

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 treatment²

*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 torsades 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 D₂ 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/mm³) should discontinue INVEGA® SUSTENNA™ and have their WBC followed until recovery.

NOW APPROVED

FOR ACUTE AND MAINTENANCE TREATMENT OF SCHIZOPHRENIA
RETHINK THE WAY YOU TREAT

NEW ONCE-MONTHLY
INVEGA® SUSTENNA™
paliperidone palmitate extended-release
injectable suspension

**ACT EARLIER
WITH NEW ONCE-MONTHLY
INVEGA® SUSTENNA™**

- Once-monthly dosing³
- Demonstrated safety and tolerability profile^{†‡3}
- Significantly delayed time to relapse in the longer-term maintenance study³

[†]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.



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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 ($C_{max\ ss} = 113\text{ ng/mL}$) 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 $C_{max\ ss} = 50\text{ ng/mL}$). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss} = 35\text{ ng/mL}$, 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 $\geq 7\%$ 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 $\geq 7\%$ 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 $\geq 7\%$ from double-blind phase to endpoint) was met by 6% of INVEGA® SUSTENNA™-treated subjects compared with

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 D₂ 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/mm³) 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; Nausea 3, 4, 4, 3, 2, 2, 2; Toothache 1, 1, 3, 1, 2, 3; Vomiting 4, 5, 4, 2, 3, 2, 2; **General disorders and administration 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, 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 aminotransferase increased 2, 0, 2, 1, 1, 1, 1; Weight increased 1, 4, 4, 1, 1, 1, 2; **Musculoskeletal and connective 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, 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, 13, 12, 10, 13; Nightmare <1, 2, 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, 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

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. ^aFor 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) ^bFor Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint ^cFor 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 ^dPercent 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/m² 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/m² 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/m² 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.

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 \geq 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 overdose 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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IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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GET  Plan

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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 emergency 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 **DOSEAGE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSEAGE 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 $\geq 5\%$ 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 $\geq 1\%$ 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 ($\geq 1\%$ 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			
Rhinorrhoea	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. **HEPATOBIILIARY 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.

DOSE 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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With the recommended starting dose —
NEW SAPHRIS® delivers effective symptom
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SAPHRIS® is an atypical
antipsychotic agent indicated for:

- Acute treatment of schizophrenia in adults
- Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults



We have a lot to look forward to

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 that seen in placebo-treated patients
- Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared to a rate of 2.6% in the placebo group
- Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature
- SAPHRIS® is not approved for the treatment of patients with dementia-related psychosis

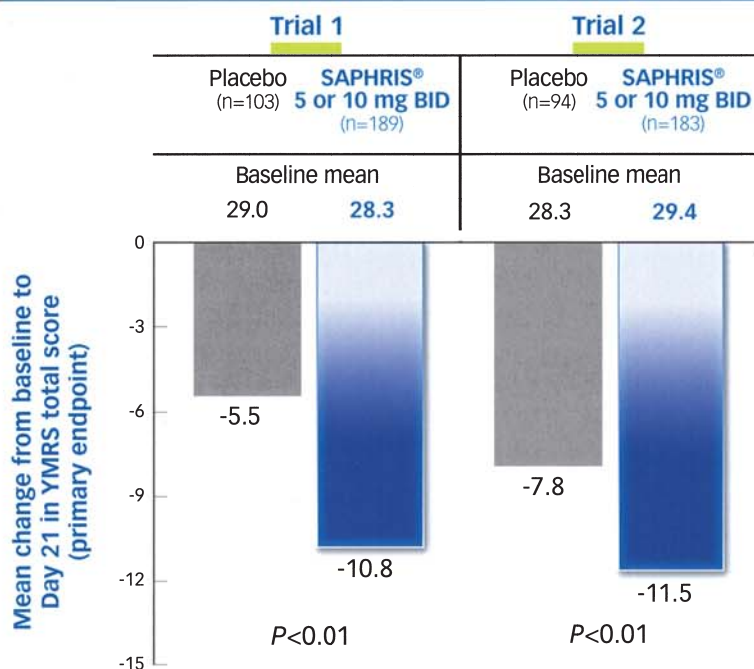
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NEW Saphris® (asenapine)
sublingual tablets 5 and 10 mg
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With the recommended starting dose Effective symptom control in acute mania...

In 2 similarly designed, 3-week, multicenter, randomized, double-blind, placebo-controlled trials in adults receiving SAPHRIS® 5 or 10 mg twice daily (BID)

SAPHRIS® demonstrated significant improvement in Young Mania Rating Scale (YMRS) total score at endpoint¹



Recommended starting dose for manic or mixed episodes associated with bipolar I disorder^a

10 mg BID



AM



PM

90% of the patients studied were maintained at the 10-mg BID dose^b

^aThe dose can be decreased to 5 mg BID if there are adverse effects.

^bOn the second and subsequent days of the trials, the dose could be lowered to 5 mg twice daily, based on tolerability, but less than 10% of patients had their dose reduced. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

Indication

- SAPHRIS® is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults
- The physician who elects to use SAPHRIS® for extended periods for either schizophrenia or bipolar I disorder should periodically reevaluate the long-term risks and benefits of the drug for the individual patient

Cerebrovascular Adverse Events

- In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. SAPHRIS® 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 administration of antipsychotic drugs, including SAPHRIS®
- NMS can cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure
- Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems

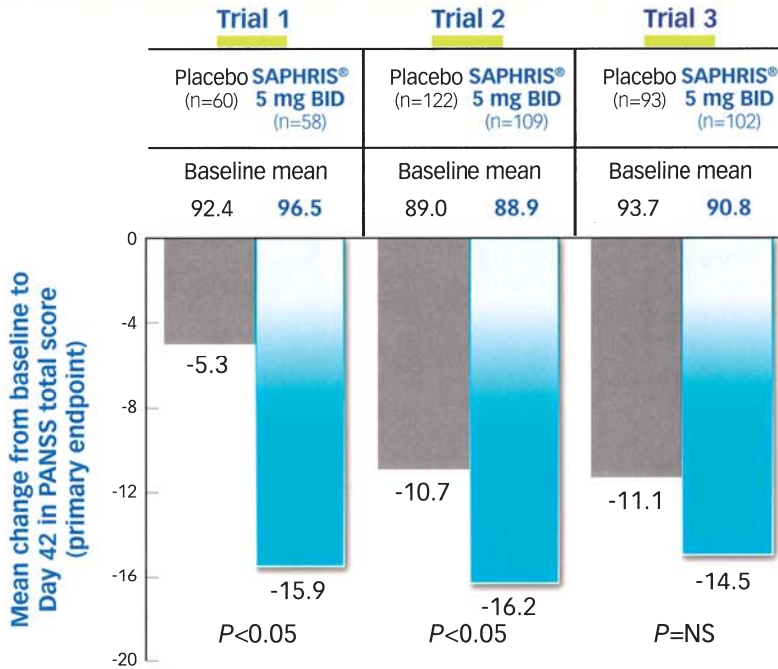
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and schizophrenia



In 2 short-term (6-week), multicenter, randomized, double-blind, placebo-controlled trials in adults

SAPHRIS® demonstrated significant improvement in Positive and Negative Syndrome Scale (PANSS) total score at endpoint¹



In Trial 3, SAPHRIS® could not be statistically distinguished from placebo

Recommended starting dose for schizophrenia

5 mg BID

In acute treatment, the recommended starting dose is also the target dose^c

^cIn controlled trials, there was no suggestion of added benefit with the higher dose, but there was a clear increase in certain adverse reactions. The safety of doses above 10 mg twice daily has not been evaluated in clinical studies.

