For my patients with schizoaffective disorder,
one treatment comes to mind:

# INVEGA®
(paliperidone)

## the first and only approved acute treatment for schizoaffective disorder[1]

## INVEGA® is an atypical antipsychotic agent indicated for the

- acute and maintenance treatment of schizophrenia[1]
- acute treatment of schizoaffective disorder as monotherapy[1]
- acute treatment of schizoaffective disorder as an adjunct to mood stabilizers and/or antidepressants*[1]

# INVEGA®
## PALIPERIDONE
*Extended-Release Tablets*

www.INVEGA.com

*In 2 clinical studies, the most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. Use of MAOIs was excluded.[1]

***For more information, including study designs and clinical data, please contact your Janssen® representative.***

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

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

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

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

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

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

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

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

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

**Reference: 1.** INVEGA® (paliperidone) [Prescribing Information]. Titusville, NJ., Ortho-McNeil-Janssen Pharmaceuticals, Inc.

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

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

 October 2009 01JN09092

# INVEGA®

(paliperidone) Extended-Release Tablets

**Brief Summary**

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

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

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

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

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

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

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

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

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

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

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

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



The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA® ($C_{max}$ ss = 113 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max}$ ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**INVEGA**® (paliperidone) Extended-Release Tablets

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

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

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

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

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

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

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

**ADVERSE REACTIONS**

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

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

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

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

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

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

**INVEGA**® (paliperidone) Extended-Release Tablets

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

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

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

**Table 1. Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizophrenia in Three Short-Term, Fixed-Dose, Placebo-Controlled Clinical Trials *: Body System or Organ Class** Dictionary-Derived Term followed by **Percent of Patients Reporting Event Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: **Total percentage of subjects with adverse reactions:** 37, 48, 47, 53, 59; **Cardiac disorders:** Atrioventricular block first degree 1, 2, 0, 2, 1; Bundle branch block 2, 3, 1, 3, <1; Sinus arrhythmia 0, 2, 1, 1, <1; Tachycardia 7, 14, 12, 12, 14; **Gastrointestinal disorders:** Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Salivary hypersecretion<10<114; **General disorders:** Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; **Nervous system disorders:** Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Extrapyramidal symptoms 8, 10, 7, 20, 18; Headache 12, 11, 12, 14, 14; Somnolence 7, 6, 9, 10, 11; **Vascular disorders:** Orthostatic hypotension 1, 2, 1, 2, 4.

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

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

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

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

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

**Cardiac disorders:** bradycardia, palpitations

**Eye disorders:** vision blurred

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

**General disorders:** edema

**Immune system disorders:** anaphylactic reaction

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

**Psychiatric disorders:** nightmare

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

**Vascular disorders:** hypotension, ischemia

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

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

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

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

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

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

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

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

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

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

Hyperkinesia group includes: Akathisia, hyperkinesia

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

Tremor group includes: Tremor

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

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

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

Dyskinesia group includes: Dyskinesia, muscle twitching

Dystonia group includes: Dystonia, muscle spasms, oculogyration

Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness

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

Tremor group includes: Tremor

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

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

**Weight Gain:** Schizophrenia Trials: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, the proportions of subjects meeting a weight gain criterion of $\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.

**INVEGA**® (paliperidone) Extended-Release Tablets

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

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

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

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

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

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

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

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

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

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

**USE IN SPECIFIC POPULATIONS**

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

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

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

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

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

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

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

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these

subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

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

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

**DRUG ABUSE AND DEPENDENCE**

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

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

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

**OVERDOSAGE**

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

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

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

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

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

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

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

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

**Manufactured by:**
ALZA Corporation, Vacaville, CA 95688 *OR*
Janssen Cilag Manufacturing, LLC, Gurabo, Puerto Rico 00778

**Manufactured for:**
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.,
Titusville, NJ 08560

OROS is a registered trademark of ALZA Corporation

 Revised: July 2009

10105905B

# PSYCHIATRY
## *BOARD REVIEW SERIES*
### THE KAUFMAN COURSES

**To Register: www.cnfp.org**

SPONSORED BY MONTEFIORE MEDICAL CENTER CREDIT DESIGNATED BY ALBERT EINSTEIN COLLEGE OF MEDICINE
Accreditation Statement: Albert Einstein College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

### CLINICAL NEUROLOGY FOR PSYCHIATRISTS
**David Myland Kaufman, MD**

This intensive three-day weekend course, offered for the 38th year, is designed for psychiatrists in practice and in residency as an update and board preparation. Focusing on essential topics, the course uses lectures, an extensive syllabus, and the new edition of *Clinical Neurology for Psychiatrists*, David M. Kaufman (6th edition, Elsevier).

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 25 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

**LOS ANGELES**
The Westin Hotel at the Los Angeles Airport
5400 West Century Boulevard
Los Angeles, CA 90045
Friday, February 12 to Sunday, February 14, 2010
7:45 AM – 5:30 PM

**NEW YORK**
The Graduate Center
City University of New York (CUNY)
Friday, March 19 to Sunday, March 21, 2010
8:15 AM – 6:00 PM

### PSYCHIATRY FOR PSYCHIATRISTS
**Andrea J. Weiss, MD and David Myland Kaufman, MD**

This two-day course will be a pre-test that complements standard psychiatry review courses and completes the review in *Clinical Neurology for Psychiatrists*. An expert group of faculty who are experienced and well-informed about modern psychiatry and test-taking strategies present essential information through a series of test-type questions utilizing an audience response system and using answers for discussions and explanations.

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 16 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

**LOS ANGELES**
The Westin Hotel at the Los Angeles Airport
5400 West Century Boulevard
Los Angeles, CA 90045
Monday, February 15 to Tuesday, February 16, 2010
7:45 AM – 5:30 PM

**NEW YORK**
The Graduate Center
City University of New York (CUNY)
Monday, March 22 to Tuesday, March 23, 2010
8:15 AM – 6:00 PM

## MAINTENANCE OF CERTIFICATION COURSES

### THE PSYCHIATRY RECERT COURSE
**Dan Smuckler, MD, Andrea J. Weiss, MD and David Myland Kaufman, MD**

This intensive two-day course designed for psychiatrists reviews the psychiatric information likely to appear on the recertification examination. It will cover current evidence-based treatments for psychiatric disorders, emphasizing clinical matters and advances in diagnosis and treatment. Presentation of the material will be in a mixed format, with both lecture and question-and-answer utilizing audience response system keypads.

