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 compared to placebo. INVEGA® SUSTENNA™, a paliperidone palmitate injection, 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 tyalpycnic 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 treatment 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 other illness known to be associated with the symptoms of neuroleptic malignant syndrome, such as sepsis, 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.

OT 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, haloperidol, risperidone, olanzapine, amoxapine, perphenazine, clozapine, quetiapine, and ziprasidone), TCAs (e.g., amitriptyline, trimipramine), 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.

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Certain circumstances may increase the risk of the occurrence of torsade de points 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 drugs known to 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 extension 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: 6.9; 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 (Cmaxss = 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 Cmaxss = 50 ng/mL). In this study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmaxss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 8.6 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 >50 msec, and the median QTcLD value was 326.4 for a QTcLD of 483 msec (predicted median Cmaxss = 50 ng/mL); 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 also possible in other age groups. 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 possible daily dose of the most appropriate agent should be selected, and treatment should be as brief as possible. Whether the antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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, epidemiologic 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 while receiving 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.
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% (1/1510) 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 paliperidone 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.

Deposit: 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 PG].

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 PG].

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]

Neuropsychiatric adverse events [see Warnings and Precautions]

QT prolongation [see Warnings and Precautions]

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]

Aspiration 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]
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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 which was more consistent with the known pharmacology, occurred 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: ocular urgency, eye rolling, vision blurred

Gastrointestinal disorders: saliva 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, dystarsia, dizziness, dystonia, hypotension, lethargy, neuropsychiatric malignant syndrome, otorrheal 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 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, in the adverse reactions that occurred at ≥2% 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 the difference in 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, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which broadly evaluates Parkinsonism, (3) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which evaluates akathisia, (4) the use of anticholinergic medications to treat emergent EPS, (5) the Abnormal Involuntary Movement Scale scores (mean change from baseline or score at the end of trial) which evaluates akathisia, (6) the number of subjects who discontinued due to EPS. The percentages of subjects who discontinued due to EPS in the four fixed-dose, double-blind, placebo-controlled trials were 1.4% and 3.4% in INVEGA® SUSTENNA™- and placebo-treated subjects, respectively.

Table 2. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medications: Scale followed by Percentage of Subjects Placebo (N=262) first, INVEGA® SUSTENNA™ 39 mg (N=130) second, 78 mg (N=132) third, 156 mg (N=132) fourth, 234 mg (N=131) fifth, 234/156 mg (N=165) sixth, 234/234 mg b (N=163) seventh, Percentage of subjects who discontinued due to EPS in the four fixed-dose, double-blind, placebo-controlled trials. a For Akathisia, percentage of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint. b For Dyskinesia, percentage of subjects with a score ≥ 3 on any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint. c 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). d For Akathisia, percentage of subjects with Barnes Akathisia Rating Scale total score ≥ 2 at endpoint. e For Dyskinesia, percentage of subjects with a score ≥ 3 on any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint. f For Parkinsonism, percent of subjects who received anticholinergic medications to treat emergent EPS.

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events MedDRA Preferred Term: EPS Group followed by Percentage of Subjects Placebo (N=262) first, INVEGA® SUSTENNA™ 39 mg (N=130) second, 78 mg (N=132) third, 156 mg (N=128) fourth, 234 mg (N=131) fifth, Percentage of subjects who discontinued due to EPS. The percentages of subjects who discontinued due to EPS in the four fixed-dose, double-blind, placebo-controlled trials. a For akathisia, percentage of subjects with Barnes Akathisia Rating Scale total score ≥ 2 at endpoint. b For dyskinesia, percentage of subjects with a score ≥ 3 on any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint.
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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 (4.6%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA® SUSTENNA™ 234 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 (4.6%) and 234/234 mg (5.3%) 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 may occur more frequently and with greater severity with high potencies 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 markedly different importance 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 laboratory parameters, 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: 10.8 to 5.3; INVEGA® SUSTENNA™: 10.3 to 7.7; 7.8 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.