Indication

- SAPHRIS® is indicated for the acute treatment of schizophrenia in adults
- The physician who elects to use SAPHRIS® for extended periods for either schizophrenia or bipolar I disorder should periodically reevaluate the long-term risks and benefits of the drug for the individual patient

Leukopenia, Neutropenia, and Agranulocytosis

- In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS®
- Patients with a preexisting low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and SAPHRIS® should be discontinued at the first sign of a decline in WBC in the absence of other causative factors

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NEW SAPHRIS®

Selected safety information — Glucose

Warnings and Precautions

Hyperglycemia and Diabetes Mellitus

- Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics
- Patients with risk factors for diabetes mellitus who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and 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 also undergo fasting blood glucose testing
- In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the antipsychotic drug

Laboratory test abnormalities:

Glucose in a long-term trial (at the end of 52 weeks)¹

- Results from a multicenter, randomized, double-blind, active-controlled, flexible-dose study of 908 adults with schizophrenia or schizoaffective disorder. SAPHRIS® patients received 5 or 10 mg BID
- Patients taking SAPHRIS® 5 or 10 mg BID experienced a mean increase from baseline in glucose of 2.4 mg/dL

Laboratory test abnormalities: Glucose in short-term trials

- Short-term bipolar mania trials were 3 weeks in duration, and short-term schizophrenia trials were 6 weeks in duration

Percent of patients with fasting glucose elevations ≥ 126 mg/dL (at endpoint)

	Bipolar mania	Schizophrenia	
SAPHRIS®	4.9%	7.4%	■ SAPHRIS® 5 or 10 mg BID
Placebo	2.2%	6%	■ SAPHRIS® 5 mg BID

Mean change from baseline in fasting serum glucose (mg/dL)

	Bipolar mania	Schizophrenia	
SAPHRIS®	-0.6	+3.2	■ SAPHRIS® 5 or 10 mg BID
Placebo	-0.6	-1.6	■ SAPHRIS® 5 mg BID

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.

Selected safety information — Weight gain



Warnings and Precautions

Weight gain in a long-term trial (at the end of 52 weeks)

- Results from a multicenter, randomized, double-blind, active-controlled, flexible-dose study of 908 adults with schizophrenia or schizoaffective disorder. SAPHRIS® patients received 5 or 10 mg BID

Percent of patients with a ≥7% increase in body weight

Overall 14.7%	By BMI category at baseline	Low BMI (<23) n=295	Medium BMI (23-27) n=290	High BMI (>27) n=302
		22%	13%	9%

Mean weight gain for SAPHRIS® patients at 52 weeks: 0.9 kg

Mean weight change from baseline by BMI

By BMI category at baseline	Low BMI (<23) n=295	Medium BMI (23-27) n=290	High BMI (>27) n=302
	1.7 kg	1.0 kg	0 kg

Weight gain in short-term trials

- Short-term bipolar mania trials were 3 weeks in duration, and short-term schizophrenia trials were 6 weeks in duration

Percent of patients with ≥7% increase in body weight

	Bipolar mania	Schizophrenia
SAPHRIS®	5.8%	4.9%
Placebo	0.5%	2.0%

■ SAPHRIS® 5 or 10 mg BID
■ SAPHRIS® 5 mg BID

In short-term bipolar mania and schizophrenia trials, there were differences in mean weight gain between SAPHRIS® and placebo groups

	Bipolar mania	Schizophrenia
SAPHRIS®	+1.3 kg	+1.1 kg
Placebo	+0.2 kg	+0.1 kg

■ SAPHRIS® 5 or 10 mg BID
■ SAPHRIS® 5 mg BID

NEW Saphris® (asenapine)
 sublingual tablets 5 and 10 mg
Treat for today and tomorrow

NEW SAPHRIS®

Additional important safety information

Warnings and Precautions

Hyperprolactinemia

- Like other drugs that antagonize dopamine D₂ receptors, SAPHRIS® can elevate prolactin levels, and the elevation can persist during chronic administration. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds

Tardive Dyskinesia (TD)

- The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase
- However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD
- If signs and symptoms appear, discontinuation should be considered

QT Prolongation

- SAPHRIS® was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo
- No patients treated with SAPHRIS® experienced QTc increases ≥ 60 msec from baseline measurements, nor did any experience a QTc of ≥ 500 msec
- SAPHRIS® should be avoided in combination with other drugs known to prolong QTc interval, in patients with congenital prolongation of QT interval or a history of cardiac arrhythmias, and in circumstances that may increase the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval

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
- SAPHRIS® is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia

Body Temperature Regulation

- Appropriate care is advised when prescribing SAPHRIS® for patients who will be experiencing conditions that 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

Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects

- SAPHRIS® may induce orthostatic hypotension and syncope
- SAPHRIS® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, conditions which would predispose them to hypotension, and in the elderly
- SAPHRIS® should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, respiratory or central nervous system depression
- Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs

Potential for Cognitive and Motor Impairment

- Somnolence was reported in patients treated with SAPHRIS®
- 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 SAPHRIS® therapy does not affect them adversely

Suicide

- The possibility of suicide attempt is inherent in psychotic illnesses and bipolar disorder. Close supervision of high-risk patients should accompany drug therapy
- Prescriptions for SAPHRIS® should be written for the smallest quantity of tablets in order to reduce the risk of overdose

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.

Additional important safety information



Warnings and Precautions

Hepatic Impairment

- SAPHRIS® is not recommended in patients with severe hepatic impairment

Drug Interactions

- The risks of using SAPHRIS® in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of SAPHRIS®, caution should be used when it is taken in combination with other centrally acting drugs or alcohol
- Coadministration of SAPHRIS® with strong CYP1A2 inhibitors (fluvoxamine) or compounds which are both CYP2D6 substrates and inhibitors (paroxetine) should be done with caution

Seizures

- SAPHRIS® should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (eg, Alzheimer's dementia)

Commonly observed adverse reactions (≥5% and at least twice that for placebo)

Short-term bipolar trials^a

	Placebo	SAPHRIS® 5 or 10 mg BID
Somnolence	6%	24%
Dizziness	3%	11%
EPS other than akathisia	2%	7%
Weight increased	<1%	5%

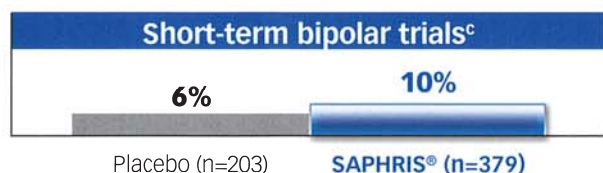
^aShort-term bipolar mania trials were 3 weeks in duration.

Short-term schizophrenia trials^b

	Placebo	SAPHRIS® 5 or 10 mg BID
Akathisia	3%	6%
Oral hypoesthesia (numbing of the tongue)	1%	5%
Somnolence	7%	13%

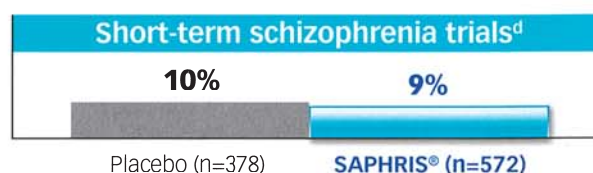
^bShort-term schizophrenia trials were 6 weeks in duration.

Rates of discontinuation due to adverse events



^cShort-term bipolar mania trials were 3 weeks in duration.

- The most common and likely drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS® (rate of at least 1% and at least twice the placebo rate) were anxiety (1.1%) and oral hypoesthesia (1.1%)



^dShort-term schizophrenia trials were 6 weeks in duration.

- There were no drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS® at the rate of at least 1% and at least twice the placebo rate

NEW Saphris® (asenapine)
sublingual tablets 5 and 10 mg
Treat for today and tomorrow

NEW SAPHRIS delivers



A starting dose with proven efficacy

In manic or mixed episodes associated with bipolar disorder:

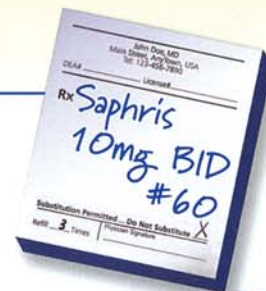
- Significant improvement in YMRS total score
- Significant improvement in the CGI-BP Severity of Illness score (mania)
- The recommended starting dose of SAPHRIS® is 10 mg sublingually twice daily

In the acute treatment of schizophrenia:

- Significant improvement in PANSS total score
- The recommended starting and target dose of SAPHRIS® is 5 mg sublingually twice daily

With documented safety and tolerability

For more information, please visit our Web site at www.SAPHRIS.com



A first-line treatment option



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 that seen in placebo-treated patients
- Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared to a rate of 2.6% in the placebo group
- Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature
- SAPHRIS® is not approved for the treatment of patients with dementia-related psychosis

Reference: 1. Data on file, Schering Corporation.

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.