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 14.5 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

**NEW YORK**
SUNY College of Optometry
Joseph and Roberta Schwarz Theater
33 West 42nd Street
(Between 5th and 6th Avenues)
New York, NY 10036
Friday, January 8 to Saturday, January 9, 2010
7:45 AM – 6:00 PM

### THE CHILD AND ADOLESCENT PSYCHIATRY RECERT COURSE
**Audrey Walker, MD, Andrea J. Weiss, MD and David Myland Kaufman, MD**

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

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 7.5 AMA PRA Category 1 Credit(s).™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

**NEW YORK**
SUNY College of Optometry
Joseph and Roberta Schwarz Theater
33 West 42nd Street
(Between 5th and 6th Avenues)
New York, NY 10036
Sunday, January 10, 2010
7:45 AM – 6:00 PM

**NEW COURSE**

**FOR MORE INFORMATION**
- **Web site** Course Information or To Register: **www.cnfp.org**
- **Write:** CCME, 3301 Bainbridge Avenue, Bronx, NY 10467
- **E-mail:** cme@montefiore.org
- **Call:** 718-920-6674 • **Fax:** 718-798-2336

# SEE ME FOR WHO I CAN BE

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

*Not an actual patient.

## Do you see your patients' full potential?

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

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

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with certain other QT-prolonging drugs. **GEODON has been associated with prolongation of the $QT_c$ interval. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. Patients who are at risk for significant electrolyte disturbances should have baseline measurements performed before initiating GEODON. Patients on diuretics should be monitored.**

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

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

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

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

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

*Please see brief summary of prescribing information on adjacent page.*

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

GEODON®
(ziprasidone HCl) Capsules

**BRIEF SUMMARY.** See package insert for full prescribing information.

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

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

**CONTRAINDICATIONS — *QT Prolongation:*** Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS — *Increased Mortality in Elderly Patients with Dementia-Related Psychosis*: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING). *QT Prolongation and Risk of Sudden Death*: GEODON use should be avoided in combination with other drugs that are known to prolong the $QT_c$ interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the $QT_c$ interval. Such drugs should not be prescribed with GEODON. A study directly comparing the $QT/QT_c$-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in $QT_c$ from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on $QT_c$ length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the $QT_c$ interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed $QT_c$ intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the $QT/QT_c$ interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller $QT/QT_c$ prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the $QT/QT_c$ prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in $QT_c$ from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in $QT_c$ from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in $QT_c$ from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a $QT_c$ interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of $QT_c$ length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the $QT_c$ interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the $QT_c$ interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged $QT_c$ intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent $QT_c$ measurements >500 msec. *Neuroleptic Malignant Syndrome (NMS)*:** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS — *General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).** Hyperprolactinemia: As with other drugs that antagonize dopamine $D_2$ receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of $QT_c$ prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent $QT_c$ measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and $C_{max}$ of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m$^2$ basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m$^2$ basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m$^2$ basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS — *Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash, and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Dystonia:*** Prolonged abnormal contractions of muscle groups may occur in susceptible individuals during first few days of treatment. Dystonia may occur at any dose level but with greater frequency and severity with high potency and at higher doses of first generation antipsychotic drugs. Elevated risk is observed in males and younger age groups. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (*<23*) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the $QT_c$ interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesterolemia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesterolemia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal symptoms, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE — *Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

Revised August 2008

# Complex puzzles. Comprehensive solutions.

At Western Psychiatric Institute and Clinic of UPMC, we take on complex disorders that some other centers won't even attempt to treat.

But whether a patient has a difficult-to-treat disorder or one more easily treated, teams of specialists in psychiatry, psychopharmacology, clinical psychology, and medicine craft complete, individualized treatment plans that draw upon the latest clinical research, much of it conducted by our own investigators. Whether we're interpreting our clinical trial data or a patient's lab results, our work to advance the understanding and treatment of bipolar disorder, eating disorders, autism, and geriatric behavioral health issues is world-class. In fact, we have one of the world's most comprehensive programs for mood disorders, with research-based treatments for patients at every level of need, at every stage of life.

With more than 400 inpatient psychiatric beds and 75 ambulatory programs, we care for people when they're feeling their worst and support them when they're at their best, back with their families in their home towns. Each year, Western Psychiatric helps some 30,000 people of all ages — at all stages of recovery, from all over the world — live healthier and more productive lives.

UPMC

upmc.com | 1-800-533-UPMC

Affiliated with the **University of Pittsburgh School of Medicine**,
UPMC is ranked among the nation's best hospitals by *U.S.News & World Report*.


## IMPORTANT SAFETY INFORMATION

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

**IMPORTANT SAFETY INFORMATION FOR INVEGA® SUSTENNA™**

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

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

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

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

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

**References: 1.** Mahmoud RA, Engelhart LM, Janagap CC, Oster G, Ollendorf D. Risperidone versus conventional antipsychotics for schizophrenia and schizoaffective disorder: symptoms, quality of life and resource use under customary clinical care. *Clin Drug Invest.* 2004;24:275-286. **2.** Keith SJ, Kane JM, Turner M, Conley RR, Nasrallah HA. Academic highlights: guidelines for the use of long-acting injectable atypical antipsychotics. *J Clin Psychiatry.* 2004;65:120-131. **3.** INVEGA® SUSTENNA™ [Prescribing Information]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc. July 2009.

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

Visit www.invegasustenna.com for more information.