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INVEGA® SUSTENNA™ (paliperidone palmitate) Extended-Release Injectable Suspension microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2B6, CYP2C9/10, 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, CYP2B6, 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 Cmax 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 in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On inhibition 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 significant CYP inhibition is observed. Paroxetine 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 Cmax and AUC of paliperidone. Although this interaction has not been studied with INVEGA® SUSTENNA™, a clinically significant interaction would not be expected between divalproex sodium and INVEGA® SUSTENNA™ intramuscular injection.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.: There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 160 mg/kg, which is 10 times the maximum recommended human 234 mg dose of INVEGA® SUSTENNA™ on a mg/m² basis.

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 5 times the maximum recommended human dose [12 mg/day] of orally administered paliperidone [INVEGA® on a mg/m² basis].

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in vivo, no adverse effects on offspring were observed at doses which were less than the maximum recommended human dose of risperidone on a mg/m² basis [see RISPERDAL® package insert].

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

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

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

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

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

Geriatric Use: Clinical studies of INVEGA® SUSTENNA™ did not include sufficient numbers of elderly patients. It is not known 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 monitored closely for any signs and symptoms 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].

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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, procainamide, quinidine, and quinine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

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

146 Antidepressants: Can't Live With Them, Can't Live Without Them
Andrew A. Nierenberg, MD, Massachusetts General Hospital, Harvard Medical School

Letter to the Editor

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CME Expert Review Supplement – Part 3

Case in Point: Evidence-Based Insights for Epilepsy Management
Pharmacologic Treatment of Epilepsy
Andrew J. Cole, MD, FRCP and Nathan B. Fountain, MD
PBA:
- Is associated with neurologic diseases such as MS, ALS, Parkinson’s disease, dementias including Alzheimer’s disease, and neurologic injuries such as stroke and TBI.\(^2\)
- It is hypothesized that these neurologic diseases and injuries impact the excitatory action of glutamate, leading to excessive glutamatergic signaling and increased electrical activity in neurons.\(^3\)\(^5\)

PBA:
- Is a distinct neurologic disorder of affect characterized by involuntary episodes of motor expression of emotion, such as laughing, crying, or related facial features.\(^3\)
- PBA is surprisingly prevalent, affecting millions of patients and caregivers in the United States alone.\(^1\)\(^6\)\(^12\)
- The disorder is also commonly known as emotional lability, pathologic laughing and crying, and emotional incontinence.\(^1\)

PBA:
- Can significantly impact patients and caregivers.\(^6\) The symptoms of PBA can be severe, with persistent and unremitting episodes.\(^13\) Involuntary crying or laughing may lead to embarrassment, anxiety, and depression, and result in social isolation.\(^1\)\(^3\)\(^13\)\(^16\)
- Addressing PBA can help improve the lives of patients and their families and caregivers, thereby reducing its physical, emotional, and social impact.

For more information, please visit www.PBAinfo.org

References:
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• Is associated with neurologic diseases such as MS, ALS, Parkinson’s disease, dementias including Alzheimer’s disease, and neurologic injuries such as stroke and TBI.1,2

• It is hypothesized that these neurologic diseases and injuries impact the excitatory action of glutamate, leading to excessive glutamatergic signaling and increased electrical activity in neurons.3-5

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• Is a distinct neurologic disorder of affect characterized by involuntary episodes of motor expression of emotion, such as laughing, crying, or related facial features.1

• PBA is surprisingly prevalent, affecting millions of patients and caregivers in the United States alone.6-12

• The disorder is also commonly known as emotional lability, pathologic laughing and crying, and emotional incontinence.1

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• Can significantly impact patients and caregivers.6 The symptoms of PBA can be severe, with persistent and unremitting episodes.13 Involuntary crying or laughing may lead to embarrassment, anxiety, and depression, and result in social isolation.6,13-16

• Addressing PBA can help improve the lives of patients and their families and caregivers, thereby reducing its physical, emotional, and social impact.

For more information, please visit www.PBAinfo.org

References: