



May 13, 2014

## **Supplemental New Drug Applications for Once-Monthly Long-Acting Therapy INVEGA® SUSTENNA® (paliperidone palmitate) Submitted to the U.S. FDA for the Treatment of Schizoaffective Disorder**

### **New submission based on positive data from a 15-month schizoaffective relapse prevention study**

**Titusville, NJ, May 13, 2014** - Janssen Pharmaceuticals, Inc., today announced the submission of supplemental New Drug Applications (sNDAs) for once-monthly atypical long-acting antipsychotic INVEGA® SUSTENNA® (paliperidone palmitate) to the U.S. Food and Drug Administration (FDA) for approval to treat schizoaffective disorder as either monotherapy or adjunctive therapy. Without treatment, the symptoms of schizoaffective disorder are complex and disabling. Currently, treatment options approved to manage the symptoms of depression, mania and psychosis associated with the condition are limited.

INVEGA® SUSTENNA® is the first long-acting injection to be studied for the treatment of schizoaffective disorder and - if approved by the FDA - will be the only long-acting injection indicated to treat this condition. INVEGA® SUSTENNA® was approved by the FDA in July 2009 as the first once-monthly atypical long-acting medication to treat schizophrenia.

"There is a significant need for additional treatment options for the one million Americans with schizoaffective disorder," said Michelle Kramer, Vice President, U.S. Neuroscience Medical Affairs, Janssen. "Having pioneered the development of atypical long-acting treatments for mental illness, Janssen is proud to expand our commitment to mental health with the submission of the sNDAs for what could potentially be the first once-monthly therapy for schizoaffective disorder."

The applications are based on a 15-month study that found INVEGA® SUSTENNA® met its primary endpoint of delayed time to and reduced risk of relapse compared to placebo and showed significant efficacy in manic and depressive mood symptoms and psychosis. In the study, INVEGA® SUSTENNA® also met its key secondary endpoint of improving and maintaining patient functioning. Results of the study were presented last week at the 167th Annual Meeting of the American Psychiatric Association (APA) in New York City.

In this study, adverse events occurring in greater than 5% of patients in either group included weight gain (8.5% in INVEGA® SUSTENNA® vs. 4.7% in placebo), insomnia (4.9% vs. 7.1%), worsening of schizoaffective disorder (3.1% vs. 5.9%), headache (5.5% vs. 3.5%) and nasopharyngitis, which is the common cold (5.5% vs. 3.5%). The most common ( $\geq 2\%$ ) movement disorders were akathisia (3.0% in INVEGA® SUSTENNA® vs. 1.8% in placebo) and tremor (1.2% vs. 2.4%). Thirteen percent (13.0%) in the INVEGA® SUSTENNA® group and 6.0% in the placebo group had  $\geq 7\%$  increase in body weight. Potentially prolactin-related adverse events were reported in 10.4% of patients in the INVEGA® SUSTENNA® group and 3.5% in the placebo group.

For additional study information, visit [ClinicalTrials.gov](http://ClinicalTrials.gov) using identifier NCT01193153.

#### **About Schizoaffective Disorder**

Schizoaffective disorder is a mental condition characterized by a loss of contact with reality - psychosis - and mood symptoms of depression and/or mania. The exact cause of schizoaffective disorder is unknown. The disorder is diagnosed via a mental health assessment conducted by a licensed mental health professional. Schizoaffective disorder is generally treated with a complex combination of medications. Besides INVEGA® (paliperidone), there are no antipsychotic medications approved for use in this disorder in the U.S. or most other countries, and no widely accepted guidelines for the treatment of the disease are available. Janssen launched INVEGA®, the first and only antipsychotic approved for the treatment of schizoaffective disorder, in 2009.

#### **About Janssen Pharmaceuticals, Inc.**

As a member of the Janssen Pharmaceutical Companies of Johnson & Johnson, Janssen Pharmaceuticals, Inc., is dedicated to addressing and resolving the major unmet medical needs of our time. Driven by our commitment to patients, healthcare professionals, and caregivers, we strive to develop sustainable and integrated healthcare solutions by working in partnership with all stakeholders on the basis of trust and transparency. Our daily work is guided by meeting goals of excellence in quality, innovation, safety, and efficacy in order to advance patient care.

Our company provides medicines for an array of illnesses and disorders in several therapeutic areas. For more information on Janssen Pharmaceuticals, Inc., visit us at [www.JanssenPharmaceuticalsInc.com](http://www.JanssenPharmaceuticalsInc.com) or follow us on Twitter at [www.twitter.com/JanssenUS](http://www.twitter.com/JanssenUS) and on YouTube at [www.YouTube.com/JanssenUS](http://www.YouTube.com/JanssenUS).

INVEGA® SUSTENNA® (paliperidone palmitate) is indicated for the treatment of schizophrenia. Efficacy was established in four short-term studies and one longer-term study in adults.