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


August 2009 01PM09034

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

**Brief Summary**

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

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

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

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## ADVERSE REACTIONS

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

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

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

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

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide

a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

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

Dystonia group includes: Dystonia, muscle spasms

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

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

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

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

**Pain Assessment and Local Injection Site Reactions:** In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

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

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

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

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

**DRUG INTERACTIONS**

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

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

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

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

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

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

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

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

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

**USE IN SPECIFIC POPULATIONS**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**DRUG ABUSE AND DEPENDENCE**

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

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

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

**OVERDOSAGE**

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

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

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

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

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

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

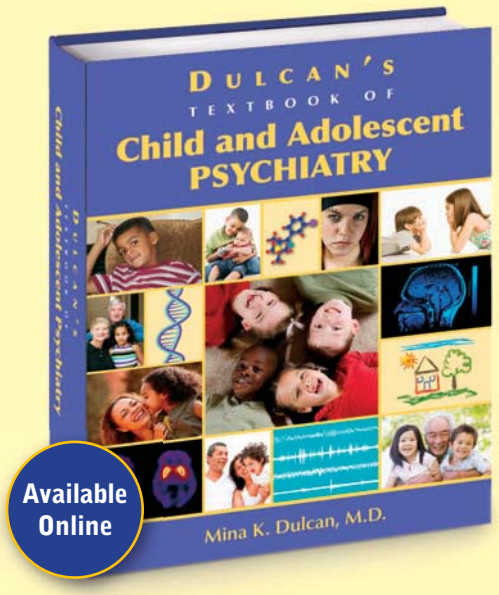
Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe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

Manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

Manufactured for:
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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

Revised: July 2009
 36348B




**Coming October 2009!**

# Dulcan's Textbook of Child and Adolescent Psychiatry

## Edited by Mina K. Dulcan, M.D.

*Special Prepublication Price of 215.00*
*until October 31, 2009 (thereafter $239.00)*

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

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

### Among its key features:

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

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

American Psychiatric Publishing, Inc.
The *First* and *Last* Word in Psychiatry

2010 • 1,104 pages • ISBN 978-1-58562-323-5 • Hardcover • Item #62323
Special Prepublication Price of $215.00 until October 31, 2009 (thereafter $239.00)

**Order Online: www.appi.org • Toll Free: 1-800-368-5777**
**Fax: 703-907-1091 • Email: appi@psych.org** • Find us on Facebook and Twitter. AH938

MetroHealth

Case Western Reserve University School of Medicine

Cleveland, Ohio

## Chair, Department of Psychiatry

Cleveland – MetroHealth System, one of the nation's most successful public health systems seeks candidates for the role of ***Chair, Department of Psychiatry***. A major teaching and research affiliate of Case Western Reserve University School of Medicine since 1914, MetroHealth is comprised of a 731 bed major medical center, a rehabilitation hospital, two long term care/skilled nursing centers, an outpatient surgery center and a network of community based healthcare centers. Metro Medical Center, a magnet status hospital offers the most advanced techniques in treating complex medical problems and is one of the premier comprehensive healthcare providers in Northeast Ohio.

The new chair will oversee the provision of psychiatric services and lead the department in recruitment of physicians and other clinical professionals. He/she will collaborate with clinical leaders and administration at MetroHealth in defining, developing and implementing strategy for psychiatric programs. The chair will be expected to enhance the department by strengthening its research, education and programmatic initiatives.

The successful candidate will be an outstanding clinician and respected academic leader with demonstrated ability to effectively inspire, recruit, manage and mentor students, residents and faculty. He/she should demonstrate an understanding of the importance of clinical outcomes, investigation, and teaching in a patient driven service culture to the success of a modern teaching and academic psychiatry department. Candidates will need to have a distinguished track record of clinical and professional accomplishments in the psychiatry field and be eligible for an appointment at the associate professor level or higher at Case Western Reserve University School of Medicine.

Nominations, inquires and expressions of interest should be directed to Christine Mackey-Ross or Linda Komnick at Witt/Kieffer, lindak@wittkieffer.com or (847)-304-8754.

**"In employment, as in education, MetroHealth System, an affiliate of Case Western Reserve University School of Medicine is committed to Equal Opportunity and Diversity."**

WITT / KIEFFER

## Department of Veterans Affairs

### Director of Residency Training

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

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

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

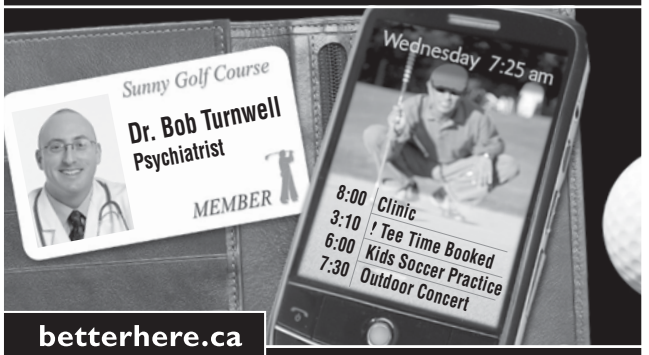
The competitive Training Director candidate will have strong academic credentials, residency administration experience at the site or program level, and demonstrated scholarly ability in a relevant field. The applicant must be board-certified in psychiatry with a minimum of 5 years of post-residency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

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

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

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

## *Life is better for Psychiatrists in Kamloops and Penticton, British Columbia, Canada*




**betterhere.ca**

### *Here's Why...*

Whether you are looking to improve your golf game, longing to hit the trails or looking for cultural enrichment, you can work and enjoy our exceptional four-season playground all in the same day. Enjoy the advantages of a less hurried lifestyle while and the urban amenities available in Kamloops and Penticton BC.

Psychiatrist candidates are eligible for funded recruitment visits and relocation support. Eligibility Canadian Royal College Fellowship (e.g., American Boards) required.

