors (such as tryptophan) is not recommended. Treatment with Pristiq and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated. **Elevated Blood Pressure-** Patients receiving Pristiq should have regular monitoring of blood pressure since dose-dependent increases were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with 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 with Pristiq. Sustained hypertension- Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered [*see Adverse Reactions (6.1)*]. Treatment with Pristiq in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits. In clinical studies, regarding the proportion of patients with sustained hypertension, the following rates were observed: placebo (0.5%), Pristiq 50 mg (1.3%), Pristiq 100 mg (0.7%), Pristiq 200 mg (1.1%), and Pristiq 400 mg (2.3%). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a 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®

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RELAPSE.*

- Patients treated with atypical oral antipsychotics may be missing their medication for about one-third of the year (110 days)[1]

RELAPSE.*

- Despite patients continuing to miss their medication, long-acting medications are being used later in treatment[2]

*While no medication can guarantee a patient will be relapse-free, using long-acting, professionally administered medication can help you recognize a missed dose and intervene.

IMPORTANT SAFETY INFORMATION

INVEGA® SUSTENNA™ (paliperidone palmitate) extended-release injectable suspension is indicated for the acute and maintenance treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION FOR INVEGA® SUSTENNA™

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis.

- **Hypersensitivity:** Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone, which is a metabolite of risperidone. Therefore paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA® SUSTENNA™.
- **Cerebrovascular Adverse Events (CAEs):** CAEs, including fatalities and stroke, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. INVEGA® SUSTENNA™ is not approved for the treatment of patients with dementia-related psychosis.
- **Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and close medical monitoring, and treatment of any concomitant serious medical problems.
- **QT Prolongation:** Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.
- **Tardive Dyskinesia (TD):** TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly women patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD. Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.
- **Hyperglycemia and Diabetes:** Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including INVEGA® SUSTENNA™. 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. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Weight Gain:** Weight gain has been observed with INVEGA® SUSTENNA™ and other atypical antipsychotic medications. Monitor weight gain.
- **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, INVEGA® SUSTENNA™ elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.
- **Orthostatic Hypotension and Syncope:** INVEGA® SUSTENNA™ may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. INVEGA® SUSTENNA™ should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension.
- **Leukopenia, Neutropenia and Agranulocytosis** have been reported with antipsychotics, including paliperidone. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a clinically significant decline in WBC and in the absence of other causative factors, discontinuation of INVEGA® SUSTENNA™ should be considered. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® SUSTENNA™ and have their WBC followed until recovery.

ACT EARLIER
WITH NEW ONCE-MONTHLY INVEGA® SUSTENNA™

- Once-monthly dosing[3]
- Demonstrated safety and tolerability profile[†‡3]
- Significantly delayed time to relapse in the longer-term maintenance study[3]

[†]Reported in 4 fixed-dose, double-blind, placebo-controlled studies (N=1803).
[‡]Reported in the longer-term maintenance study (N=849).

- **Potential for Cognitive and Motor Impairment:** Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA® SUSTENNA™. INVEGA® SUSTENNA™ has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® SUSTENNA™ does not affect them adversely, and should use caution when operating machinery.
- **Seizures:** INVEGA® SUSTENNA™ should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold.
- **Suicide:** The possibility of suicide attempt is inherent in schizophrenia. Close supervision of high-risk patients should accompany drug therapy.
- **Administration:** For intramuscular injection only. Care should be taken to avoid inadvertent injection into a blood vessel.
- **Commonly Observed Adverse Reactions for INVEGA® SUSTENNA™:** The most common adverse reactions in clinical trials in patients with schizophrenia (≥5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

References: 1. 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. **2.** Keith SJ, Kane JM, Turner M, Conley RR, Nasrallah HA. Academic highlights: guidelines for the use of long-acting injectable atypical antipsychotics. *J Clin Psychiatry.* 2004;65:120-131. **3.** INVEGA® SUSTENNA™ [Prescribing Information]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc. July 2009.

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

Visit www.invegasustenna.com for more information.

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

August 2009 01PM09034

INVEGA® SUSTENNA™ (paliperidone palmitate)
Extended-Release Injectable Suspension

Brief Summary

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

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions]*

INVEGA® SUSTENNA™ (paliperidone palmitate) is indicated for the acute and maintenance treatment of schizophrenia in adults *[see Clinical Studies (14) in full PI]*.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA® SUSTENNA™ (paliperidone palmitate) 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: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Oral paliperidone and INVEGA® SUSTENNA™ were not marketed at the time these studies were performed and are not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions]*.

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

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

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

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

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA® SUSTENNA™ administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA® SUSTENNA™, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

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

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

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

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

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

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA® SUSTENNA™. 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.

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.

Weight Gain: Weight gain has been observed with INVEGA® SUSTENNA™ and other atypical antipsychotics. In the 13-week study involving 234 mg initiation dosing, the proportion of subjects with an abnormal weight increase ≥ 7% showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA® SUSTENNA™ 39 mg, 156 mg, and 234 mg groups, respectively. In the two 13-week, fixed-dose, double-blind, placebo-controlled trials (pooled data), the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were 6%, 9%, and 10% in the INVEGA® SUSTENNA™ 39 mg, 78 mg, and 156 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, 8% and 6% in the INVEGA® SUSTENNA™ 78 mg and 156 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label period (9-week flexible-dose transition phase followed by a 24-week maintenance phase flexible-dose and minimum 12-week fixed dose) of the maintenance trial, 12% of INVEGA® SUSTENNA™-treated subjects met this criterion; the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion (weight gain of ≥ 7% from double-blind phase to endpoint) was met by 6% of INVEGA® SUSTENNA™-treated subjects compared with

INVEGA® SUSTENNA™ (paliperidone palmitate) Extended-Release Injectable Suspension

3% of placebo-treated subjects; the mean weight change from double-blind baseline was +0.5 kg for INVEGA® SUSTENNA™ compared with –1.0 kg for placebo. Similar results were observed in the open-label extension phase of this study.

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

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1) in full PI]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA® SUSTENNA™-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies were similar to those observed in the short-term studies.

INVEGA® SUSTENNA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

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

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

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

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA® SUSTENNA™ *[see Adverse Reactions]*. Antipsychotics, including INVEGA® SUSTENNA™, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures: In the four fixed-dose double-blind placebo-controlled studies, <1% (1/1293) of subjects treated with INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA® SUSTENNA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

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

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

Priapism: Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA® SUSTENNA™, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): No cases of TTP were observed during clinical studies with oral paliperidone or INVEGA® SUSTENNA™. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA® SUSTENNA™ to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Administration: INVEGA® SUSTENNA™ is intended for intramuscular injection, and care must be taken to avoid inadvertent injection into a blood vessel *[see Dosage and Administration (2.3) in full PI]*.

Antiemetic Effect: An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Use in Patients with Concomitant Illness: Clinical experience with INVEGA® SUSTENNA™ in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3) in full PI]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA® SUSTENNA™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA® SUSTENNA™, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions]*.

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

ADVERSE REACTIONS

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

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

Throughout this section, a distinction is made between adverse events and adverse reactions. Adverse events are events reported by the clinician investigator and there is no attempt to assign causality to the study drug. Adverse reactions are adverse events that are considered to be reasonably associated with the use of INVEGA® SUSTENNA™ (adverse drug reactions) based on a predetermined method of assessment, e.g., a comparison of adverse event rates for drug and placebo groups for the event of interest. It is not possible to reliably establish causality by considering individual adverse event reports for drug-treated patients. Thus, the section overall is labeled Adverse Reactions, however, individual subsections are labeled adverse reactions or adverse events, depending on what is included in the subsection.

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 most common (at least 5% in any INVEGA® SUSTENNA™ group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder.