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SAPHRIS®

(asenapine) sublingual 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 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 that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. 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. SAPHRIS® (asenapine) is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

1.1 Schizophrenia

SAPHRIS is indicated for the acute treatment of schizophrenia in adults [see Clinical Studies (14.1)]. The physician who elects to use SAPHRIS for extended periods in schizophrenia should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient [see Dosage and Administration (2.1)].

1.2 Bipolar Disorder

SAPHRIS is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults [see Clinical Studies (14.2)]. If SAPHRIS is used for extended periods in bipolar disorder, the physician should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient [see Dosage and Administration (2.2)].

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 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 reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions (5.1)].

5.3 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SAPHRIS. 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. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) 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 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.

5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause Tardive Dyskinesia (TD) is unknown.

The risk of developing TD 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 TD, 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, SAPHRIS should be prescribed in a manner that is most likely to minimize the occurrence of TD. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of TD appear in a patient on SAPHRIS, drug discontinuation should be considered. However, some patients may require treatment with SAPHRIS despite the presence of the syndrome.

5.5 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. In clinical trials of SAPHRIS, the occurrence of any adverse reaction related to glucose metabolism was less than 1% in both the SAPHRIS and placebo treatment groups. 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, which did not include SAPHRIS, suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics included in these studies.

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 antipsychotic drug.

5.6 Weight Gain

In short-term schizophrenia and bipolar mania trials, there were differences in mean weight gain between SAPHRIS-treated and placebo-treated patients. In short-term, placebo-controlled schizophrenia trials, the mean weight gain was 1.1 kg for SAPHRIS-treated patients compared to 0.1 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 4.9% for SAPHRIS-treated patients versus 2% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean weight gain for SAPHRIS-treated patients was 1.3 kg compared to 0.2 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 5.8% for SAPHRIS-treated patients versus 0.5% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia or schizoaffective disorder, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 14.7%. Table 1 provides the mean weight change from baseline and the proportion of patients with a weight gain of $\geq 7\%$ categorized by Body Mass Index (BMI) at baseline:

TABLE 1: Weight Change Results Categorized by BMI at Baseline: Comparator-Controlled 52-Week Study in Schizophrenia

	BMI < 23 SAPHRIS N=295	BMI 23 - ≤ 27 SAPHRIS N=290	BMI > 27 SAPHRIS N=302
Mean change from Baseline (kg)	1.7	1	0
% with $\geq 7\%$ increase in body weight	22%	13%	9%

5.7 Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects

SAPHRIS may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its α_1 -adrenergic antagonist activity. In short-term schizophrenia trials, syncope was reported in 0.2% (1/572) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0.3% (1/378) of patients treated with placebo. In short-term bipolar mania trials, syncope was reported in 0.3% (1/379) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0% (0/203) of patients treated with placebo. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, syncope was reported in 0.6% (11/1953) of patients treated with SAPHRIS.

Four normal volunteers in clinical pharmacology studies treated with either intravenous, oral, or sublingual SAPHRIS experienced hypotension, bradycardia, and sinus pauses. These spontaneously resolved in 3 cases, but the fourth subject received external cardiac massage. The risk of this sequence of hypotension, bradycardia, and sinus pause might be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

Patients should be instructed about nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). SAPHRIS should be used with caution in (1) 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); and (2) in the elderly. SAPHRIS should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, respiratory or central nervous system depression [see Drug Interactions (7)]. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

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 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 SAPHRIS should be discontinued at the first sign of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue SAPHRIS and have their WBC followed until recovery.

5.9 QT Prolongation

The effects of SAPHRIS on the QT/QTc interval were evaluated in a dedicated QT study. This trial involved SAPHRIS doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily, and placebo, and was conducted in 151 clinically stable patients with schizophrenia, with electrocardiographic assessments throughout the dosing interval at baseline and steady state. At these doses, SAPHRIS was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo. No patients treated with SAPHRIS experienced QTc increases ≥60 msec from baseline measurements, nor did any patient experience a QTc of ≥500 msec.

Electrocardiogram (ECG) measurements were taken at various time points during the SAPHRIS clinical trial program (5 mg or 10 mg twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for SAPHRIS and placebo in these short-term trials. There were no reports of Torsade de Pointes or any other adverse reactions associated with delayed ventricular repolarization.

The use of SAPHRIS should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalolol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that 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 bradycardia; hypokalemia or hypomagnesemia; and presence of congenital prolongation of the QT interval.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D₂ receptors, SAPHRIS can elevate prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecostasia, 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. In SAPHRIS clinical trials, the incidences of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo [see Adverse Reactions (6.2)].

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. 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.

5.11 Seizures

Seizures were reported in 0% and 0.3% (0/572, 1/379) of patients treated with doses of 5 mg and 10 mg twice daily of SAPHRIS, respectively, compared to 0% (0/503, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, seizures were reported in 0.3% (5/1953) of patients treated with SAPHRIS. As with other antipsychotic drugs, SAPHRIS should be used with caution 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 patients 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was reported in patients treated with SAPHRIS. It was usually transient with the highest incidence reported during the first week of treatment. In short-term, fixed-dose, placebo-controlled schizophrenia trials, somnolence was reported in 15% (41/274) of patients on SAPHRIS 5 mg twice daily and in 13% (26/208) of patients on SAPHRIS 10 mg twice daily compared to 7% (26/378) of placebo patients. In short-term, placebo-controlled bipolar mania trials of therapeutic doses (5-10 mg twice daily), somnolence was reported in 24% (90/379) of patients on SAPHRIS compared to 6% (13/203) of placebo patients. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, somnolence was reported in 18% (358/1953) of patients treated with SAPHRIS. Somnolence (including sedation) led to discontinuation in 0.6% (12/1953) of patients in short-term, placebo-controlled trials.

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 SAPHRIS therapy does not affect them adversely.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. In the short-term placebo-controlled trials for both schizophrenia and acute bipolar disorder, the incidence of adverse reactions suggestive of body temperature increases was low (≤1%) and comparable to placebo. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, the incidence of adverse reactions suggestive of body temperature increases (pyrexia and feeling hot) was ≤1%. Appropriate care is advised when prescribing SAPHRIS for patients who will be experiencing conditions that 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.

5.14 Suicide

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

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia was reported in 0.2% and 0% (1/572, 0/379) of patients treated with therapeutic doses (5-10 mg twice daily) of SAPHRIS as compared to 0% (0/378, 0/203) of patients treated with placebo

in short-term schizophrenia and bipolar mania trials, respectively. During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, dysphagia was reported in 0.1% (2/1953) of patients treated with SAPHRIS.

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SAPHRIS is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia [see also Warnings and Precautions (5.1)].

5.16 Use in Patients with Concomitant Illness

Clinical experience with SAPHRIS in patients with certain concomitant systemic illnesses is limited [see Clinical Pharmacology (12.3)].

SAPHRIS has not been evaluated 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 SAPHRIS, caution should be observed in cardiac patients [see Warnings and Precautions (5.6)].

6 ADVERSE REACTIONS

The most common adverse reactions (≥5% and at least twice the rate on placebo) in schizophrenia were akathisia, oral hypoesthesia, and somnolence.

The most common adverse reactions (≥5% and at least twice the rate on placebo) in bipolar disorder were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight increased.

The information below is derived from a clinical trial database for SAPHRIS consisting of over 3350 patients and/or normal subjects: exposed to one or more sublingual doses of SAPHRIS. Of these subjects, 1953 (1480 in schizophrenia and 473 in acute bipolar mania) were patients who participated in multiple-dose effectiveness trials of therapeutic doses (5 or 10 mg twice daily, with a total experience of approximately 611 patient-years). A total of 486 SAPHRIS-treated patients were treated for at least 24 weeks and 293 SAPHRIS-treated patients had at least 52 weeks of exposure.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced a treatment-emergent adverse event of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2 Clinical Studies Experience

Adult Patients with Schizophrenia: The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of three 6-week fixed-dose trials and one 6-week flexible-dose trial) in which sublingual SAPHRIS was administered in doses ranging from 5 to 10 mg twice daily.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9% of SAPHRIS-treated subjects and 10% of placebo subjects discontinued due to adverse reactions. There were no drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS at the rate of at least 1% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in SAPHRIS-Treated Schizophrenic Patients: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 2.