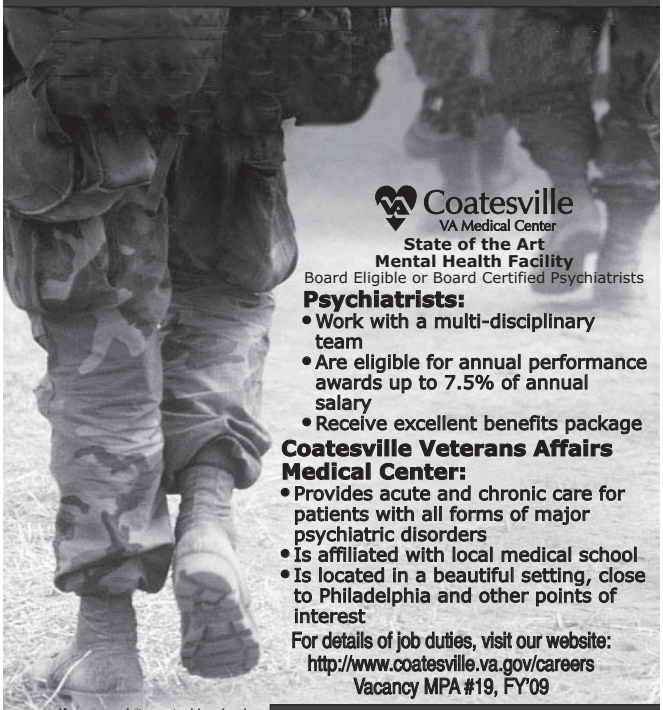
Contact us today and find out why it's better here.

Penticton Kamloops Penticton Kamloops

betterhere.ca 1-877-522-9722 physicianrecruitment@interiorhealth.ca

Interior Health

## SERVING THOSE WHO HAVE SERVED OUR COUNTRY



Coatesville VA Medical Center

**State of the Art Mental Health Facility**

Board Eligible or Board Certified Psychiatrists

**Psychiatrists:**

- Work with a multi-disciplinary team
- Are eligible for annual performance awards up to 7.5% of annual salary
- Receive excellent benefits package

**Coatesville Veterans Affairs Medical Center:**

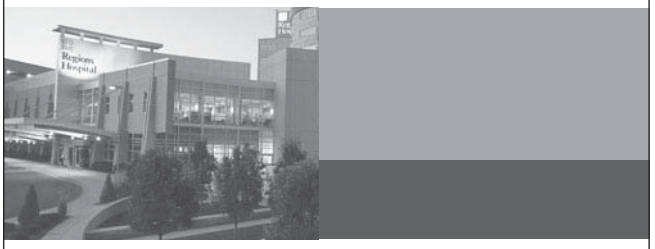
- Provides acute and chronic care for patients with all forms of major psychiatric disorders
- Is affiliated with local medical school
- Is located in a beautiful setting, close to Philadelphia and other points of interest

**For details of job duties, visit our website:**
**http://www.coatesville.va.gov/careers**
**Vacancy MPA #19, FY'09**

If you are interested in sharing your skills and your passion to care for Veterans at Coatesville VA Medical Center, please forward your curriculum vitae to:

Coatesville VA Medical Center (11D)
1400 Blackhorse Hill Road, Coatesville, PA 19320
Attn: Ken Whitehall, AO/COS
Fax: 610-380-4391

# Patient Centered
## *Care Focused*



## Assistant Medical Director Behavioral Health – Inpatient Care

HealthPartners Medical Group is a top multi-specialty group based in Minneapolis/St. Paul, Minnesota. Regions Hospital is our busy NAMI "Provider of the Year" hospital in St. Paul, home to our ER-based short-stay psychiatric unit and inpatient psychiatric facilities.

We are recruiting for an Inpatient Behavioral Health Medical Director at Regions Hospital. In addition to maintaining substantive patient care responsibilities, this consensus-building leader will measure and improve quality of inpatient psychiatric care and patient flow; oversee our Psychiatric Consultation & Liaison Service; engage and supervise Regions Hospital inpatient psychiatrists, moonlighters and Advanced Practice Providers; develop and implement inpatient mental health policies/procedures; and ensure hospital regulatory requirements are met (JCAHO, CMS, MN DMS, etc.). In addition, there will be a substantial role with our psychiatric residents, medical students and NP/PA fellows.

Qualified candidates will have at least two (2) years' experience leading and motivating hospital-based Inpatient Behavioral Health care teams, and at least five (5) years' recent inpatient practice experience. Board Certification in Psychiatry and active, valid MN medical licensure are required. We offer a competitive compensation and benefits package, paid malpractice coverage and a rewarding work environment.

Meet with Dr. Michael Trangle, Associate Medical Director, during the Institute on Psychiatric Services (IPS) Conference, October 8-11, in New York. To make arrangements, please forward your CV and cover letter to: **lori.m.fake@healthpartners.com** or call (800) 472-4695 x1. Apply online at **www.healthpartners.jobs**. EOE

HealthPartners®
*Medical Group*

www.healthpartners.com
www.regionshospital.com

### Enjoy Quality of Life…Practice Quality Medicine…

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

***Flexible schedule with limited call***

***New state of the art facility with 23 inpatient beds***

***24 hour Access Center with an experienced staff***

***Great potential for program growth and development***

We offer a competitive salary, comprehensive benefits and retirement package, paid time off, paid professional liability insurance, CME allowance, relocation assistance, and sign on bonus.

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

**Don't miss an opportunity to become a staff physician with a leader in healthcare!** Please contact Tiffany Ellington, Director of Physician Recruitment, at mcleodphysicianrecruiting.org or 843-777-5169.

**DEPARTMENT OF VETERANS AFFAIRS**
**MEDICAL CENTER**
**DAYTON, OHIO**

The Dayton Veterans Affairs Medical Center (VAMC), in collaboration with Wright State University Boonshoft School of Medicine in Dayton, Ohio, seeks a **Medical Director (Opiate Treatment Program)**, full-time **Psychiatrists**, and one part-time **Psychiatrist (Dual Diagnosis)**, to provide direct patient care in both the residential and outpatient settings. The incumbents must be well versed in the major treatment modalities for diagnosing and treating a wide variety of psychiatric disorders in Veterans. The Medical Center is a 539-bed multi-specialty Dean's Committee Hospital.

Applicants should be board-certified or board eligible. Graduating residents and fellows may apply; have a license from one of the 50 states; and be a citizen or permanent resident or the USA.