The data described in this section are derived from a clinical trial database (Phase 2 and 3) consisting of a total of 2770 subjects with schizophrenia who received at least one dose of INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 2770 INVEGA® SUSTENNA™-treated subjects, 1293 received INVEGA® SUSTENNA™ in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA® SUSTENNA™ in the maintenance trial (of whom 205 continued to receive INVEGA® SUSTENNA™ during the double-blind placebo-controlled phase of this study), and 628 received INVEGA® SUSTENNA™ in two non-placebo controlled trials (a noninferiority active-comparator trial and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA® SUSTENNA™ initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

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.

The majority of all adverse reactions were mild to moderate in severity.

Commonly-Observed Adverse Events in Double-Blind, Placebo-Controlled Clinical Trials: *Table 1* lists the adverse events reported in 2% or more of INVEGA® SUSTENNA™-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

Table 1. Incidence of Treatment Emergent Adverse Events in ≥ 2% of INVEGA® SUSTENNA™-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials: System Organ Class Adverse Event followed by **Placebo[a] (N=510)** first, **39 mg (N=130)** second, **78 mg (N=302)** third, **156 mg (N=312)** fourth, **234/39 mg[b] (N=160)** fifth, **234/156 mg[b] (N=165)** sixth, **234/234 mg[b] (N=163)** seventh: Total percentage of subjects with adverse event: 70, 75, 68, 69, 63, 60, 63; **Gastrointestinal disorders:** Abdominal discomfort/Abdominal pain upper 1, 0, 3, 3, 1, 2, 3; Constipation 5, 3, 5, 5, 2, 4, 1; Diarrhea 2, 0, 3, 2, 1, 2, 2; Dry mouth 1, 3, 1, 0, 1, 1, 1; Nausea 3, 4, 4, 3, 2, 2, 2; Toothache 1, 1, 1, 3, 1, 2, 3; Vomiting 4, 5, 4, 2, 3, 2, 2; **General disorders andadministration site conditions:** Asthenia 0, 2, 1, <1, 0, 1, 1; Fatigue 1, 1, 2, 2, 1, 2, 1; Injection site reactions 2, 0, 4, 6, 9, 7, 10; **Infections and infestations:** Nasopharyngitis 2, 0, 2, 2, 4, 2, 2; Upper respiratory tract infection 2, 2, 2, 2, 1, 2, 4; Urinary tract infection 1, 0, 1, <1, 1, 1, 2; **Injury, poisoning and procedural complications:** Skin laceration <1, 2, <1, 0, 1, 0, 0; **Investigations:** Alanine aminotransferaseincreased 2, 0, 2, 1, 1, 1, 1; Weight increased 1, 4, 4, 1, 1, 1, 2; **Musculoskeletal andconnective tissue disorders:** Back pain 2, 2, 1, 3, 1, 1, 1; Musculoskeletal stiffness 1, 1, <1, <1, 1, 1, 2; Myalgia 1, 2, 1, <1, 1, 0, 2; Pain in extremity 1, 0, 2, 2, 2, 3, 0; **Nervous system disorders:** Akathisia 3, 2, 2, 3, 1, 5, 6; Dizziness 1, 6, 2, 4, 1, 4, 2; Extrapyramidal disorder 1, 5, 2, 3, 1, 0, 0; Headache 12, 11, 11, 15, 11, 7, 6; Somnolence/sedation 3, 5, 7, 4, 1, 5, 5; **Psychiatric disorders:** Agitation 7, 10, 5, 9, 8, 5, 4; Anxiety 7, 8, 5, 3, 5, 6, 6; Insomnia 15, 15, 15, 13, 12, 10, 13; Nightmare <1, 2, 0, 0, 0, 0, 0; Suicidal ideation 2, 0, 1, 2, 2, 2, 1; **Respiratory, thoracic and mediastinal disorders:** Cough 1, 2, 3, 1, 0, 1, 1; **Vascular disorders:** Hypertension 1, 2, 1, 1, 1, 1, 0. Percentages are rounded to whole numbers. Table includes adverse events that were reported in 2% or more of subjects in any of the INVEGA® SUSTENNA™ dose groups and which occurred at greater incidence than in the placebo group. [a] Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design. [b] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [See Clinical Studies (14) in full PI]

Adverse events for which the paliperidone palmitate incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain upper, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse events were collapsed and are grouped under "Injection site reactions".

Adverse Reactions Observed During the Premarketing Evaluation of INVEGA® SUSTENNA™ Not Listed in Table 1: The following additional adverse reactions occurred in INVEGA® SUSTENNA™-treated subjects in the above four fixed-dose, double-blind, placebo-controlled trials, in the double-blind phase of the maintenance trial, or in INVEGA® SUSTENNA™-treated subjects with schizophrenia who participated in other Phase 3 trials, and were not reported in Table 1. They were determined to be adverse reactions based upon reasons to suspect causality such as timing of onset or termination with respect to drug use, plausibility in light of the drug's known pharmacology, occurrence at a frequency above that expected in the treated population or occurrence of an event typical of drug-induced adverse reactions.

Cardiac disorders: bradycardia, bundle branch block, postural orthostatic tachycardia syndrome, tachycardia
Ear and labyrinth disorders: vertigo
Endocrine disorders: hyperprolactinemia
Eye disorders: oculogyric crisis, eye rolling, vision blurred
Gastrointestinal disorders: salivary hypersecretion, stomach discomfort
Investigations: blood cholesterol increased, blood glucose increased
Metabolism and nutrition disorders: decreased appetite, increased appetite
Nervous system disorders: convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, neuroleptic malignant syndrome, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope
Psychiatric disorders: restlessness
Reproductive system and breast disorders: amenorrhea, erectile dysfunction, galactorrhea, gynecomastia, menstruation irregular, sexual dysfunction
Skin and subcutaneous tissue disorders: pruritus generalized, rash
Vascular disorders: orthostatic hypotension

Discontinuations Due to Adverse Events: The percentages of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled trials were 5.0% and 7.8% in INVEGA® SUSTENNA™- and placebo-treated subjects, respectively.

Dose-Related Adverse Reactions: Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials, among the adverse reactions that occurred at ≥ 2% incidence in the subjects treated with INVEGA® SUSTENNA™, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA® SUSTENNA™-treated subjects from the four fixed-dose studies.

Demographic Differences: An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects ≥ 65 years of age.

Extrapyramidal Symptoms (EPS): Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline or score at the end of trial) which broadly evaluates

INVEGA® SUSTENNA™ (paliperidone palmitate) Extended-Release Injectable Suspension

Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, (4) the Abnormal Involuntary Movement Scale scores (mean change from baseline or scores at the end of trial) *(Table 2)*, and (5) incidence of spontaneous reports of EPS *(Table 3)*.

Table 2. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication: Scale followed by **Percentage of Subjects Placebo (N=262)** first, **INVEGA® SUSTENNA™ 39 mg (N=130)** second, **78 mg (N=223)** third, **156 mg (N=228)** fourth: Parkinsonism[a] 9, 12, 10, 6; Akathisia[b] 5, 5, 6, 5; Dyskinesia[c] 3, 4, 6, 4; Use of Anticholinergic Medications[d] 12, 10, 12, 11. [a] For Parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items) [b] For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint [c] For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint [d] Percent of subjects who received anticholinergic medications to treat emergent EPS

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term: EPS Group followed by **Percentage of Subjects Placebo (N=262)** first, **INVEGA® SUSTENNA™ 39 mg (N=130)** second, **78 mg (N=223)** third, **156 mg (N=228)** fourth: Overall percentage of subjects with EPS-related adverse events 10, 12, 11, 11; Parkinsonism 5, 6, 6, 4; Hyperkinesia 2, 2, 2, 4; Tremor 3, 2, 2, 3; Dyskinesia 1, 2, 3, 1; Dystonia 0, 1, 1, 2.

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of Parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA® SUSTENNA™ 156 mg group (18% and 11%, respectively) than in the INVEGA® SUSTENNA™ 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study involving 234 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA® SUSTENNA™ 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA® SUSTENNA™ 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

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

Laboratory Test Abnormalities: In the pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials, a between-group comparison revealed no medically important differences between INVEGA® SUSTENNA™ and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® SUSTENNA™ and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® SUSTENNA™ was associated with increases in serum prolactin [see Warnings and Precautions]. The results from the 13-week study involving 234 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the maintenance trial exhibited comparable findings.