TABLE 2: Adverse Reactions Reported in 2% or More of Subjects in one of the SAPHRIS Dose Groups and Which Occurred at Greater Incidence Than in the Placebo group in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo N=378	SAPHRIS 5 mg twice daily N=274	SAPHRIS 10 mg twice daily N=208	All SAPHRIS ^a 5 or 10 mg twice daily N=572
Gastrointestinal disorders				
Constipation	6%	7%	4%	5%
Dry mouth	1%	3%	1%	2%
Oral hypoesthesia	1%	6%	7%	5%
Salivary hypersecretion	0%	<1%	4%	2%
Stomach discomfort	1%	<1%	3%	2%
Vomiting	5%	4%	7%	5%
General disorders				
Fatigue	3%	4%	3%	3%
Irritability	<1%	2%	1%	2%
Investigations				
Weight increased	<1%	2%	2%	3%
Metabolism disorders				
Increased appetite	<1%	3%	0%	2%
Nervous system disorders				
Akathisia ^a	3%	4%	11%	6%
Dizziness	4%	7%	3%	5%
Extrapyramidal symptoms (excluding akathisia) ^a	7%	9%	12%	10%
Somnolence ^b	7%	15%	13%	13%
Psychiatric disorders				
Insomnia	13%	16%	15%	15%
Vascular disorders				
Hypertension	2%	2%	3%	2%

^a Akathisia includes: akathisia and hyperkinesia.

^b Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia).

^c Somnolence includes the following events: somnolence, sedation, and hypersomnia.

^d Also includes the Flexible-dose trial (N=90).

Dose-Related Adverse Reactions: Of all the adverse reactions listed in Table 2, the only apparent dose-related adverse reaction was akathisia.

Adult Patients with Bipolar Mania: The following findings are based on the short-term placebo-controlled trials for bipolar mania (a pool of two 3-week flexible-dose trials) in which sublingual SAPHRIS was administered in doses of 5 mg or 10 mg twice daily.

Adverse Reactions Associated with Discontinuation of Treatment: Approximately 10% (38/379) of SAPHRIS-treated patients in short-term, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with about 6% (12/203) on placebo. The most common adverse reactions associated with discontinuation in subjects treated with SAPHRIS (rates at least 1% and at least twice the placebo rate) were anxiety (1.1%) and oral hypoesthesia (1.1%) compared to placebo (0%).

Adverse Reactions Occurring at an Incidence of 2% or More Among SAPHRIS-Treated Bipolar Patients: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute therapy (up to 3-weeks in patients with bipolar mania) are shown in Table 3.

TABLE 3: Adverse Reactions Reported in 2% or More of Subjects in one of the SAPHRIS Dose Groups and Which Occurred at Greater Incidence Than in the Placebo Group in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo N=203	SAPHRIS 5 or 10 mg twice daily* N=379
Gastrointestinal disorders		
Dry mouth	1%	3%
Dyspepsia	2%	4%
Oral hypoesthesia	<1%	4%
Toothache	2%	3%
General disorders		
Fatigue	2%	4%
Investigations		
Weight increased	<1%	5%
Metabolism disorders		
Increased appetite	1%	4%
Musculoskeletal and connective tissue disorders		
Arthralgia	1%	3%
Pain in extremity	<1%	2%
Nervous system disorders		
Akathisia	2%	4%
Dizziness	3%	11%
Dysgeusia	<1%	3%
Headache	11%	12%
Other extrapyramidal symptoms (excluding akathisia) [†]	2%	7%
Somnolence [‡]	6%	24%
Psychiatric disorders		
Anxiety	2%	4%
Depression	1%	2%
Insomnia	5%	6%

* SAPHRIS 5 to 10 mg twice daily with flexible dosing.

[†] Extrapyramidal symptoms included: dystonia, blepharospasm, torticollis, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, gait disturbance, masked facies, and tremor (excluding akathisia).

[‡] Somnolence includes the following events: somnolence, sedation, and hypersomnia.

Dystonia: Antipsychotic 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.

Extrapyramidal Symptoms: In the short-term, placebo-controlled schizophrenia and bipolar mania trials, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). The mean change from baseline for the all-SAPHRIS 5 mg or 10 mg twice daily treated group was comparable to placebo in each of the rating scale scores.

In the short-term, placebo-controlled schizophrenia trials, the incidence of reported EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 10% versus 7% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 6% versus 3% for placebo. In short-term placebo-controlled bipolar mania trials, the incidence of EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 7% versus 2% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 4% versus 2% for placebo.

Laboratory Test Abnormalities: Glucose: The effects on fasting serum glucose levels in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes (see also Warnings and Precautions (5.5)). In the short-term placebo-controlled schizophrenia trials, the mean increase in fasting glucose levels for SAPHRIS-treated patients was 3.2 mg/dL compared to a decrease of 1.6 mg/dL for placebo-treated patients. The proportion of patients with fasting glucose elevations ≥ 126 mg/dL (at Endpoint), was 7.4% for SAPHRIS-treated patients versus 6% for placebo-treated patients. In the short-term, placebo-controlled bipolar mania trials, the mean decreases in fasting glucose levels for both SAPHRIS-treated and placebo-treated patients were 0.6 mg/dL. The proportion of patients with fasting glucose elevations ≥ 126 mg/dL (at Endpoint), was 4.9% for SAPHRIS-treated patients versus 2.2% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of fasting glucose was 2.4 mg/dL.

Lipids: The effects on total cholesterol and fasting triglycerides in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes. In short-term,

placebo-controlled schizophrenia trials, the mean increase in total cholesterol levels for SAPHRIS-treated patients was 0.4 mg/dL compared to a decrease of 3.6 mg/dL for placebo-treated patients. The proportion of patients with total cholesterol elevations ≥ 240 mg/dL (at Endpoint) was 8.3% for SAPHRIS-treated patients versus 7% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in total cholesterol levels for SAPHRIS-treated patients was 1.1 mg/dL compared to a decrease of 1.5 mg/dL in placebo-treated patients. The proportion of patients with total cholesterol elevations ≥ 240 mg/dL (at Endpoint) was 8.7% for SAPHRIS-treated patients versus 8.6% for placebo-treated patients. In short-term, placebo-controlled schizophrenia trials, the mean increase in triglyceride levels for SAPHRIS-treated patients was 3.8 mg/dL compared to a decrease of 13.5 mg/dL for placebo-treated patients. The proportion of patients with elevations in triglycerides ≥ 200 mg/dL (at Endpoint) was 13.2% for SAPHRIS-treated patients versus 10.5% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean decrease in triglyceride levels for SAPHRIS-treated patients was 3.5 mg/dL versus 17.9 mg/dL for placebo-treated subjects. The proportion of patients with elevations in triglycerides ≥ 200 mg/dL (at Endpoint) was 15.2% for SAPHRIS-treated patients versus 11.4% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean decrease from baseline of total cholesterol was 6 mg/dL and the mean decrease from baseline of fasting triglycerides was 9.8 mg/dL.

Transaminases: Transient elevations in serum transaminases (primarily ALT) in the short-term schizophrenia and bipolar mania trials were more common in treated patients but mean changes were not clinically relevant. In short-term, placebo-controlled schizophrenia trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 1.6 units/L compared to a decrease of 0.4 units/L for placebo-treated patients. The proportion of patients with transaminase elevations ≥ 3 times ULN (at Endpoint) was 0.9% for SAPHRIS-treated patients versus 1.3% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 8.9 units/L compared to a decrease of 4.9 units/L in placebo-treated patients. The proportion of patients with transaminase elevations ≥ 3 times upper limit of normal (ULN) (at Endpoint) was 2.5% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. No cases of more severe liver injury were seen.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of ALT was 1.7 units/L.

Prolactin: The effects on prolactin levels in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant changes in mean change in baseline. In short-term, placebo-controlled schizophrenia trials, the mean decreases in prolactin levels were 6.5 ng/mL for SAPHRIS-treated patients compared to 10.7 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥ 4 times ULN (at Endpoint) were 2.6% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in prolactin levels was 4.9 ng/mL for SAPHRIS-treated patients compared to a decrease of 0.2 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥ 4 times ULN (at Endpoint) were 2.3% for SAPHRIS-treated patients versus 0.7% for placebo-treated patients.

In a long-term (52-week), double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean decrease in prolactin from baseline for SAPHRIS-treated patients was 26.9 ng/mL.