Dayton VAMC employees enjoy excellent federal benefits and competitive salaries.

Dayton, the birthplace of flight, is located in the beautiful rolling hills of Southwestern Ohio and offers the convenience of a city, without the hassles. The metropolitan area has five universities, excellent school systems, museums, theaters, and other recreational opportunities, and is the home of Wright-Patterson Air Force Base.

- Dayton VAMC employees enjoy excellent federal benefits and competitive salaries.
- Recruitment incentive and moving/relocation expenses may be authorized.
- Medical Malpractice Claims coverage is provided under the Federal Tort Claims Act.
- The Dayton VA Medical Center has active affiliations with the Wright State University Boonshoft School of Medicine and the School of Professional Psychology.
- Faculty positions and resident teaching opportunities are available at the Wright State University Boonshoft School of Medicine.

Send curriculum vitae with three references to:

Dave Drew, Acting Chief Mental Health Service, Dayton VA Medical Center
Mental Health Service, 4100 West Third Street, Dayton, OH 45428
E-mail: Dave.Drew@va.gov, Tel: 937-268-6511, ext. 2667, Fax: 937-267-3924

*The VA is an Equal Opportunity Employer*

# Department of Veterans Affairs

## Psychiatrists - VA Boston Healthcare System

The VA Boston Healthcare System (VABHS) is recruiting academically oriented psychiatrists for a number of key positions in our growing Mental Health Service, which has strong and longstanding affiliations with Harvard Medical School (HMS) and Boston University School of Medicine (BUSM) VABHS is a New England regional referral center for veterans' health care.

### Medical Director, Consultation-Liaison Psychiatry
**West Roxbury Campus:**

VABHS is seeking a Medical Director for the Psychiatry Consultation-Liaison service, West Roxbury campus. We seek a board certified academic psychiatrist with at least 5 years' post-residency experience full time (or equivalent) on an academic C-L service, demonstrated excellence in clinical teaching, strong administrative skills, and the motivation and ability to lead this outstanding clinical teaching service. The C-L service receives more than 1000 consultation requests per year, and is an integral part of a vibrant and exceptional academic environment that features nationally recognized training and research programs, and several VA Clinical Centers of Excellence. Academic appointment is through HMS, commensurate with qualifications. The Medical Director oversees the VA-Brigham Women's Hospital Psychosomatic Fellowship and BUSM and HMS resident and medical student C-L rotations.

### Psychiatrist with expertise in PTSD and treatment for Returning Veterans – Brockton Campus:

VABHS is recruiting a full-time board-certified (board eligible if less than 2 years post-residency) psychiatrist with psychiatric expertise in the treatment of emotional trauma. This position is divided evenly between inpatient and outpatient programs. In the inpatient role, the candidate will join a well-staffed multidisciplinary inpatient treatment team to provide direct clinical services to Returning Veterans or veterans with PTSD. In the outpatient role, the candidate will join a vibrant multidisciplinary PTSD and Center for Returning Veterans treatment team that provides evidence-based clinical care to veterans of all eras including a large cohort of veterans who have recently returned from Iraq and Afghanistan. Duties include support of the academic mission of the medical center, including supervision of psychiatry residents and the opportunity to participate in teaching and research. This position offers a faculty appointment at Harvard Medical School commensurate with experience.

### Outpatient Psychiatrist
**Jamaica Plain and Causeway Campuses:**

We are seeking a full-time board-certified (board eligible if less than 2 years post-residency) psychiatrist in outpatient care at our Jamaica Plain and Causeway campuses. In this role, the candidate will join a vibrant multidisciplinary PTSD and Center for Returning Veterans treatment team that provides evidence-based clinical care to veterans of all eras including Returning Veterans. The candidate will also join an active teaching oriented team involved in the treatment of schizophrenia. There is a significant role for this psychiatrist in the training and supervision of residents and there is the potential to collaborate in clinical research. This position offers a faculty appointment at Boston University School of Medicine commensurate with experience.

**The above positions offer a highly competitive VA salary and exist in an outstanding academic environment with prominent teaching and research programs.**

*Please send a letter of interest, CV, and contact information for three references to:*
**Gary Kaplan, MD, Director, Mental Health Service, VA Boston Healthcare System, 940 Belmont Street, Brockton, MA 02301. Phone: 774-826-2473; email: Gary.Kaplan@va.gov with a copy to vhabhsjobs@med.va.gov**

### Emergency Department Moonlighting Positions
**Brockton Campus:**

VABHS is recruiting board certified (board eligible if less than 5 years post-residency) psychiatrists to provide direct clinical services and clinical supervision of psychiatry residents on evenings and weekends in the Urgent Care Department on our Brockton campus. This position offers competitive compensation and the possibility of an academic appointment for qualified individuals. Hours are 4pm-11pm weekdays and 7am-3pm or 3pm-11pm on Saturdays and Sundays.

*Please send a letter of interest, CV, and contact information for three references to:*
**Ronald Gurrera, MD, Director of Urgent Care Services, Mental Health Service, VA Boston Healthcare System, 940 Belmont Street, Brockton, MA 02301. Phone: 774-826-2473; email: Ronald.Gurrera@va.gov with a copy to vhabhsjobs@med.va.gov.**

VA Boston is an Affirmative Action/Equal Opportunity Employer with a strong institutional commitment to diversity in all areas. These positions will be filled without discrimination. You must be a U.S. citizen to apply.


***Practice innovative psychiatry in a world class system.***

As a VA psychiatrist, you'll be part of an interdisciplinary care team driven to develop innovative approaches to mental health care. You'll translate scientific evidence into daily practice as you tackle one of today's most timely issues – helping America's Veterans reclaim their mental health.