Pain Assessment and Local Injection Site Reactions: In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials, the mean intensity of injection pain reported by subjects 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: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

In the 13-week study involving 234 mg initiation dosing, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA® SUSTENNA™ and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA® SUSTENNA™ groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA® SUSTENNA™ and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA® SUSTENNA™ and placebo groups.

Adverse Reactions Reported With Oral Paliperidone: The following is a list of additional adverse reactions that have been reported with oral paliperidone in subjects with schizophrenia:

Cardiac disorders: atrioventricular block first degree, palpitations, sinus arrhythmia
Gastrointestinal disorders: abdominal pain, swollen tongue
General disorders and administration site conditions: edema
Immune system disorders: anaphylactic reaction
Musculoskeletal and connective tissue disorders: muscle rigidity
Nervous system disorders: tremor
Reproductive system and breast disorders: priapism, breast discharge
Vascular disorders: ischemia

Adverse Reactions Reported With Risperidone: Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the ADVERSE REACTIONS sections of the package inserts for those products.

DRUG INTERACTIONS

Since paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3) in full PI]*, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Potential for INVEGA® SUSTENNA™ to Affect Other Drugs: Given the primary CNS effects of paliperidone *[see Adverse Reactions]*, INVEGA® SUSTENNA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA® SUSTENNA™ is administered with other therapeutic agents that have this potential *[see Warnings and Precautions]*.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

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

Potential for Other Drugs to Affect INVEGA® SUSTENNA™: Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

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

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

Co-administration of a single dose of an oral paliperidone extended-release 12 mg tablet with divalproex sodium extended-release tablets (two 500 mg tablets once daily at steady-state) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Although this interaction has not been studied with INVEGA® SUSTENNA™, a clinically significant interaction would not be expected between divalproex sodium and INVEGA® SUSTENNA™ intramuscular injection.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.: There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 160 mg/kg, which is 10 times the maximum recommended human 234 mg dose of INVEGA® SUSTENNA™ on a mg/m^2 basis.

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human dose [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see RISPERDAL® package insert).

There are no adequate and well controlled studies of INVEGA® SUSTENNA™ in pregnant women. INVEGA® SUSTENNA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

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Labor and Delivery: The effect of INVEGA® SUSTENNA™ on labor and delivery in humans is unknown.

Nursing Mothers: In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA® SUSTENNA™ should not breast feed infants.

Pediatric Use: Safety and effectiveness of INVEGA® SUSTENNA™ in patients < 18 years of age have not been established.

Geriatric Use: Clinical studies of INVEGA® SUSTENNA™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment *[see Clinical Pharmacology (12.3) in full PI]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5) in full PI]*.

Renal Impairment: INVEGA® SUSTENNA™ has not been systematically studied in patients with renal impairment [see Clinical Pharmacology (12.3) in full PI]. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), recommended initiation of INVEGA® SUSTENNA™ is with a dose of 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle.

INVEGA® SUSTENNA™ is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Hepatic Impairment: INVEGA® SUSTENNA™ has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

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

Abuse: Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

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

OVERDOSAGE

Human Experience: No cases of overdose were reported in premarketing studies with INVEGA® SUSTENNA™. Because INVEGA® SUSTENNA™ is to be administered by health care professionals, the potential for overdosage by patients is low.

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

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

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the prolonged-release characteristics of INVEGA® SUSTENNA™ and the long apparent half-life of paliperidone when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

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

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

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RC PSYCH PUBLICATIONS

Nidotherapy

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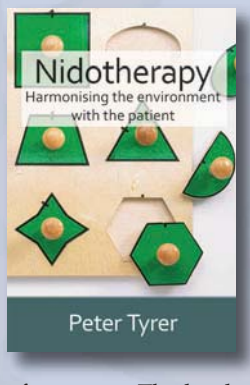

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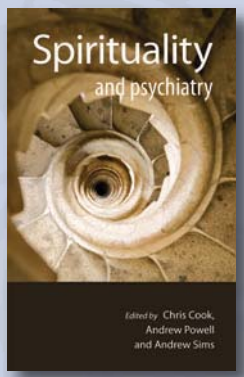
Spirituality and Psychiatry

Edited by Chris Cook, Andrew Powell and Andrew Sims

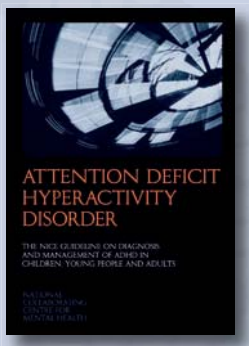


Spirituality is a crucial but sometimes overlooked aspect of mental well-being and psychiatric care. This comprehensive and evidence-based text explores the nature of spirituality, its relationship to religion, and the reasons for its importance in clinical practice. The prevention and management of illness, as well as the maintenance of recovery are discussed. Different chapters focus on the key subspecialties of psychiatry. Contributors include psychiatrists, psychotherapists, mental healthcare chaplains and a social worker. This book will be of wide interest to all mental health professionals.

978-1-904671-71-8, paperback, 318 pages, 2009, $50

Attention Deficit Hyperactivity Disorder

The NICE Guideline on Diagnosis and Management of ADHD in Children, Young People and Adults

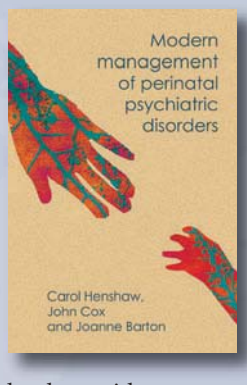


ADHD is a common disorder associated with serious impairments in childhood and significant difficulties in adulthood. This guideline from the National Institute for Health and Clinical Excellence (NICE) sets out clear recommendations, based on the best available evidence, for health care professionals on how to work with and implement physical, psychological and service-level interventions for people with ADHD. It includes sections on: parent training; interventions for children in educational settings; dietary interventions; a comparison of psychological and pharmacological treatments; service users' own experiences; and a specially commissioned study of children's views of stimulant medication.

978-1-854334-71-8, paperback, 662 pages + CD-ROM, 2009, $70

Modern Management of Perinatal Psychiatric Disorders

Carol Henshaw, John Cox and Joanne Barton



The management of mental health problems is a core component of maternity care. Pregnancy and childbirth may be accompanied by recurrence of pre-existing psychiatric problems, and conditions such as postnatal depression and puerperal psychosis may arise following delivery. Correct management of these problems is essential for both the mother and the developing infant. This book provides a comprehensive overview of mental health problems associated with pregnancy and the year after delivery. Key topics covered include: issues for children and families; screening for and prevention of mental disorders in relation to childbirth; and transcultural issues.

978-1-904671-36-7, paperback, 294 pages, 2009, $50

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SEE ME FOR WHO I CAN BE

Lisa, 32*
Part-time Caterer
Diagnosis: Bipolar Disorder
Recent Episode: Mixed

*Not an actual patient.

Do you see your patients' full potential?

GEODON is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic symptoms.

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 been associated with prolongation of the QT_c interval. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. Patients who are at risk for significant electrolyte disturbances should have baseline measurements performed before initiating GEODON. Patients on diuretics should be monitored.**

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

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

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

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

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

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, hypercholesterolemia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesterolemia, 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 symptoms, 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

IMPORTANT SAFETY INFORMATION

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

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

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

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

www.pfizerpro.com/chantix

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

THIS YEAR, HELP THEM KEEP THEIR RESOLUTION

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

CHANTIX® + GET QUIT® Plan

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

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

According to the US Public Health Service

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

CHANTIX® (varenicline) TABLETS

THE POWER TO HELP THEM QUIT

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

Brief summary of full Prescribing Information.