## IMPORTANT SAFETY INFORMATION FOR INVEGA® SUSTENNA® (paliperidone palmitate)

### 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.
- INVEGA® SUSTENNA® is not approved for the treatment of patients with dementia-related psychosis.
- [See full Prescribing Information for Warnings and Precautions \(5.1\).](#)

**Contraindications:** Paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any components of the formulation.

**Cerebrovascular Adverse Reactions:** Cerebrovascular Adverse Reactions (e.g., stroke, transient ischemic attacks), including fatalities, were reported in placebo-controlled trials in elderly patients with dementia-related psychosis taking oral risperidone, aripiprazole, and olanzapine. The incidence of Cerebrovascular Adverse Reactions 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 QTc interval and in patients with risk factors for prolonged QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

**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 female 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 (see full Prescribing Information). Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

**Hyperglycemia and Diabetes Mellitus:** Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death have been reported in patients treated with all atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

**Dyslipidemia:** Undesirable alterations have been observed in patients treated with atypical antipsychotics.

**Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

**Orthostatic Hypotension and Syncope:** INVEGA® SUSTENNA® may induce orthostatic hypotension in some patients due to its alpha-blocking activity. INVEGA® SUSTENNA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

**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<sup>3</sup>) should discontinue INVEGA® SUSTENNA® and have their WBC followed until recovery.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sub>2</sub> 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.

**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 performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® SUSTENNA® does not adversely affect them.

**Seizures:** INVEGA® SUSTENNA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

**Administration:** For intramuscular injection only. Care should be taken to avoid inadvertent injection into a blood vessel.

**Drug Interactions:** Strong CYP3A4/P-glycoprotein (P-gp) inducers: It may be necessary to increase the dose of INVEGA® SUSTENNA® when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine, rifampin, St. John's wort) is co-administered. Conversely on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA® SUSTENNA®.

**Pregnancy/Nursing:** Patients should be advised to notify their physician if they become pregnant/intend to become pregnant or intend to nurse during treatment with INVEGA® SUSTENNA®.

**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.

INVEGA® (paliperidone) extended-release tablets are indicated for the treatment of schizophrenia in adults and adolescents (12-17 years of age). The efficacy of INVEGA® in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents (12-17 years of age), as well as one maintenance trial in adults.

INVEGA® (paliperidone) extended-release tablets are indicated for the treatment of schizoaffective disorder as monotherapy and an adjunct to mood stabilizers and/or antidepressant therapy in adults. The efficacy of INVEGA® in schizoaffective disorder was established in two 6-week trials in adults.

## **IMPORTANT SAFETY INFORMATION FOR INVEGA® (paliperidone)**

**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® is not approved for the treatment of patients with dementia-related psychosis.

**Contraindications:** Paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any of the components in the formulation.

**Cerebrovascular Adverse Events (CAEs):** CAEs (e.g., stroke, transient ischemia attacks), including fatalities, were reported in placebo-controlled trials in elderly patients with dementia-related psychosis taking oral risperidone, aripiprazole, and

olanzapine. The incidence of CAEs was significantly higher than with placebo. INVEGA® is not approved for the treatment of patients with dementia-related psychosis.

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

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

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

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. The metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

**Hyperglycemia and Diabetes -** Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death has been reported in patients treated with atypical antipsychotics (APS), including INVEGA®. Patients starting treatment with APS who have or are at risk for diabetes mellitus 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. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

**Dyslipidemia -** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

**Weight Gain -** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. When treating adolescent patients with INVEGA®, weight gain should be assessed against that expected with normal growth.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sub>2</sub> receptors, INVEGA® elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

**Gastrointestinal:** INVEGA® should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing. Rare instances of obstructive symptoms have been reported in patients with known strictures taking non-deformable formulations. INVEGA® should only be used in patients who are able to swallow the tablet whole.

**Orthostatic Hypotension and Syncope:** INVEGA® may induce orthostatic hypotension in some patients due to its alpha-blocking activity. INVEGA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of MI or ischemia, conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with anti-hypertensive medications). Monitoring should be considered in patients who are vulnerable 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® 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<sup>3</sup>) should discontinue INVEGA® and have their WBC followed until recovery.

**Potential for Cognitive and Motor Impairment:** Somnolence was reported in subjects treated with INVEGA®. INVEGA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® does not adversely affect them.

**Seizures:** INVEGA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

**Suicide:** The possibility of suicide attempt is inherent in psychotic illnesses. Close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity of tablets to reduce the risk of overdose.

**Drug Interactions:** Strong CYP3A4/P-glycoprotein (P-gp) inducers: It may be necessary to increase the dose of INVEGA® when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine, rifampin, St. John's wort) is co-administered. Conversely on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA®.

**Commonly Observed Adverse Reactions:** The most commonly observed adverse reactions in clinical trials occurring at an incidence of ≥5% and at least 2 times placebo in the treatment of schizophrenia were: Adults - extrapyramidal symptoms, tachycardia, and akathisia; Adolescents (12-17 years of age) were: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia. The most commonly observed adverse reactions in clinical trials occurring at an incidence of ≥5% and at least 2 times placebo in the treatment of schizoaffective disorder were: Adults - extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

Please see full Prescribing Information including Boxed Warning for INVEGA® SUSTENNA® (paliperidone palmitate) and INVEGA® (paliperidone) at [www.invegasustenna.com](http://www.invegasustenna.com) and [www.invega.com](http://www.invega.com).

(This press release contains "forward-looking statements," as defined in the Private Securities Litigation Reform Act of 1995, regarding product development. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Pharmaceuticals, Inc. or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and difficulties inherent in new product development, including obtaining regulatory approvals; competition, including technological advances, new products and patents attained by competitors; manufacturing difficulties or delays; changes in governmental laws and regulations; and trends toward health care cost containment. A further list and description of risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2013, including in Exhibit 99 thereto, and in its subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at [www.sec.gov](http://www.sec.gov), [www.jnj.com](http://www.jnj.com) or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies or Johnson & Johnson undertakes to update any forward-looking statements as a result of new information or future events or developments.)

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