- Practice model based on care needs, not insurance company regulations
- Diverse professional opportunities
- Computerized Patient Record System
- One license/50 states
- Paid medical liability coverage
- Stable health and retirement benefits
- Exceptional education support opportunities (subject to funding availability)
- 26 days annual paid vacation

*Hiring Veterans and non-Veterans*

Department of Veterans Affairs
An Equal Opportunity Employer

***Apply today at***
**www.VAcareers.va.gov/MHP**
***or call* 1-800-949-0002**

## *Mental Health Care Professionals*

*Psychiatrists/Psychologists/Social Workers*
*Clinical Nurse Specialists/Addiction Therapists*

Join VA Northern California Health Care System's (NCHCS) mental health care team and support America's heroes. NCHCS is now hiring mental health care professionals to be part of our interdisciplinary care team; you'll treat patients struggling with the full range of emotional and mental disorders, including PTSD, traumatic brain injuries, mood disorders, substance abuse disorders, and sexual trauma. You'll work in an environment where innovation is encouraged, and scientific evidence directs our practice.

We are now hiring for full and part time positions in Sacramento, Fairfield, Redding and Chico. Call today and be a part of VA's Mental Health Enhancement Initiative.

- Interdisciplinary care team model of practice
- Practice model is based on care needs, not insurance company regulations
- Your out of state license allows you to practice at any of our facilities
- Diverse professional opportunities – clinical, leadership, research, education, and national policy development
- Salary is competitive and based on credentials and experience
- Exceptional paid time off package
- Excellent health and retirement benefits
- Student loan reimbursement of up to $38,000 for psychiatrists, psychologists and psychiatric nurses

Please email Erica Settlemyer, Human Resources Specialist at erica.settlemyer@va.gov

*Department of Veterans Affairs is an Equal Opportunity Employer*

## Atascadero State Hospital

**BE/BC Psychiatrist**

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

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

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

For a prompt and confidential review, send CV to:

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

**We are an equal opportunity employer.**

---

**VA** LONG BEACH
HEALTHCARE SYSTEM

*A Division of VA Desert Pacific*

VA Long Beach Healthcare System is seeking two board certified or board eligible psychiatrists to provide outpatient care who demonstrate excellent clinical care and the ability to work collaboratively with other mental health and primary care providers. Competitive salary, depending on qualifications, with competitive benefits and recruitment incentives are possible. The Veterans Administration is an Equal Opportunity Employer.

To find out more about this exciting opportunity contact:

Larry Albers, MD, Chief of Mental Health
larry.albers@va.gov
562-826-5758

---

# Professor or Associate Professor of Autism

## Harvard Medical School and Director of the Lurie Family Autism Center at Massachusetts General Hospital

Massachusetts General Hospital and Harvard Medical School are jointly seeking a clinical, academic and scientific leader to fill the position of Professor or Associate Professor in the field of Autism at Harvard Medical School and Director of the Lurie Family Autism Center at Massachusetts General Hospital

We are seeking an outstanding clinician, investigator, and teacher who is a distinguished national and international leader in autism. Expertise in leading a complex clinical, research and academic center is imperative. She/he should have a strong vision for achieving excellence in a multi-disciplinary autism center encompassing clinical care, scientific investigation, policy development and advocacy, and training, and an understanding of the opportunities, challenges and special requirements of working within a large academic medical center. Organizational, fiscal, fundraising and interpersonal skills are essential. Candidates should have received an M.D., PhD, or M.D. /Ph.D. degree and be Board Certified in their specialty. Academic credentials should be of sufficient strength to warrant appointment as Professor or Associate Professor at Harvard Medical School.

Interested individuals should send a letter of application and current CV in hard copy and electronic format to:

***Ronald E. Kleinman, MD***
***Chair, ad hoc Search Committee for***
***Director of the Lurie Family Autism Center***
***Chief of Pediatrics, Massachusetts General Hospital***
***55 Fruit Street, Boston, MA 02114***
***rkleinman@partners.org***

*Harvard Medical School and Partners Healthcare System are equal opportunity/affirmative action employers with strong institutional commitments to diversity in their faculty. Women and minority candidates are particularly encouraged to apply.*

HARVARD MEDICAL SCHOOL
MASSACHUSETTS GENERAL HOSPITAL

---

# APA Member Benefits and Services That Make a Difference

- **Bank of America Credit Cards and Financial Tools** — Earn WorldPoints™ Rewards
- **APA Job Bank** — Online career search and recruitment
- **The Psychiatrists' Program** — Medical malpractice insurance for psychiatrists
- **Car Rentals** — Substantial discounts from Alamo, Avis, Budget, Hertz, or National
- **Solveras Payment Systems** — Affordable tools to effectively manage patient payments
- **Magazine Subscriptions** — Save up to 50% off regular subscription rates on magazines
- **Retirement and Investment Planning** — Meet your short and long-term retirement and financial planning goals
- **Legal Consultation** — Find money-saving legal advice with APA's Legal Consultation Plan

*Learn more about these benefits and savings at*
www.psych.org/members corner

***Questions?*** Contact APA Answer Center
Call Toll-Free: **1-888-35-PSYCH**
*From outside the U.S. and Canada call:* ***1-703-907-7300***
Email: **apa@psych.org**

# Index to Advertisers October 2009

The publication of an advertisement in this journal does not imply endorsement of the product or service by the American Psychiatric Association.




## Subscription and Business Information

The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1000 Wilson Blvd., Suite 1825, Arlington, VA 22209-3901. Subscriptions (per year): individual $205.00, international $308.00. For additional subscription options, including single issues and student rates, please contact Customer Service at 1-800-368-5777 or email appi@psych.org. Institutional subscriptions are tier priced. For institutional site license or pricing information, contact Customer Service or visit http://highwire.stanford.edu/tfocis/.

Business communications, address changes, and subscription questions from APA members should be directed to the Division of Member Services: (888) 35-PSYCH (toll-free). Nonmember subscribers should call the Circulation Department (800) 368-5777. Author inquiries should be directed to the Journal editorial office: (703) 907-7885 or (703) 907-7884; fax (703) 907-1096; e-mail ajp@psych.org.

Business Management: Nancy Frey, Director, Publishing Services; Laura G. Abedi, Associate Director, Production; Alison Jones, Advertising Prepress Manager; Robert Pursell, Director, Sales and Marketing.

Pharmaceutical Print Advertising: Frank Cox, Kathleen Harrison, Valentin Torres, Pharmaceutical Media, Inc. 30 East 33rd Street, New York, NY 10016. (212) 685-5010; fax (212) 685-6126; e-mail vtorres@pminy.com.

Nonpharmaceutical and Online Sales: Brian Skepton, (703) 907-7332; e-mail bskepton@psych.org.

Pages are produced using Adobe FrameMaker+ SGML 6.0. Printed by RR Donnelley, Mendota, IL., on acid-free paper effective with Volume 164, Number 11, November 2007.

Periodicals postage paid at Arlington, VA, and additional mailing offices. POSTMASTER: Send address changes to The American Journal of Psychiatry, Circulation Department, American Psychiatric Association, 1000 Wilson Blvd., Suite 1825, Arlington, VA 22209-3901.

Indexed in Abstracts for Social Workers, Academic Abstracts, Biological Abstracts, Chemical Abstracts, Chicago Psychoanalytic Literature Index, Cumulative Index to Nursing Literature, Excerpta Medica, Hospital Literature Index, Index Medicus, International Nursing Index, Nutrition Abstracts, Psychological Abstracts, Science Citation Index, Social Science Source, and Social Sciences Index.

**Venlafaxine Extended Release Tablets (venlafaxine hydrochloride)**

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

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

**INDICATIONS AND USAGE:** Venlafaxine Extended Release Tablets (venlafaxine hydrochloride) are indicated for the treatment of major depressive disorder (MDD) and Social Anxiety Disorder (SAD), also known as Social Phobia, as defined by DSM-IV. Efficacy of venlafaxine in MDD was shown in both short-term trials and a longer-term trial. Efficacy in SAD was established in short-term trials. **CONTRAINDICATIONS:** Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) [see Warnings and Precautions, Potential for interaction with Monoamine Oxidase inhibitors]. **WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk:** Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration (2.5) and Warnings and Precautions (5.7) in the full prescribing information for a description of the risks of discontinuation of Venlafaxine Extended-Release Tablets*]. **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Venlafaxine Extended Release Tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Potential for Interaction With Monoamine Oxidase Inhibitors: Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine hydrochloride, or who recently discontinued venlafaxine hydrochloride prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Venlafaxine Extended Release Tablets should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine hydrochloride before starting an MAOI.** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that Venlafaxine Extended Release Tablets are not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions:** The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with SSRIs and SNRIs alone, including Venlafaxine Extended Release Tablets, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (including MAOIs), with other antipsychotics, or with other dopamine antagonists [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms including mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms *[see Drug Interactions (7.10)]*. Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. The concomitant use of Venlafaxine Extended Release Tablets with MAOIs is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.2)]*. If concomitant treatment of Venlafaxine Extended Release Tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Venlafaxine Extended Release Tablets with serotonin precursors (such as tryptophan supplements) is not recommended *[see Drug Interactions (7.10)]*. Treatment with Venlafaxine Extended Release Tablets and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the patient develops any symptoms of serotonin syndrome or NMS, and supportive symptomatic treatment should be initiated. **Sustained Hypertension:** Venlafaxine hydrochloride is associated with sustained dose-related increases in blood pressure (BP) in some patients. Sustained BP increases could have adverse consequences. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by BP increases. Preexisting hypertension should be controlled before Venlafaxine Extended Release Tablets therapy is initiated. It is recommended that patients receiving Venlafaxine Extended Release Tablets have regular monitoring of BP. For patients experiencing sustained increase in BP, either dose reduction or discontinuation should be considered. **Elevations in Systolic and Diastolic Blood Pressure (SBP, DBP):** In placebo-controlled premarketing studies, there were changes in mean BP. In most indications, a dose-related increase in SBP and DBP was evident. Across all trials, 1.4% of patients receiving extended-release venlaxafine hydrochloride experienced a ≥15 mm Hg increase in supine DBP with BP ≥105 mm Hg, compared to 0.9% of patients in the placebo groups. One percent of patients receiving venlaxafine hydrochloride experienced a ≥20 mm Hg increase in supine SBP with BP ≥180 mm Hg compared to 0.3% of patients in the placebo groups. **Mydriasis:** Mydriasis has been reported in association with venlafaxine hydrochloride; patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma should be monitored. **Discontinuation of Treatment with Venlafaxine Extended Release Tablets:** Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials and retrospective surveys of trials in MDD and SAD. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been associated with the appearance of new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. During marketing of venlafaxine hydrochloride extended-release capsules, other SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration (2.4) in full prescribing information*]. **Insomnia and Nervousness:** Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with venlafaxine hydrochloride extended-release capsules than with placebo in pooled analyses of short-term MDD and other clinical studies, as shown in *Table 5 in the full prescribing information*. **Changes in Weight:** In some placebo-controlled trials in MDD, 4% of the patients treated with venlafaxine hydrochloride extended-release capsules and 1% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 6 months of treatment. The safety and efficacy of venlafaxine therapy in combination with weight loss agents have not been established. Co-administration of Venlafaxine Extended Release Tablets and weight loss agents is not recommended. Venlafaxine Extended Release Tablets are not indicated for weight loss alone or in combination with other products. **Changes in Height:** Pediatric Patients: In the six-month, open-label MDD study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (<12 years old) than for adolescents (≥12 years old). **Changes in Appetite:** Adult Patients: Treatment-emergent anorexia was more commonly reported for patients treated with venlafaxine hydrochloride extended-release capsules than for placebo-treated patients in the pool of short-term, double-blind, placebo-controlled MDD (8% vs 4%) and SAD (20% vs 2%) studies. Pediatric Patients: In placebo-controlled trials in MDD and another disorder, 10% of patients aged 6-17 treated with venlafaxine hydrochloride extended-release capsules for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia. **Activation of Mania/Hypomania:** Mania or hypomania occurred during MDD studies in 0.3% of patients treated with extended release venlafaxine compared with 0% of placebo patients. With immediate release venlafaxine, the rate was 0.5% compared with 0% of placebo patients. No reports of mania or hypomania were reported in trials with SAD. As with all drugs effective in the treatment of MDD, Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of mania. **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Venlafaxine Extended Release Tablets. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Use in Specific Populations (8.5) in full prescribing information*]. Discontinuation of Venlafaxine Extended Release Tablets should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. **Seizures:** In all premarketing venlafaxine hydrochloride MDD trials, seizures were reported in 0.3% of venlafaxine hydrochloride-treated patients. Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures. **Abnormal Bleeding:** SSRIs and SNRIs, including Venlafaxine Extended Release Tablets, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Venlafaxine Extended Release Tablets and other drugs that affect coagulation. **Serum Cholesterol Elevation:** Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine hydrochloride-treated patients and 0.0% of patients receiving placebo for at least 3 months in trials. Measurement of serum cholesterol levels should be considered during long-term treatment. **Interstitial Lung Disease and Eosinophilic Pneumonia:** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine therapy have been rarely reported. The possibility of these adverse reactions should be considered in venlafaxine-treated patients who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo prompt medical evaluation, and discontinuation of venlafaxine therapy should be considered. **Use in Patients with Heart Disease:** Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Venlafaxine Extended Release Tablets to patients with diseases or conditions that could affect hemodynamic responses. Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing. As increases in heart rate (mean increase of 4 beats per minute in MDD trials and 5 beats per minute in SAD trials) were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction). **ADVERSE REACTIONS: Clinical Studies Experience: Short-Term, Placebo-Controlled Trials:** ***Adverse Events Leading to Discontinuation of Treatment:*** Approximately 11% of the 357 patients who received venlafaxine hydrochloride extended-release capsules in MDD trials discontinued treatment due to an adverse reaction (vs 6% of the 285 placebo-treated patients). Adverse reactions that led to treatment discontinuation in at least 2% of drug-treated patients were nausea, dizziness and somnolence. Approximately 17% of the 277 patients in SAD trials who received venlafaxine hydrochloride extended-release capsules discontinued treatment due to an adverse reaction (vs 5% of the 274 placebo-treated patients). Adverse reactions that led to treatment discontinuation in at least 2% of drug-treated patients were nausea, insomnia, impotence, headache, dizziness and somnolence. **Adverse Events Occurring at an Incidence of 5% or More:** Major Depressive Disorder: Note in particular the following adverse reactions that occurred in at least 5% of the patients receiving venlafaxine hydrochloride extended-release capsules and at a rate at least twice that of the placebo group for all placebo-controlled trials for the MDD indication (see Table 6): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional reactions occurred in at least 5% of patients treated with venlafaxine hydrochloride extended-release capsules (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning. Social Anxiety Disorder: Note in particular the following adverse reactions that occurred in at least 5% of the patients receiving venlafaxine hydrochloride extended-release capsules and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the SAD indication (see Table 7): Asthenia, gastrointestinal complaints (anorexia, constipation, dry mouth, nausea), CNS complaints (dizziness, insomnia, libido decreased, nervousness, somnolence), abnormalities of sexual function (abnormal ejaculation, impotence, libido decreased, orgasmic dysfunction), yawn, sweating, and abnormal vision. **Adverse Events Occurring at an Incidence of 2% or More:** MDD and SAD trials included patients receiving venlafaxine hydrochloride extended-release capsules in doses ranging from 75 mg to 225 mg/day for up to 12 weeks. The prescriber should be aware that the following adverse reactions figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to adverse reaction incidence rate in the population studied. [See **TABLE 6** in full Prescribing Information.] **TABLE 6: Treatment Emergent Adverse Reaction Incidence in Short-Term Placebo-Controlled Clinical Trials with Venlafaxine Hydrochloride Extended-Release Capsules in Patients with Major Depressive Disorder.** This table reports adverse events that occurred in 2%

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

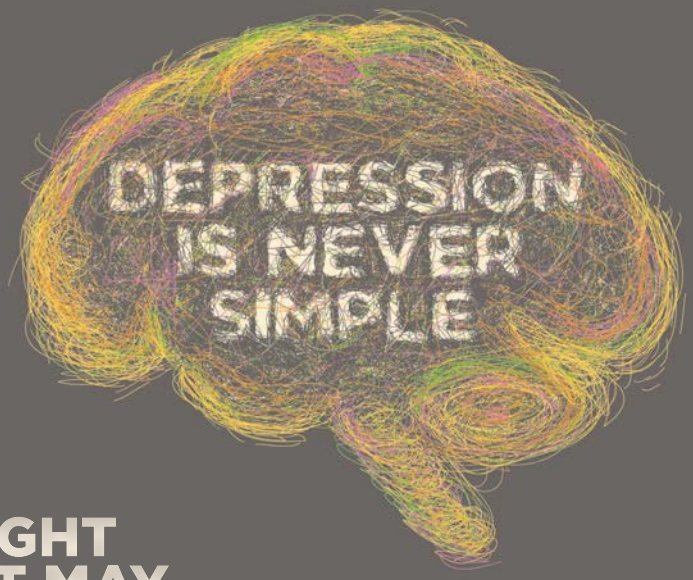
**To report SUSPECTED ADVERSE REACTIONS, contact Upstate Pharma, LLC Pharmaceutical Corp. at 1-888-299-1053 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

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

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

 2E-01/2009

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




# BUT THE RIGHT TREATMENT MAY MAKE A DIFFERENCE

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

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

4 WORDS
1 TABLET
WRITE IT RIGHT

Venlafaxine Extended Release Tablets (VENLAFAXINE HYDROCHLORIDE)
37.5 mg 75 mg 150 mg 225 mg

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

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

## INDICATIONS AND IMPORTANT SAFETY INFORMATION

**WARNING: Suicidality and Antidepressants**

***See full Prescribing Information for complete boxed warning.***

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

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

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

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

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

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

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

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

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

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

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

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


TA1135-0409

Upstate Pharma, LLC is a wholly owned subsidiary of UCB, Inc.

Marketed by:
UPSTATE PHARMA, LLC

For:
Osmotica Pharmaceutical®