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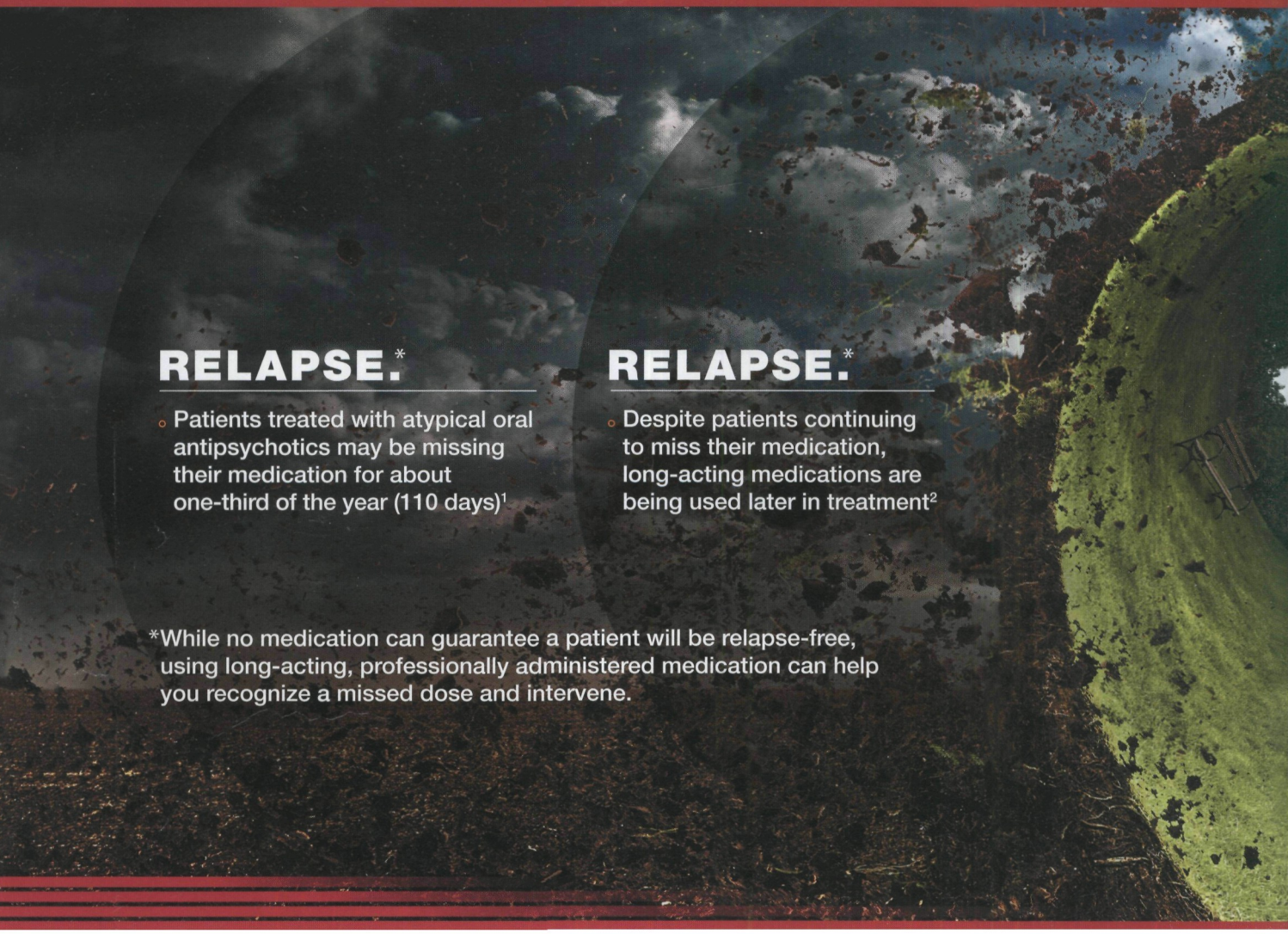
APRIL 2010 • VOL. 15 • NO. 4

Index Medicus citation: ***CNS Spectr***

www.cnsspectrums.com

https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press



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.

https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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.
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August 2009 01PM09034

https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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.

https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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- 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 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

https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

INVEGA® SUSTENNA™ 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human dose [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m² basis).

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

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

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

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

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

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

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

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

https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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

Revised: July 2009

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https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

CNS SPECTRUMS®

Volume 15 • Number 4

First in Applied Neuroscience

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CNS Spectrums' editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.

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CNS Spectrums (ISSN 1092-8529) is published monthly by MBL Communications, Inc., 333 Hudson Street, 7th Floor, New York, NY 10013. Periodicals postage paid at New York, NY, and additional mailing offices. POSTMASTER: Send address changes to *CNS Spectrums*, 333 Hudson St., 7th Floor, New York, NY 10013.

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https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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https://doi.org/10.1017/S1092852900000018 Published online by Cambridge University Press

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[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]

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[1]
- 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[6,13-16]
- Addressing PBA can help improve the lives of patients and their families and caregivers,[6] thereby reducing its physical, emotional, and social impact

Pseudobulbar Affect | PBA

For more information, please visit www.PBAinfo.org

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PBA-0910-0001

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