Other Adverse Reactions Observed During the Premarketing Evaluation of SAPHRIS:

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with sublingual SAPHRIS at multiple doses of ≥ 5 mg twice daily during any phase of a trial within the database of adult patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions already listed in other parts of Adverse Reactions (6), or those considered in Warnings and Precautions (5) or Overdosage (10) are not included. Although the reactions reported occurred during treatment with SAPHRIS, they were not necessarily caused by it. Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Blood and lymphatic disorders: <1/1000 patients: thrombocytopenia; $\geq 1/1000$ patients and <1/100 patients: anemia

Cardiac disorders: $\geq 1/1000$ patients and <1/100 patients: tachycardia, temporary bundle branch block

Eye disorders: $\geq 1/1000$ patients and <1/100 patients: accommodation disorder

Gastrointestinal disorders: $\geq 1/1000$ patients and <1/100 patients: oral paraesthesia, glossodynia, swollen tongue

General disorders: <1/1000 patients: idiosyncratic drug reaction

Investigations: $\geq 1/1000$ patients and <1/100 patients: hyponatremia

Nervous system disorders: $\geq 1/1000$ patients and <1/100 patients: dysarthria

7 DRUG INTERACTIONS

The risks of using SAPHRIS in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of SAPHRIS, caution should be used when it is taken in combination with other centrally-acting drugs or alcohol.

Because of its $\alpha 1$ -adrenergic antagonism with potential for inducing hypotension, SAPHRIS may enhance the effects of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect SAPHRIS

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors of several of these enzyme pathways on asenapine clearance were studied.

TABLE 4: Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Recommendation
	Coadministered drug	Asenapine	C _{max}	AUC _{0-∞}	
Fluvoxamine (CYP1A2 inhibitor)	25 mg twice daily for 8 days	5 mg Single Dose	+13%	+29%	Coadminister with caution*

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations. AUC: Area under the curve.

TABLE 4: Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers (cont)

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Recommendation
	Coadministered drug	Asenapine	C _{max}	AUC _{0-∞}	
Paroxetine (CYP2D6 inhibitor)	20 mg once daily for 9 days	5 mg Single Dose	-13%	-9%	No SAPHRIS dose adjustment required [see Drug Interactions (7.2)]
Imipramine (CYP1A2/2C19/3A4 inhibitor)	75 mg Single Dose	5 mg Single Dose	+17%	+10%	No SAPHRIS dose adjustment required
Cimetidine (CYP3A4/2D6/1A2 inhibitor)	800 mg twice daily for 8 days	5 mg Single Dose	-13%	+1%	No SAPHRIS dose adjustment required
Carbamazepine (CYP3A4 inducer)	400 mg twice daily for 15 days	5 mg Single Dose	-16%	-16%	No SAPHRIS dose adjustment required
Valproate (UGT1A4 inhibitor)	500 mg twice daily for 9 days	5 mg Single Dose	2%	-1%	No SAPHRIS dose adjustment required

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations. AUC: Area under the curve.

7.2 Potential for SAPHRIS to Affect Other Drugs

Coadministration with CYP2D6 Substrates: *In vitro* studies indicate that asenapine weakly inhibits CYP2D6.

Following coadministration of dextromethorphan and SAPHRIS in healthy subjects, the ratio of dextromethorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indication of CYP2D6 inhibition, treatment with SAPHRIS 5 mg twice daily decreased the DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032. In a separate study, coadministration of a single 75-mg dose of imipramine with a single 5-mg dose of SAPHRIS did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate). Thus, *in vivo*, SAPHRIS appears to be at most a weak inhibitor of CYP2D6. Coadministration of a single 20-mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg SAPHRIS twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure. Asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

SAPHRIS should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of SAPHRIS in pregnant women. In animal studies, asenapine increased post-implantation loss and decreased pup weight and survival at doses similar to or less than recommended clinical doses. In these studies there was no increase in the incidence of structural abnormalities caused by asenapine. SAPHRIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Asenapine was not teratogenic in reproduction studies in rats and rabbits at intravenous doses up to 1.5 mg/kg in rats and 0.44 mg/kg in rabbits. These doses are 0.7 and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 10 mg twice daily given sublingually on a mg/m² basis. Plasma levels of asenapine were measured in the rabbit study, and the area under the curve (AUC) at the highest dose tested was 2 times that in humans receiving the MRHD.

In a study in which rats were treated from day 6 of gestation through day 21 postpartum with intravenous doses of asenapine of 0.3, 0.9, and 1.5 mg/kg/day (0.15, 0.4, and 0.7 times the MRHD of 10 mg twice daily given sublingually on a mg/m² basis), increases in post-implantation loss and early pup deaths were seen at all doses, and decreases in subsequent pup survival and weight gain were seen at the two higher doses. A cross-fostering study indicated that the decreases in pup survival were largely due to prenatal drug effects. Increases in post-implantation loss and decreases in pup weight and survival were also seen when pregnant rats were dosed orally with asenapine.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Asenapine is excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SAPHRIS is administered to a nursing woman. It is recommended that women receiving SAPHRIS should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of SAPHRIS in the treatment of schizophrenia and bipolar mania did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Of the approximately 2250 patients in premarketing clinical studies of SAPHRIS, 1.1% (25) were 65 years of age or over. Multiple factors that might increase the pharmacodynamic response to SAPHRIS, causing poorer tolerance or orthostasis, could be present in elderly patients, and these patients should be monitored carefully.

Elderly patients with dementia-related psychosis treated with SAPHRIS are at an increased risk of death compared to placebo. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning*].

8.6 Renal Impairment

The exposure of asenapine following a single dose of 5 mg was similar among subjects with varying degrees of renal impairment and subjects with normal renal function [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

In subjects with severe hepatic impairment who were treated with a single dose of SAPHRIS 5 mg, asenapine exposures (on average), were 7-fold higher than the exposures observed in subjects with normal hepatic function. Thus, SAPHRIS is not recommended in patients with severe hepatic impairment (Child-Pugh C) [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Human Experience: In premarketing clinical studies involving more than 3350 patients and/or healthy subjects, accidental or intentional acute overdosage of SAPHRIS was identified in 3 patients. Among these few reported cases of overdose, the highest estimated ingestion of SAPHRIS was 400 mg. Reported adverse reactions at the highest dosage included agitation and confusion.

Management of Overdosage: There is no specific antidote to SAPHRIS. The possibility of multiple drug involvement should be considered. An electrocardiogram should be obtained and management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms.

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 SAPHRIS-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.



Manufactured by Catalent UK Swindon Zydus Ltd., Blagrove, Swindon, Wiltshire, SN5 8RU, UK.
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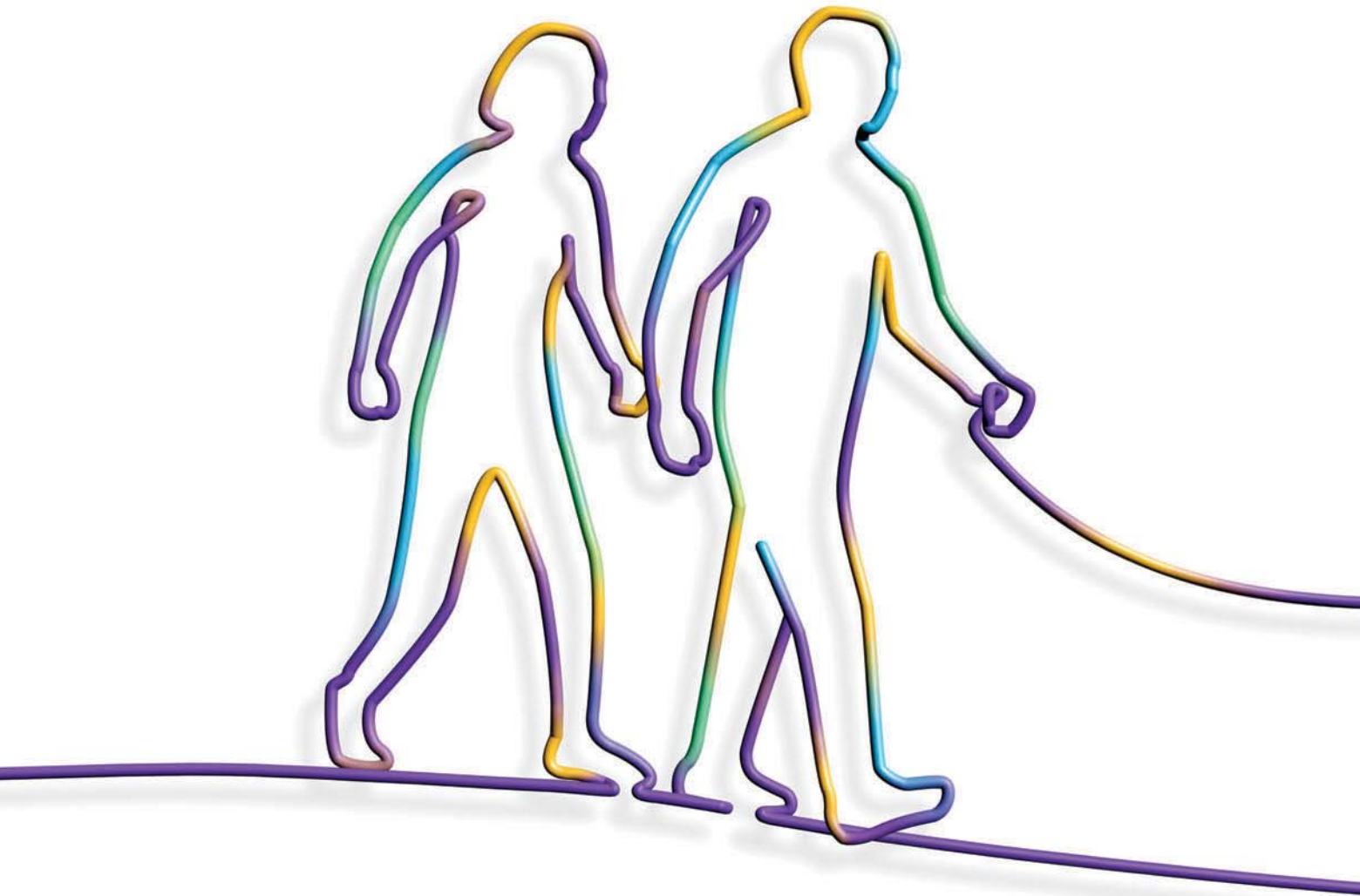
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Important Treatment Considerations for PRISTIQ

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

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

Contraindications

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

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality,

and unusual changes in behavior, especially during the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.

- Development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions have been reported with SNRIs and SSRIs alone, including PRISTIQ treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs that impair the metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. If concomitant use with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.

FOR MAJOR DEPRESSIVE DISORDER

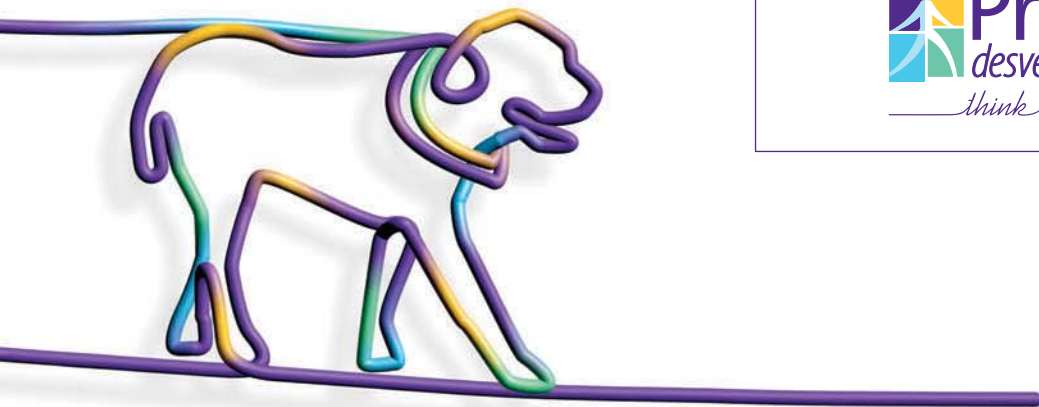
Help your patients

on a path forward with proven SNRI therapy

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

PRISTIQ 50 mg:

- SNRI therapy with efficacy proven in 8-week clinical studies
- Discontinuation rate due to adverse events comparable to placebo in 8-week clinical studies
- One recommended therapeutic dose from the start¹



- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose rather than abrupt cessation is recommended whenever possible.
- The recommended dose in patients with severe renal impairment or

end-stage renal disease (ESRD) is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.

- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

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

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

Please see brief summary of Prescribing Information on adjacent pages.

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

Pristiq[®]
EXTENDED-RELEASE TABLETS



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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. **Monamine 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]. Dose 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. **Hypotension**—Hypotension can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hypotension appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hypotension 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 hypotension 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 $\geq 5\%$ 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 $\geq 2\%$ 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, Paresthesia, 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, Dysacusis; Vascular Disorders:** Hot flush. **Sexual function adverse reactions**—Table 4 shows the incidence of sexual function adverse reactions that occurred in $\geq 2\%$ of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). **Men Only:** Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; **Women Only:** Anorgasmia; **Other adverse reactions observed in premarketing clinical studies:** Other infrequent adverse reactions occurring at an incidence of $< 2\%$ in MDD patients treated with Pristiq were: **Immune system disorders**—Hypersensitivity. **Investigations**—Weight increased, liver function test abnormal, blood prolactin increased. **Nervous system disorders**—Convulsion, syncope, extrapyramidal disorder. **Musculoskeletal and connective tissue disorders**—Musculoskeletal stiffness. **Psychiatric disorders**—Depersonalization, hypomania. **Respiratory, thoracic and mediastinal disorders**—Epistaxis. **Vascular disorders**—Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [see Warnings and Precautions (5.7)]. **Discontinuation events**—Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of $\geq 5\%$ include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information]. **Laboratory**—ECG and vital sign changes observed in MDD clinical studies—The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. **Lipids**—Elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [see Warnings and Precautions (5.8)]. **Proteinuria**—Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. **ECG changes**—Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. **Vital sign changes**—Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. **Orthostatic hypotension**—In the short-term, placebo-controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease ≥ 30 mm Hg from supine to standing position) occurred more frequently in patients ≥ 65 years of age receiving Pristiq (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients < 65 years of age receiving Pristiq (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218). **Adverse Reactions Identified During Post-Approval Use**—The following adverse reaction has been identified during post-approval use of Pristiq. Because post-approval reactions are reported

voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: *Skin and subcutaneous tissue disorders* – Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents**–The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [see *Warnings and Precautions* (5.13)]. **Monoamine Oxidase Inhibitors (MAOIs)**– Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [see *Contraindications* (4.2)]. **Serotonergic Drugs**– Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is administered 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 administered 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 effect [see *Warnings and Precautions* (5.12)]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment**– In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6) in the full prescribing information]. **Hepatic Impairment**– The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see *Clinical Pharmacology* (12.6)].

OVERDOSAGE: Human Experience with Overdosage– There is limited clinical experience with desvenlafaxine succinate overdose 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 overdose 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 overdose 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 overdose, 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 overdose with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR).

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

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- Full name
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IMPORTANT SAFETY INFORMATION FOR INVEGA®

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

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

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

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

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

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly women patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD. Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

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

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are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, INVEGA® elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

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

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including paliperidone. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a decline in WBC and in the absence of other causative factors, discontinuation of INVEGA® should be considered. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms

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

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

or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue INVEGA® and have their WBC followed until recovery.

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

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

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

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

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



INVEGA®

(paliperidone) Extended-Release Tablets

Brief Summary

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA® was not marketed at the time these studies were performed. INVEGA® is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions].

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

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

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

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

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

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

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults

INVEGA® (paliperidone) Extended-Release Tablets

with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA® (C_{max} ss = 113 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which C_{max} ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.

For the three fixed-dose efficacy studies in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA® 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA® had a QTcLD exceeding 500 msec at any time in any of these three studies.

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

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

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

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

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

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA® was not marketed at the time these studies were performed, it is not known if INVEGA® is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperprolactinemia: Like other drugs that antagonize dopamine D₂ receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

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

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

Potential for Gastrointestinal Obstruction: Because the INVEGA® tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA® should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA® should only be used in patients who are able to swallow the tablet whole [see *Dosage and Administration (2.3) and Patient Counseling Information (17.8) in full PI*].

A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract.

Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

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

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

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue INVEGA® and have their WBC followed until recovery.

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

Seizures: During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. Like other antipsychotic drugs, INVEGA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

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

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for INVEGA® should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

subjects received flexible doses of INVEGA® (3-12 mg once daily). Both studies included subjects who received INVEGA® either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

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

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia: Table 1 enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those that occurred in 2% or more of subjects treated with INVEGA® in any of the dose groups, and for which the incidence in INVEGA®-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

Table 1. Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizophrenia in Three Short-Term, Fixed-Dose, Placebo-Controlled Clinical Trials*: Body System or Organ Class Dictionary-Derived Term followed by Percent of Patients Reporting Event Placebo (N=355) first, INVEGA® 3 mg once daily (N=127) second, 6 mg once daily (N=235) third, 9 mg once daily (N=246) fourth, 12 mg once daily (N=242) fifth: Total percentage of subjects with adverse reactions: 37, 48, 47, 53, 59; Cardiac disorders: Atrioventricular block first degree 1, 2, 0, 2, 1; Bundle branch block 2, 3, 1, 3, <1; Sinus arrhythmia 0, 2, 1, 1, <1; Tachycardia 7, 14, 12, 12, 14; Gastrointestinal disorders: Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Salivary hypersecretion <1, <1, 1, 4; General disorders: Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; Nervous system disorders: Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Extrapyrimal symptoms 8, 10, 7, 20, 18; Headache 12, 11, 12, 14, 14; Somnolence 7, 6, 9, 10, 11; Vascular disorders: Orthostatic hypotension 1, 2, 1, 2, 4.

* Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies; one study included once-daily INVEGA® doses of 3 mg and 9 mg, the second study included 6 mg, 9 mg, and 12 mg, and the third study included 6 mg and 12 mg [see Clinical Studies (14) in full PI]. Extrapyrimal symptoms includes the terms dyskinesia, dystonia, extrapyramidal disorder, hypertonia, muscle rigidity, oculogyration, parkinsonism, and tremor. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Adverse reactions for which the INVEGA® incidence was equal to or less than placebo are not listed in the table, but included the following: vomiting.

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

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

Monotherapy versus Adjunctive Therapy: The designs of the two placebo-controlled, 6-week, double-blind trials in subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In

the subject population evaluated for safety, 230 (55%) subjects received INVEGA® as monotherapy and 190 (45%) subjects received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥ 3% difference) in subjects receiving INVEGA® as monotherapy.

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

Cardiac disorders: bradycardia, palpitations

Eye disorders: vision blurred

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

General disorders: edema

Immune system disorders: anaphylactic reaction

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

Psychiatric disorders: nightmare

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

Vascular disorders: hypotension, ischemia

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

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

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

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

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

Extrapyrimal Symptoms (EPS): Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS (Table 3), and (4) incidence of spontaneous reports of EPS (Table 4). For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA® 3 mg and 6 mg doses for any of these EPS measures.

Table 3. Treatment-Emergent Extrapyrimal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies: EPS Group followed by Percentage of Patients Placebo (N=355) first, INVEGA® 3 mg once daily (N=127) second, 6 mg once daily (N=235) third, 9 mg once daily (N=246) fourth, 12 mg once daily (N=242) fifth: Parkinsonism^a 9, 11, 3, 15, 14; Akathisia^b 6, 6, 4, 7, 9; Use of anticholinergic medications^c 10, 10, 9, 22, 22. a: For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items); b: For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2; c: Percent of patients who received anticholinergic medications to treat emergent EPS

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

Dyskinesia group includes: Dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms, oculogyration, trismus

Hyperkinesia group includes: Akathisia, hyperkinesia

Parkinsonism group includes: Bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism
Tremor group includes: Tremor

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

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

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

Dyskinesia group includes: Dyskinesia, muscle twitching

Dystonia group includes: Dystonia, muscle spasms, oculogyration

Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness

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

Tremor group includes: Tremor

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

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

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

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

Other Findings Observed During Clinical Trials: The safety of INVEGA® was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA® in adults with schizophrenia [see Clinical Studies (14) in full PI]. In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

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

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

DRUG INTERACTIONS

Potential for INVEGA® to Affect Other Drugs: Given the primary CNS effects of paliperidone [see Adverse Reactions], INVEGA® should be used with caution in

combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

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

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

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

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

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

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

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

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

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

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

USE IN SPECIFIC POPULATIONS

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

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

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated during the period of organogenesis with up to 8 times the maximum recommended human dose of paliperidone (on a mg/m² basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, there were increases in pup deaths seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m² basis (see risperidone package insert).

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

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

Geriatric Use: The safety, tolerability, and efficacy of INVEGA® were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA® (3 mg to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA® (3 mg to 15 mg once daily) [see Clinical Studies (14) in full PI]. There were no subjects ≥ 65 years of age in the schizoaffective disorder studies.

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

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

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

DRUG ABUSE AND DEPENDENCE

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

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

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

OVERDOSAGE

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

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

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

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

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

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

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

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

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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.

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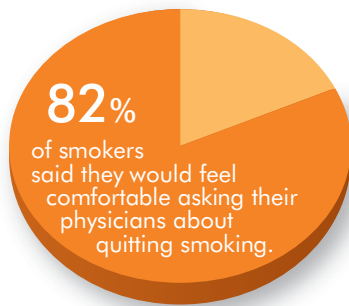
Please see accompanying brief summary of Prescribing Information.

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 smoke⁶ 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.

Nearly 80% of CHANTIX® (varenicline) patients found GETQUIT to be helpful in a recent survey.⁷

Many CHANTIX patients have already used GETQUIT, and here are just a few things they've had to say:

“ ONLY smokers/former smokers know what this process entails. The GETQUIT Plan knows, too. Thanks for knowing what to say or suggest at each step of the way. ”

“ Daily check-ins, online support, and CHANTIX. What a combo. ”

“ It worked for me, and this support, both web-based and phone service, was truly a huge help. Thanks. ”

Encourage patients to enroll as soon as you write a prescription.

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(varenicline) TABLETS

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GET  Plan

GETQUIT is designed to help you continue the support you already provide, and it's free with every CHANTIX prescription. So why not provide your patients extra support at no extra cost?

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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.

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.

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.

www.pfizerpro.com/chantix Please see accompanying brief summary of Prescribing Information.

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 **DOSE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSE 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. 0.3% 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 dose 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 $\geq 5\%$ 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 $\geq 1\%$ 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 group events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies ($\geq 1\%$ 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	3	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
RESPIRATORY/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
Pruritus	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. **HEPATOBIILIARY 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:** 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:** Bradypnea, 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

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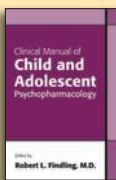
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 9:00am-4:00pm

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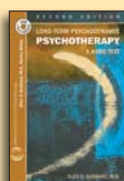


Sunday, May 23
 9:00am-4:00pm

Director: Jesse Wright, M.D., Ph.D., with Judith Beck, Ph.D., Robert Goisman, M.D., and Donna Sudak, M.D.

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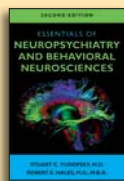


Sunday, May 23
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Director: Glen O. Gabbard, M.D., with Robert Michels, M.D., John Gunderson, M.D., and Gabrielle Hobday, M.D.

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Neuropsychiatry for Veterans



Wednesday, May 26
 8:00am-12:00pm

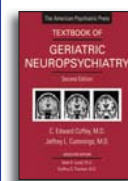
Presented by Stuart C. Yudofsky, M.D., and Thomas Kosten, M.D., with Thomas Newton, M.D., Kimberly Arlinghaus, M.D., and Robin Hurly, M.D.

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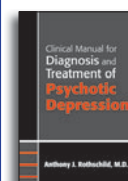


Advances in Neuropsychiatry: The Neuropsychiatry of Emotion and Its Disorders

Monday, May 24
 8:00am-12:00pm

Presented by C. Edward Coffey, M.D., and Randolph B. Schiffer, M.D., with Matthew Menza, M.D., Michael Trimble, M.D., and Robert G. Robinson, M.D.

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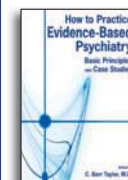


Psychopharmacologic, ECT, and Psychotherapeutic Treatment of Psychotic (Delusional) Depression

Monday, May 24
 1:00pm-5:00pm

Presented by Anthony J. Rothschild, M.D., with Brandon Guardiano, Ph.D.

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How to Practice Evidence-Based Psychiatry: Principles and Case Studies

Tuesday, May 25
 8:00am-12:00pm

Presented by C. Barr Taylor, M.D.

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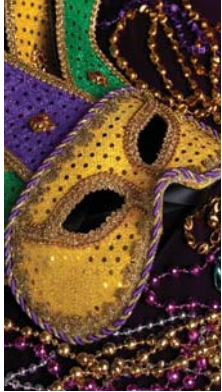
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1. Stop by one of the APA Membership Booths either in the Registration area (near the Registrar) or in the APA Member Center (Exhibit Halls B–D) to fill out an APA Membership Application. The application must be submitted on-site during the meeting at one of these locations.
2. Additional documentation—proof of ACGME-AOA or RCPS(C)—approved psychiatry residency training and a current, valid medical license must be received by APA no later than June 30, 2010.

How Does the Rebate Work?

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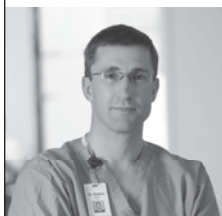
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GEODON® (ziprasidone HCl) Capsules

GEODON® (ziprasidone mesylate) injection for intramuscular use

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 is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients.

DOSAGE AND ADMINISTRATION

Schizophrenia GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment. Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials. **Maintenance Treatment**—While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically stable and then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving GEODON. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment. **Bipolar I Disorder Acute Treatment of Manic or Mixed Episodes**—Dose Selection: Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range 40 mg to 80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg. **Maintenance Treatment** (as an adjunct to lithium or valproate)—Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg to 80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment. **Acute Treatment of Agitation in Schizophrenia Intramuscular Dosing**—The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied. If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon

as possible. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended. Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously. Intramuscular Preparation for Administration GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration. Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **Dosing in Special Populations Oral:** Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. GEODON is not approved for use in children or adolescents. **Intramuscular:** Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

CONTRAINDICATIONS

QT Prolongation Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone 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 ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone 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. Ziprasidone is also contraindicated with other 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**]. Ziprasidone 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 is not approved for the treatment of dementia-related psychosis (see **BOXED WARNING).**

QT Prolongation and Risk of Sudden Death Ziprasidone 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 ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see **CONTRAINDICATIONS**).

QT Prolongation in Clinical Trials A study directly comparing the QT/QT_c prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for ziprasidone 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 ziprasidone on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole

200 mg twice daily). In placebo-controlled trials, oral ziprasidone 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%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. **QT Prolongation and Torsade De Pointes** 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. Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) (see **ADVERSE REACTIONS**). A study evaluating the QT/QT_c prolonging effect of intramuscular ziprasidone, 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 ziprasidone (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 ziprasidone 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 ziprasidone 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 patients had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone 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, ziprasidone'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 ziprasidone 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. **Electrolyte Disturbances May Increase The Risk of QT Prolongation** It is recommended that patients being considered for ziprasidone 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 ziprasidone 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, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone 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** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical anti-psychotics. 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. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia.

PRECAUTIONS

Leukopenia, Neutropenia, and Agranulocytosis In clinical trial and postmarketing experience, events of leukopenia/neutropenia and agranulocytosis (including fatal cases) have been reported temporally related to antipsychotic agents. 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 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 GEODON at the first sign of decline in WBC in the absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue GEODON and have their WBC followed until recovery. **Rash** In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued. **Orthostatic Hypotension** Ziprasidone 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 the patients treated with ziprasidone. Ziprasidone 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). **Seizures** In clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone 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 ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **BOXED WARNING** and **Increased Mortality in Elderly Patients with Dementia-Related Psychosis** in **WARNINGS**). **Hyperprolactinemia** As with other drugs that antagonize dopamine D₂ receptors, ziprasidone 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 reaction in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone 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 ziprasidone therapy does not affect them adversely. **Priapism** One case of priapism was reported in the premarketing database. **Body Temperature Regulation** Although not reported with ziprasidone 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. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce overdose risk. **Patients With Concomitant Illnesses** Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited. Ziprasidone 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 ziprasidone, 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 assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients. **Laboratory Tests** Patients being considered for ziprasidone treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Discontinue ziprasidone in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**).

DRUG INTERACTIONS

(1) Ziprasidone should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents. (4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists. **Effect of Other Drugs on Ziprasidone** *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of ziprasidone. Ketoconazole, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of ziprasidone by about 35-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect ziprasidone pharmacokinetics. Co-administration of 30 mL of Maalox® did not affect ziprasidone pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benzotropine, propranolol, or lorazepam. **Effect of Ziprasidone on Other Drugs** *In vitro* studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement. Ziprasidone 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. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone 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 ziprasidone 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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Lifetime carcinogenicity studies were conducted with ziprasidone 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. Ziprasidone 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** in **PRECAUTIONS**). **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:** Ziprasidone increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced.

USE IN SPECIFIC POPULATIONS

Pregnancy *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of ziprasidone on labor and delivery in humans is unknown. **Nursing Mothers** It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed. **Pediatric Use** The safety and effectiveness of ziprasidone in pediatric patients have not been established. **Geriatric Use** Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, 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 ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**). *Bipolar Mania:* Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone 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 of ≥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 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: 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 ziprasidone 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 (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo. **Dystonia** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. 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. Elevated risk of acute dystonia is observed in males and younger age groups. **Vital Sign Changes** Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. Weight gain was reported as an adverse event in 0.4% of both ziprasidone and placebo patients. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain ($>7\%$ of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a “low” baseline BMI, no mean change for patients with a “normal” BMI, and a 1.3 kg mean weight loss for patients who entered the program with a “high” BMI. **ECG Changes** Ziprasidone is associated with an increase in the QT_c interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone 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 Ziprasidone in Schizophrenia** 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 adverse events are those occurring in fewer than 1/1000 patients. *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 trans-peptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. *Endocrine*—Rare: hypothyroidism, hyperthyroidism, thyroiditis. *Hemic and Lymphatic System*—Infrequent: anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy. Rare: thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. *Metabolic and Nutritional Disorders*—Infrequent: thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase

increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia. Rare: BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. *Musculoskeletal System*—Frequent: myalgia. Infrequent: tenosynovitis. Rare: myopathy. *Nervous System*—Frequent: agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy. Infrequent: paralysis. Rare: myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. *Respiratory System*—Frequent: dyspnea. Infrequent: pneumonia, epistaxis. Rare: hemoptysis, laryngismus. *Skin and Appendages*—Infrequent: maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. *Special Senses*—Frequent: fungal dermatitis. Infrequent: conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia. Rare: eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. *Urogenital System*—Infrequent: impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria. Rare: gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Findings Observed in Trials of Intramuscular Ziprasidone** In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone ($\geq 5\%$) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence of $\geq 1\%$ in Short-Term Fixed-Dose Intramuscular Trials** The following list enumerates the treatment-emergent adverse events that occurred in $\geq 1\%$ of patients during acute therapy with intramuscular ziprasidone: *Body as a Whole*—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. *Cardiovascular*—postural hypotension, hypertension, bradycardia, vasodilation. *Digestive*—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. *Nervous*—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. *Respiratory*—rhinitis. *Skin and Appendages*—furunculosis, sweating. *Urogenital*—dysmenorrhea, priapism. **Other Events Observed During Post-marketing Use** Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following—*Cardiac Disorders*: Tachycardia, torsade de pointes (in the presence of multiple confounding factors), (see **WARNINGS**); *Digestive System Disorders*: Swollen Tongue; *Reproductive System and Breast Disorders*: Galactorrhea, priapism; *Nervous System Disorders*: Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders*: Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders*: Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders*: Enuresis, urinary incontinence; *Vascular Disorders*: Postural hypotension, syncope.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Ziprasidone is not a controlled substance.

OVERDOSAGE

In premarketing trials in over 5400 patients, accidental or intentional overdosage of oral ziprasidone 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 (200/95).



SEE ME FOR WHO I CAN BE

LISA, 32*

Part-time Caterer
Diagnosis: Bipolar Disorder



*Not an actual patient.

Now FDA-approved for the maintenance treatment of bipolar I disorder in adults as an adjunct to lithium or valproate

GEODON is indicated for acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder and for maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. For full symptoms and diagnostic criteria, see the *DSM-IV-TR*[®] (2000).

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

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

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

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

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

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

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