CHANTIX®
(varenicline) Tablets

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

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

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

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

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

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

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

WARNINGS
Neuropsychiatric Symptoms and Suicidality

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

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

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

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

Angioedema and Hypersensitivity Reactions.

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

Serious Skin Reactions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Post-Marketing Experience:

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

Special Populations

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

Dosing in elderly patients and patients with impaired hepatic function No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See **PRECAUTIONS, Geriatric Use**).

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

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

Rx only

July 2009, Version 4.0

Pfizer

Pfizer U.S. Pharmaceuticals

SEROQUEL XR

A different option for bipolar depression, a different type of depression

Proven to work by itself in bipolar depression[1,2]

- SEROQUEL XR demonstrated significant antidepressant efficacy in bipolar depression[2]
- Established safety profile[1,3]
- SEROQUEL XR is covered for 88% of patients nationwide with no prior authorization*†[4]

Individual costs and benefit design may vary by plan. Costs to patients may vary by plan. Please consult with individual plans for specific information. Fingertip Formulary® as of June 2009.

AstraZeneca does not endorse any individual commercial, Medicare Part D, or Medicaid plan or plans.

*"Patients" means all covered lives (commercial, Medicare, and Medicaid) at Tiers 1-7 in the US calculated by Fingertip Formulary as of June 2009 that do not require additional information to the health plan in order for SEROQUEL XR to be covered. Data include covered lives whose prescriptions may be subject to step therapy requirements.

†Individual plan coverage may vary.

Indications

- SEROQUEL XR is indicated for the treatment of acute depressive episodes associated with bipolar disorder, acute manic or mixed episodes associated with bipolar I disorder as monotherapy, and as an adjunct to lithium or divalproex; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex, and acute and maintenance treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment and the appropriate dose

Important Safety Information About SEROQUEL XR

- **Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6-1.7 times) of death, compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning)**
- **Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Patients of all ages started on therapy should be 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. SEROQUEL XR is not approved for use in patients under the age of 18 years (see Boxed Warning)**

Important Safety Information About SEROQUEL XR (continued)

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing
- In long-term clinical trials of quetiapine, hyperglycemia (fasting glucose ≥126 mg/dL) was observed in 10.7% of patients receiving quetiapine (mean exposure 213 days) vs 4.6% in patients receiving placebo (mean exposure 152 days)
- Clinically significant increases in cholesterol (7%-16% for quetiapine vs 3%-9% for placebo) and triglycerides (8%-23% for quetiapine vs 5%-16% for placebo) have been observed in clinical trials
- The proportion of patients in clinical trials meeting a weight gain criterion of ≥7% of body weight was 5%-23% for quetiapine vs 0%-7% for placebo
- A potentially fatal symptom complex, sometimes referred to as Neuroleptic Malignant Syndrome (NMS), has been reported in association with administration of antipsychotic drugs, including quetiapine. Rare cases of NMS have been reported with quetiapine. 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 management of NMS should include immediate discontinuation of antipsychotic drugs
- Leukopenia, neutropenia, and agranulocytosis (including fatal cases) have been reported temporally related to atypical antipsychotics, including quetiapine. Patients with a pre-existing low white blood cell (WBC) count or a history of drug induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. In these patients, SEROQUEL XR should be discontinued at the first sign of a decline in WBC absent other causative factors. Patients with neutropenia should be carefully monitored, and SEROQUEL XR should be discontinued in any patient if the absolute neutrophil count is <1000/mm^3
- Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. Quetiapine should be prescribed in a manner that is most likely to minimize the occurrence of TD
- Warnings and Precautions also include the risk of orthostatic hypotension, cataracts, seizures, hyperprolactinemia, and dysphagia. Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany drug therapy
- The most commonly reported adverse reactions associated with the use of SEROQUEL XR vs placebo in clinical trials for schizophrenia and bipolar disorder were somnolence (25%-52% vs 10%-13%), dry mouth (12%-37% vs 1%-7%), constipation (6%-10% vs 3%-6%), dyspepsia (5%-7% vs 1%-4%), dizziness (10%-13% vs 4%-11%), orthostatic hypotension (7% vs 5%), weight gain (7% vs 1%), increased appetite (12% vs 6%), fatigue (6%-7% vs 2%-4%), dysarthria (5% vs 0%), and nasal congestion (5% vs 1%)

Please see Brief Summary of Prescribing Information, including Boxed Warnings, on adjacent pages.

References: 1. SEROQUEL XR Prescribing Information. **2.** Data on file, 273559, AstraZeneca Pharmaceuticals LP. **3.** Data on file, 272710, AstraZeneca Pharmaceuticals LP. **4.** Fingertip Formulary. June 2009.

290631 11/09 www.SEROQUELXR.com

Once-daily
SEROQUEL XR®
quetiapine fumarate
extended-release tablets
50, 150, 200, 300 & 400 mg

Bipolar depression. Find it. Treat it.

AstraZeneca

SEROQUEL XR®

(quetiapine fumarate) Extended-Release Tablets

BRIEF SUMMARY: For full Prescribing Information, see package insert.

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 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. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions*].

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 SEROQUEL XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL XR is not approved for use in pediatric patients [see *Warnings and Precautions*].

INDICATIONS AND USAGE

Schizophrenia

SEROQUEL XR is indicated for the acute and maintenance treatment of schizophrenia.

The efficacy of SEROQUEL XR in schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of SEROQUEL. [see **Clinical Studies** (14.1) in full Prescribing Information].

Bipolar Disorder

SEROQUEL XR is indicated for the treatment of:

- acute depressive episodes associated with bipolar disorder
- acute manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or divalproex therapy and
- maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

The efficacy of SEROQUEL XR in bipolar disorder was established, in part, on the basis of extrapolation from the established effectiveness of SEROQUEL [see **Clinical Studies** (14.2) in full Prescribing Information].

DOSAGE AND ADMINISTRATION

SEROQUEL XR tablets should be swallowed whole and not split, chewed or crushed.

It is recommended that SEROQUEL XR be taken without food or with a light meal (approximately 300 calories) [see **Clinical Pharmacology** (12.3) in full Prescribing Information]

Schizophrenia

Usual Dose for Acute Treatment

SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg/day. Patients should be titrated within a dose range of 400 – 800 mg/day depending on the response and tolerance of the individual patient [see **Clinical Studies** (14.1) in full Prescribing Information]. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Maintenance Treatment

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, a longer-term schizophrenia study with SEROQUEL XR has shown this drug to be effective in delaying time to relapse in patients who were stabilized on SEROQUEL XR at doses of 400 to 800 mg/day for 16 weeks [see **Clinical Studies** (14.1) in full Prescribing Information]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see **Clinical Studies** (14.1) in full Prescribing Information].

Bipolar Disorder

Depressive Episodes Associated with Bipolar Disorder

Usual Dose for Acute Treatment

SEROQUEL XR should be administered once daily in the evening to reach 300 mg/day by Day 4.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3	Day 4
SEROQUEL XR	50 mg	100 mg	200 mg	300 mg

Bipolar Mania

Usual Dose for Acute Monotherapy or Adjunct Therapy (with lithium or divalproex)

SEROQUEL XR should be administered once daily in the evening starting with 300 mg on Day 1 and 600 mg on Day 2. SEROQUEL XR can be adjusted between 400 mg and 800 mg beginning on Day 3 depending on the response and tolerance of the individual patient.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3
SEROQUEL XR	300 mg	600 mg	400 mg to 800 mg

Maintenance Treatment for Bipolar Disorder

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, maintenance of efficacy in Bipolar I Disorder was demonstrated with SEROQUEL (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase [see **Clinical Studies** (14.2) in full Prescribing Information]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see **Clinical Studies** (14.2) in full Prescribing Information].

Dosing in Special Populations: Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions [see **Use in Specific Populations**]. When indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on SEROQUEL XR 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the response and tolerance of the individual patient.

Patients with hepatic impairment should be started on SEROQUEL XR 50 mg/day. The dose can be increased daily in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance of the patient.

Re-initiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting therapy of patients who have been off SEROQUEL XR for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off SEROQUEL XR for less than one week, gradual dose escalation may not be required and the maintenance dose may be reinitiated.

Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets

Patients who are currently being treated with SEROQUEL (immediate release formulation) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Switching from Antipsychotics

There are no systematically collected data to specifically address switching patients from other antipsychotics to SEROQUEL XR, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate SEROQUEL XR therapy in place of the next scheduled injection. The need for continuing existing extrapyramidal syndrome medication should be re-evaluated periodically.

CONTRAINDICATIONS

None

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 compared to placebo. SEROQUEL XR (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning*].

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. 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 children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 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. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are as follows: <18 years of age—14 additional cases compared to placebo; 18-24 years of age—5 additional cases compared to placebo; 25-64—1 fewer case compared to placebo; ≥65 years of age—6 fewer cases compared to placebo.

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 major depressive disorder 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.

Families and caregivers of patients being treated with antidepressants for major depressive disorder 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 SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (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; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

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 quetiapine. 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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions 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 (eg, 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.

Adults: In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar maintenance, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +5.0 mg/dL for quetiapine and –0.05 mg/dL for placebo. The exposure-adjusted rate of any increased blood glucose level (≥126 mg/dL) for patients more than 8 hours since a meal (however, some patients may not have been precluded from calorie intake from fluids during fasting period) was 18.0 per 100 patient years for SEROQUEL (10.7% of patients; n=556) and 9.5 for placebo per 100 patient years (4.6% of patients; n=581).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with quetiapine and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dL or a non fasting blood glucose ≥200 mg/dL was 3.5% for quetiapine and 2.1% for placebo. The mean change in glucose from baseline was 2.70 mg/dL for quetiapine and 1.06 mg/dL for placebo.

In a 24-week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥200 mg/dL was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥126 mg/dL was 2.6%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in 2 hour glucose from baseline was -1.8 mg/dL for quetiapine.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a placebo-controlled quetiapine monotherapy study of adolescent patients (13–17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL compared to placebo was –0.75 mg/dL vs –1.70 mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescent patients (10–17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for quetiapine compared to placebo was 3.62 mg/dL vs –1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level (<100 mg/dL) or a baseline borderline fasting glucose level (≥100 mg/dL and <126 mg/dL) had a treatment-emergent blood glucose level of ≥126 mg/dL.

Hyperlipidemia

Adults: In clinical trials with SEROQUEL XR the percentage of patients with the following Shifts from Normal Baseline to Clinically Significant Levels of cholesterol and triglycerides have been reported [see **Adverse Reactions**].

Schizophrenia Trial (6 weeks duration)

9% of patients on SEROQUEL XR had Cholesterol ≥240 mg/dL vs 9% of patients on placebo. 18% of patients on SEROQUEL XR had Triglycerides ≥200 mg/dL vs 5% of patients on placebo.

Bipolar Depression Trial (8 weeks duration)

7% of patients on SEROQUEL XR had Cholesterol ≥240 mg/dL vs 3% of patients on placebo. 8% of patients on SEROQUEL XR had Triglycerides ≥200 mg/dL vs 8% of patients on placebo.

Bipolar Mania Trial (3 weeks duration)

7% of patients on SEROQUEL XR had Cholesterol ≥240 mg/dL vs 4% of patients on placebo. 15% of patients on SEROQUEL XR had Triglycerides ≥200 mg/dL vs 6% of patients on placebo.

Children and Adolescents:

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In clinical trials with SEROQUEL the percentage of patients with the following Shifts from Normal Baseline to Clinically Significant Levels of cholesterol and triglycerides have been reported.

Schizophrenia Trial (13-17 years, 6 weeks duration)

12% of patients on SEROQUEL had Cholesterol ≥240 mg/dL vs 2% of patients on placebo. 17% of patients on SEROQUEL had Triglycerides ≥200 mg/dL vs 8% of patients on placebo.

Bipolar Mania Trial (10-17 years, 3 weeks duration)

10% of patients on SEROQUEL had Cholesterol ≥240 mg/dL vs 3% of patients on placebo. 22% of patients on SEROQUEL had Triglycerides ≥200 mg/dL vs 13% of patients on placebo.

Weight Gain

Adults: In clinical trials with SEROQUEL XR the following increases in weight have been reported.

Proportion of Patients with Weight Gain ≥7% of Body Weight (Adults)

Schizophrenia Trial (6 weeks duration)

10% of patients on SEROQUEL XR vs 5% of patients on placebo

Bipolar Mania Trial (3 weeks duration)

5.1% of patients on SEROQUEL XR vs 0% of patients on placebo.

Bipolar Depression Trial (8 weeks duration)

8.2% of patients on SEROQUEL XR vs 0.8% of patients on placebo.

In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significant greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In two clinical trials with SEROQUEL, one in bipolar mania and one in schizophrenia, reported increases in weight are included below. When treating pediatric patients with SEROQUEL XR for any indication, weight gain should be assessed against that expected for normal growth. The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group and in the bipolar mania trial it was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group.

Proportion of Patients with Weight Gain ≥7% of Body Weight (Children and Adolescents)

Schizophrenia Trial (6 weeks duration)

21% of patients on SEROQUEL vs 7% of patients on placebo

Bipolar Mania Trial (3 weeks duration)

12% of patients on SEROQUEL vs 0% of patients on placebo.

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL. After 26 weeks of treatment, the

mean increase in body weight was 4.4 kg. Forty-five percent of the patients gained ≥7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

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, including quetiapine. Rare cases of NMS have been reported with quetiapine. 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 exclude cases where the clinical presentation includes both serious medical illness (eg, 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 (CNS) 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 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 including quetiapine. 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, SEROQUEL XR 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 appear to 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 on SEROQUEL XR, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

Orthostatic Hypotension

Quetiapine 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 0.3% (4/1239) of the patients treated with SEROQUEL XR, compared with 0.3% (2/619) on placebo. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo. Orthostatic hypotension, dizziness, and syncope may lead to falls.

Quetiapine 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 which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Leukopenia, Neutropenia and Agranulocytosis

In clinical trials and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including SEROQUEL XR. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing 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 should discontinue SEROQUEL XR at the first sign of a decline in WBC in 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 SEROQUEL XR and have their WBC followed until recovery [see **Adverse Reactions**].

Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies. Lens changes have also been observed in patients during long-term quetiapine treatment, but a causal relationship to quetiapine use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment.

Seizures

During clinical trials with SEROQUEL XR, seizures occurred in 0.1% (1/1239) of patients treated with SEROQUEL XR compared to 0.5% (3/619) on placebo. During clinical trials with SEROQUEL, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo. As with other antipsychotics, quetiapine fumarate should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism

Adults: In SEROQUEL XR clinical trials, 0.5% (4/806) of patients on SEROQUEL XR vs 0% (0/262) on placebo experienced decreased free thyroxine and 2.7% (21/786) on SEROQUEL XR vs 1.2% (3/256) on placebo experienced increased thyroid stimulating hormone (TSH); however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. No patients had reactions of hypothyroidism. Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of thyroid binding globulin were unchanged. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of these patients with TSH increases needed replacement thyroid treatment.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts to potentially clinically important thyroid function values at any time for SEROQUEL treated patients and placebo-treated patients for elevated TSH was 2.9% vs 0.7%, respectively and for decreased total thyroxine was 2.8% vs 0%, respectively. Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

Hyperprolactinemia

Adults: During clinical trials with quetiapine, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts in prolactin levels to a clinically significant value (>20 µg/L males; >26 µg/L females at any time) was 13.4% for SEROQUEL compared to 4% for placebo in males and 8.7% for SEROQUEL compared to 0% for placebo in females.

Like other drugs that antagonize dopamine D2 receptors, SEROQUEL XR elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Increases in Blood Pressure (Children and Adolescents)

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure

(≥20 mmHg) was 15.2% for SEROQUEL and 5.5% for placebo; the incidence of increases at any time in diastolic blood pressure (≥10 mmHg) was 40.6% for SEROQUEL and 24.5% for placebo.

Transaminase Elevations

Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of placebo-controlled trials ranged between 1% and 2% for SEROQUEL XR compared to 2% for placebo. In schizophrenia trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with quetiapine.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event reported in patients treated with quetiapine especially during the 3-day period of initial dose titration. In schizophrenia trials, somnolence was reported in 24.7% of patients on SEROQUEL XR compared to 10.3% of placebo patients. In a bipolar depression clinical trial, somnolence was reported in 51.8% of patients on SEROQUEL XR compared to 12.9% of placebo patients. In a clinical trial for bipolar mania, somnolence was reported in 50.3% of patients on SEROQUEL XR compared to 11.9% of placebo patients. Since quetiapine 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 quetiapine therapy does not affect them adversely. Somnolence may lead to falls.

Priapism

One case of priapism in a patient receiving quetiapine was reported prior to market introduction. While a causal relationship to use of quetiapine has not been established, other drugs with α-adrenergic blocking effects have been reported to induce priapism, and it is possible that quetiapine may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL XR for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

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. SEROQUEL XR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In three, 6-week clinical studies in patients with schizophrenia (N=951), the incidence of treatment emergent suicidal ideation or suicide attempt was 0.6% in SEROQUEL XR treated patients and 0.9% in placebo-treated patients.

In an 8-week clinical study in patients with bipolar depression (N=137 for SEROQUEL XR and 140 for placebo), the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% for SEROQUEL XR treated patients and 1.4% for placebo.

In a 3-week clinical study in patients with bipolar mania (N=311, 151 for SEROQUEL XR and 160 for placebo), the incidence of treatment emergent suicidal ideation or suicide attempt was 1.3% for SEROQUEL XR compared to 3.8% for placebo.

Use in Patients with Concomitant Illness

Clinical experience with SEROQUEL XR in patients with certain concomitant systemic illnesses is limited.

SEROQUEL XR 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 orthostatic hypotension with SEROQUEL XR, caution should be observed in cardiac patients [see **Warnings and Precautions**].

Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine fumarate. Gradual withdrawal is advised.

ADVERSE REACTIONS

Clinical Studies Experience

The information below is derived from a clinical trial database for SEROQUEL XR consisting of 1239 patients exposed to SEROQUEL XR for the treatment of schizophrenia and bipolar disorder in placebo-controlled trials.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

There was no difference in the incidence and type of adverse reactions associated with discontinuation (6.4% for SEROQUEL XR vs 7.5% for placebo) in a pool of controlled schizophrenia trials. In a single clinical trial in patients with bipolar depression, 13% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 4% on placebo. In a single clinical trial in patients with bipolar mania, 4.6% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 8.1% on placebo.

Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Short-Term, Placebo-Controlled Trials

The following is the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) in ≥5% patients treated with SEROQUEL XR (doses ranging from 300 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.[1]

SEROQUEL XR (n=951) vs placebo (n=319): Dry Mouth 12% vs 1%; Constipation 6% vs 5%; Dyspepsia 5% vs 2%; Somnolence 25% vs 10%; Dizziness 10% vs 4%; and Orthostatic Hypotension 7% vs 5%

[1] Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed, but included the following: headache, insomnia, and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (25%), dry mouth (12%), dizziness (10%), and dyspepsia (5%).

The following is the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar depression (up to 8 weeks) in ≥5% patients treated with SEROQUEL XR 300 mg/day where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.[1]

SEROQUEL XR (N=137) vs placebo (n=140): Dry Mouth 37% vs 7%; Constipation 8% vs 6%; Dyspepsia 7% vs 1%; Fatigue 6% vs 2%; Weight Gain 7% vs 1%; Increased Appetite 12% vs 6%; Somnolence 52% vs 13%; and Dizziness 13% vs 11%

[1] Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed, but included the following: headache and insomnia.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (52%), dry mouth (37%), increased appetite (12%), weight gain (7%), dyspepsia (7%), and fatigue (6%).

The following is the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar mania (up to 3 weeks) in ≥5% patients treated with SEROQUEL XR (doses ranging from 400 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.[1]

SEROQUEL XR (N=151) vs placebo (n=160): Dry Mouth 34% vs 7%; Constipation 10% vs 3%; Dyspepsia 7% vs 4%; Fatigue 7% vs 4%; Weight Gain 7% vs 1%; Somnolence 50% vs 12%; Dizziness 10% vs 4%; Dysarthria 5% vs 0%; and Nasal Congestion 5% vs 1%

[1] Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed, but included the following: headache.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (50%), dry mouth (34%), dizziness (10%), constipation (10%), weight gain (7%), dysarthria (5%), and nasal congestion (5%).

Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Long-Term, Placebo-Controlled Trials

In a longer-term placebo-controlled trial, adult patients with schizophrenia who remained clinically stable on SEROQUEL XR during open-label treatment for at least 4 months were randomized to placebo (n=103) or to continue on their current SEROQUEL XR (n=94) for up to 12 months of observation for possible relapse, the adverse reactions reported were generally consistent with those reported in the short-term, placebo-controlled trials. Insomnia (8.5%) and headache (7.4%) were the only adverse events reported by 5% or more patients.

Adverse Reactions that occurred in <5% of patients and were considered drug-related (incidence greater than placebo and consistent with known pharmacology of drug class) in order of decreasing frequency:

heart rate increased, hypotension, weight increased, tremor, akathisia, increased appetite, blurred vision, postural dizziness, pyrexia, dysarthria, dystonia, drooling, syncope, tardive dyskinesia, dysphagia, leukopenia, and rash.

Adverse Reactions in clinical trials with quetiapine and not listed elsewhere in the label:

abnormal dreams and nightmares, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels, restless legs syndrome, and elevations in serum creatine phosphokinase (not associated with NMS).

Extrapyramidal Symptoms:

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.

Adults: In placebo-controlled clinical trials with quetiapine, utilizing doses up to 800 mg per day, the incidence of any adverse reactions potentially related to EPS ranged from 8% to 11% for quetiapine and 4% to 11% for placebo.

In three-arm placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 8% for SEROQUEL XR and 8% for SEROQUEL (without evidence of being dose related), and 5% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) was generally low and did not exceed 3% for any treatment group.

At the end of treatment, the mean change from baseline in Simpson-Angus Scale total score and Barnes Akathisia Rating Scale Global Assessment score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups. The incidence of extrapyramidal symptoms was consistent with that seen with the profile of SEROQUEL in schizophrenia patients.

In a placebo-controlled clinical trial for the treatment of bipolar depression utilizing 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 4.4% for SEROQUEL XR and 0.7% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dystonia, hypertonia) did not exceed 1.5% for any individual adverse reaction.

In a placebo-controlled clinical trial for the treatment of bipolar mania, utilizing the dose range of 400-800 mg/day of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 6.6% for SEROQUEL XR and 3.8% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dystonia, restlessness, and cogwheel rigidity) did not exceed 2.0% for any adverse reaction.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% for SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% for SEROQUEL and 1.1% for placebo.

Increased Appetite

Adults: Data on increased appetite appear earlier within this section and in "Adverse Reactions that occurred in <5% of Patients" (both in this section).

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increased appetite was 7.6% for SEROQUEL compared to 2.4% for placebo. In a 26-week open-label study that enrolled patients from the above two pediatric trials, the incidence of increased appetite was 10% for SEROQUEL.

Vital Signs and Laboratory Values

Hyperglycemia, hyperlipidemia, weight gain and orthostatic hypotension have been reported with quetiapine [see **Warnings and Precautions**].

Neutrophil Counts

In three-arm SEROQUEL XR placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $<1.5 \times 10^9$/L was 1.5% in patients treated with SEROQUEL XR and 1.5% for SEROQUEL, compared to 0.8% in placebo-treated patients.

In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $<1.0 \times 10^9$/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine, compared to 0.1% (2/1349) in patients treated with placebo. Patients with a pre-existing 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 should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors [see **Warnings and Precautions**].

ECG Changes:

3.9% of SEROQUEL XR patients, and 3.4% of placebo patients, had tachycardia (>120 bpm) at any time during the trials. SEROQUEL XR was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute for placebo. This is consistent with the rates for SEROQUEL. The incidence of adverse reactions of tachycardia was 3% for SEROQUEL XR compared to 1% for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. The slight tendency for tachycardia may be related to quetiapine's potential for inducing orthostatic changes [see **Warnings and Precautions**].

Post Marketing Experience

Adverse reactions reported since market introduction which were temporally related to SEROQUEL therapy includes anaphylactic reaction and galactorrhea.

Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy hyponatremia, myocarditis rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and decreased platelets.

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been reported.

DRUG INTERACTIONS

The risks of using SEROQUEL XR in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL XR, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine.

Because of its potential for inducing hypotension, SEROQUEL XR may enhance the effects of certain antihypertensive agents.

SEROQUEL XR may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Quetiapine

Phenytoin

Coadministration of quetiapine (250 mg three times/day) and phenytoin (100 mg three times/day) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL XR may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate) [see **Dosage and Administration**].

Divalproex

Coadministration of quetiapine (150 mg twice daily) and divalproex (500 mg twice daily) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine

Thioridazine (200 mg twice daily) increased the oral clearance of quetiapine (300 mg twice daily) by 65%.

Cimetidine

Administration of multiple daily doses of cimetidine (400 mg three times daily for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg three times daily). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors

Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL XR is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, erythromycin, protease inhibitors).

Fluoxetine, Imipramine, Haloperidol, and Risperidone

Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg twice daily), haloperidol (7.5 mg twice daily), or risperidone (3 mg twice daily) with quetiapine (300 mg twice daily) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam

The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg three times daily dosing.

Divalproex

The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10 to 12% when divalproex (500 mg twice daily) was administered with quetiapine (150 mg twice daily). The mean oral clearance of total valproic acid (administered as divalproex 500 mg twice daily) was increased by 11% in the presence of quetiapine (150 mg twice daily). The changes were not significant.

Lithium

Concomitant administration of quetiapine (250 mg three times daily) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine

Administration of multiple daily doses up to 750 mg/day (on a three times daily schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of SEROQUEL XR use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of SEROQUEL XR on labor and delivery in humans is unknown.

Nursing Mothers
SEROQUEL XR was excreted into human milk. Caution should be exercised when SEROQUEL XR is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years [see **Warnings and Precautions** and **Adverse Reactions**].

Geriatric Use
Sixty-eight patients in clinical studies with SEROQUEL XR were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL XR in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL XR, 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 in the elderly. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients.

Renal Impairment
Clinical experience with SEROQUEL XR in patients with renal impairment is limited.

Hepatic Impairment
Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed [see **Dosage and Administration** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

DRUG ABUSE AND DEPENDENCE
Controlled Substance
SEROQUEL XR is not a controlled substance.

Abuse
SEROQUEL XR has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL XR (eg, development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE
Human Experience
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose [see **Warnings and Precautions**]. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

Management of Overdosage
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL XR. Similarly it is reasonable to expect that the α-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL XR. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since β stimulation may worsen hypotension in the setting of quetiapine-induced α blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PATIENT COUNSELING INFORMATION
Information for Patients
[see Medication Guide in full Prescribing Information]

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL XR and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL XR.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [see **Warnings and Precautions**].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is not approved for elderly patients with dementia-related psychosis [see **Warnings and Precautions**].

Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should be monitored [see **Warnings and Precautions**].

Hyperlipidemia

Patients should be advised that elevations in total cholesterol, LDL and triglycerides may occur [see **Warnings and Precautions**].

Weight Gain

Patients should be advised that they may experience weight gain [see **Warnings and Precautions**].

Neuroleptic Malignant Syndrome (NMS)

Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever [see **Warnings and Precautions**].

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing, which may lead to falls), especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [see **Warnings and Precautions**].

Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL XR [see **Warnings and Precautions**].

Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation (which may lead to falls), especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine [see **Warnings and Precautions**].

Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine [see **Use in Specific Populations**].

Concomitant Medication

As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs [see **Warnings and Precautions**].

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see **Warnings and Precautions**].

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Challenges in the Diagnosis of Schizoaffective Disorder

Schizoaffective disorder is a difficult-to-manage mental illness that may affect approximately one-third of all patients who present with acute or chronic psychosis. It is less prevalent than schizophrenia, yet is still one of the more common, chronic, and disabling mental illnesses.[1-3]

Schizoaffective disorder represents a significant challenge for patients and their families—even arriving at a proper diagnosis can be difficult.[2]

The essential feature of schizoaffective disorder is an uninterrupted period of illness, during which the characteristic symptoms of schizophrenia (eg, delusions, hallucinations, and negative symptoms) are experienced along with either a major depressive, manic, or mixed mood episode.[2]

But the timing of when these symptoms appear is also important: a patient must experience a period of at least 2 weeks free from mood symptoms while still experiencing schizophrenia-like symptoms. However, the mood episode must represent a substantial portion of the total duration of the illness.[2]

References: 1. National Alliance on Mental Illness of Franklin County. *Schizoaffective Disorder Fact Sheet.* National Alliance on Mental Illness; 2007. **2.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed [text revision]. Washington, DC: APA; 2000. **3.** Canuso CM, Kosik-Gonzalez C, Kalali K, et al. Frequency of schizoaffective disorder diagnosis in patients with psychotic disorders using the Mini-International Neuropsychiatric Interview [abstract]. *Schizophr Res.* 2008;98:67.

Models used for illustrative purposes only.

A reconsideration of schizoaffective disorder—symptomatology and timing—may be of great benefit.

Successfully distinguishing schizoaffective disorder from other mental illnesses requires a carefully conducted longitudinal history with patients and caregivers.[2] For those patients with previous diagnoses of schizophrenia or mood disorders who are still struggling for better mental wellness, a reconsideration of schizoaffective disorder—symptomatology and timing—may be of great benefit.

discovery treatment education outreach

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CHANTIX® (varenicline) TABLETS + GET QUIT® Plan

Recommend free personalized support with every CHANTIX prescription.

You play an important role in helping your patients quit smoking, but you can't be there at every step to provide behavioral support. That's why the GETQUIT Plan was created. GETQUIT is on call to help provide smoking cessation follow-up and 24/7 personalized online and phone support. It's free for patients taking CHANTIX. So why not offer these benefits with every prescription?

Learn more at www.getquit.com.

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

IMPORTANT SAFETY INFORMATION

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

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

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

www.pfizerpro.com/chantix

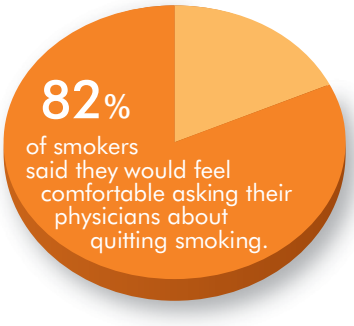
Please see accompanying brief summary of Prescribing Information.

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

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

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

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



You can help make a difference in minutes.

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

Two questions may help start the quit conversation.

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

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

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

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

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

Give your patients a plan with their prescription.

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

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

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

Trained, professional support.

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

Patient follow-up.

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

Customizable support.

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

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

Brief summary of full Prescribing Information.

CHANTIX®
(varenicline) Tablets

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

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

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

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

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

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

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

WARNINGS
Neuropsychiatric Symptoms and Suicidality

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

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

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

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

Angioedema and Hypersensitivity Reactions.

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

Serious Skin Reactions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Post-Marketing Experience:

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

Special Populations

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

Dosing in elderly patients and patients with impaired hepatic function No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See **PRECAUTIONS, Geriatric Use**).

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

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

Rx only

July 2009, Version 4.0

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Chief, Department of Psychiatry

UMDNJ–Robert Wood Johnson Medical School at Camden, New Jersey, Cooper University Hospital offers an excellent opportunity for a Board Certified Chief, Department of Psychiatry, interested in stimulating the growth and development of the department, including outpatient and inpatient services, enhancing the education of students and residents, and research participation. This is a full time faculty position in the Department of Psychiatry located in Camden, New Jersey. There is tremendous opportunity to rapidly expand the outpatient practice of Psychiatry in the suburbs of Southern New Jersey. The department consists of a dynamic team of six BC/BE Adult and Child Psychiatrists. The planned expansion to a four year medical school with Rowan University offers a unique opportunity to serve in a leadership role in the formation of a cutting edge, state-of-the-art medical school. Board Certification and a commitment to the education of residents and medical students is essential. Academic appointment with UMDNJ – Robert Wood Johnson Medical School at Camden will be commensurate with experience. Competitive guaranteed salary and excellent benefits offered.

Please submit curriculum vitae to the Search Committee Chair:

Robin L. Perry, M.D.
Chief, Department of Obstetrics and Gynecology
3 Cooper Plaza, Suite 221
Camden, NJ 08103

Email: perry-robin@cooperhealth.edu
boardman-eileen@cooperhealth.edu (Administrative Director)
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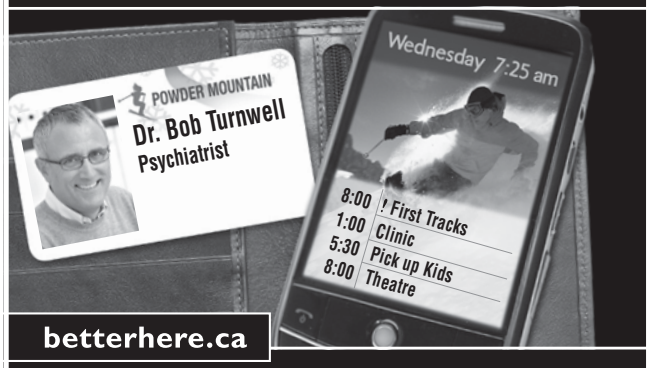

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PSYCHIATRIST

The Department of Psychiatry and the Lineberger Comprehensive Cancer Center of the University of North Carolina (UNC) School of Medicine at Chapel Hill are seeking an early career psychiatrist to join the UNC Psycho-oncology Service.

DESCRIPTION

This is a full time fixed-term position at the (Clinical track) Clinical Assistant or Clinical Associate Professor level. This clinical service is a component of the UNC Comprehensive Cancer Support Program.

Responsibilities will include: providing inpatient and outpatient clinical consultation and psychiatric management for cancer patients; medical leadership for a multidisciplinary psycho-oncology team; teaching medical students, residents, and other health care trainees and clinicians; and participation in the clinical research activities of the Comprehensive Cancer Support Program.

The successful candidate should have strong clinical skills, a record of scholarly achievement; evidence of effective leadership and demonstrated ability to promote a collegial environment that fosters ongoing collaboration. Candidates should have clinical experience working with cancer patients as evidenced by completion of a fellowship in psycho-oncology or psychosomatic medicine, or similar training at the interface of psychiatry and medicine. Special consideration will be given to candidates with an established record of extramural funding.

Applicants must have an M.D. and be eligible for North Carolina licensure. Rank and salary will be commensurate with experience.

CONTACT

Applicants should forward curriculum vitae and three letters of reference to Donald L. Rosenstein, M.D., Director, Comprehensive Cancer Support Program, 3134 Physicians Office Building, 170 Manning Drive, CB# 7305, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7305

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For consideration, please send your curriculum vitae to: **Staten Island University Hospital, Attn: Dr. Mark Jarrett, 500 Seaview Ave, Staten Island, NY 10305. Email: mark_jarrett@siuh.edu. Fax: (718) 226-8109**
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Send CV by December 21, 2009 to:

Ena Casas
Department of Psychiatry
University of Illinois at Chicago
1601 W. Taylor, M/C 912
Chicago, IL 60612

Fax: 312-413-1228

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Adult Psychiatrist

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

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

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

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

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

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

SAINT LOUIS UNIVERSITY

Department of Veterans Affairs

Director of Residency Training

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

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

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

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

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

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

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

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Interested candidates possessing the requirements listed should forward a resume or CV to:

Kathleen M. Carr, SPHR, Ancora Psychiatric Hospital
301 Spring Garden Road, Ancora, NJ 08037-9699
Fax: 609-567-7294, Email: aph.resume@dhs.state.nj.us

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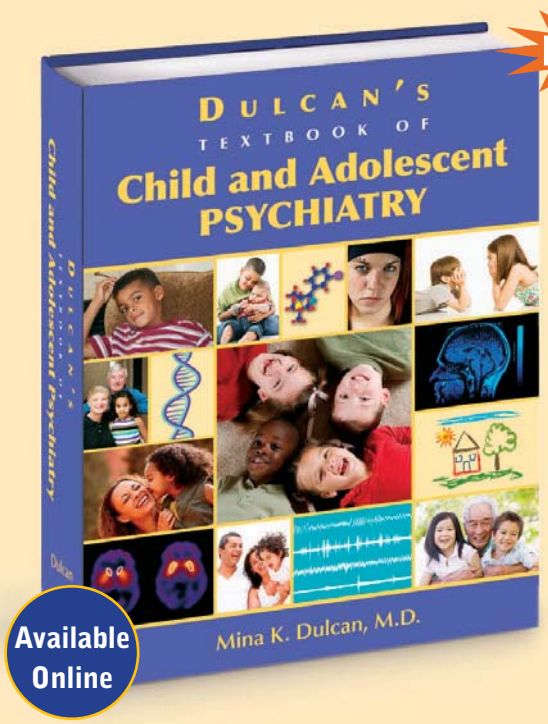

Dulcan's Textbook of Child and Adolescent Psychiatry

Edited by Mina K. Dulcan, M.D.

Dulcan's Textbook of Child and Adolescent Psychiatry supplants the previous textbook edited by Jerry Wiener and Mina Dulcan—not with a new edition, but rather a new book that offers a fresh look at the field of child mental health. It preserves Wiener's vision of a clinically focused textbook useful to trainees and practitioners in a variety of specialties, providing the most up-to-date and comprehensive text in child and adolescent psychiatry as presented by more than 110 contributors who distill their knowledge and expertise into a single authoritative volume.

Each chapter highlights what we know about evidence-based practices in assessment and treatment, while sections on future research point toward current pressing questions. At the end of each chapter are educational summary points. Of the 65 chapters, 56 feature new lead authors, chosen to represent the expertise of disciplines ranging from pediatrics and neurology to sleep medicine and family therapy.

AMONG ITS KEY FEATURES:

- Chapters on evaluation are developmentally focused, with a separate chapter for each age range.
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- Eighteen chapters on specific disorders encompass clinical description, diagnosis, epidemiology, comorbidity, etiology, prevention, prognosis, evaluation, treatment approaches, and research directions.
- Special topics include new chapters on bereavement and traumatic grief; ethnic, cultural, and religious issues; aggression and violence; and fundamentals of genetics relevant to child and adolescent psychiatry.
- Additional chapters address special clinical considerations such as children of ill parents AND legal/ethical issues
- Wide-ranging emphasis on treatment—expanded from seven to eighteen chapters—includes psychopharmacology, brain-based innovative treatments, and a spectrum of psychosocial approaches that focus on individual, family, therapeutic milieu, and systemic models of care.
- A new section on consultation provides guidance on interactions with schools, primary care practitioners, and the juvenile justice system.

Scholarly and practical, *Dulcan's Textbook of Child and Adolescent Psychiatry* is a core resource for child and adolescent psychiatry training and will also serve as a reference for practitioners in psychiatry, pediatrics, neurology, psychology, nursing, and social work.

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