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Janssen Investigational Treatment for Schizophrenia Shows Positive Efficacy, Delays Relapse

Independent Data Monitoring Committee Recommends Halting Trial and Unblinding Data Based on Treatment Efficacy

TITUSVILLE, N.J., March 20, 2014 /PRNewswire/ -- Janssen Research & Development, LLC announced today that following an Independent Data Monitoring Committee (IDMC) recommendation based on positive efficacy, it has halted early a Phase 3 clinical study of paliperidone palmitate 3-month formulation, an investigational treatment for symptoms of schizophrenia in adults.

"We are really excited about this news because a medication's ability to delay time to relapse in schizophrenia has significant clinical and societal implications," said Husseini K. Manji, MD, Global Head, Neuroscience, Janssen Research & Development. "Being able to delay relapse can prove to be beneficial clinically to patients, to their caregivers and to the community."

The international, randomized, multicenter, double-blind clinical trial evaluated the efficacy of paliperidone palmitate 3-month formulation compared with placebo in delaying time to first occurrence of relapse of symptoms of schizophrenia. Study patients who were randomized to treatment were first stabilized with INVEGA® SUSTENNA® (paliperidone palmitate one-month formulation), an approved treatment for schizophrenia, prior to receiving the investigational 3-month formulation.

The primary outcome measure of the study was the time to first relapse event in the double-blind phase of the study. Time to relapse is defined as the time between randomization to treatment in the double-blind phase and the first documentation of a relapse. The study began in April 2012 and 509 patients were enrolled.

The planned interim analysis was conducted after 60 percent (42 events) of projected relapses occurred. The primary analysis of this study will be based on the interim results of the efficacy endpoint of time to first relapse. Events experienced by study patients after the decision to stop the study will be included in an additional analysis of the primary efficacy endpoint.

The study results will be presented at a future medical congress and will also be submitted for publication in a peer-reviewed journal.

The recommendation to stop and unblind the clinical study at this interim analysis was made by an independent data monitoring committee based on pre-specified criteria, specifically, achieving a statistically significant difference from placebo in delaying time to relapse based upon the interim analysis after 42 relapse events have occurred.

Study investigators will have the opportunity to switch patients enrolled in the study to standard of care treatment for schizophrenia.

Following a final analysis of the study and discussions with the U.S. Food and Drug Administration (FDA), Janssen Research & Development, LLC plans to file a New Drug Application with the U.S. FDA for paliperidone palmitate 3 month formulation by the end of 2014.

INVEGA® SUSTENNA® and the paliperidone palmitate 3-month formulation utilize Alkermes' proprietary NanoCrystal® technology, which enables solubility of poorly water-soluble compounds.

About Paliperidone Palmitate (INVEGA® SUSTENNA®)

INVEGA® SUSTENNA® (paliperidone palmitate) is indicated for the treatment of schizophrenia in an injection administered once monthly after starting doses. 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^3) should discontinue INVEGA® SUSTENNA® and have their WBC followed until recovery.
- **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.
- **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 inducers: It may be necessary to increase the dose of INVEGA® SUSTENNA® when a CYP3A4 strong inducer
(e.g. carbamazepine, rifampin, St. John's wort) is added. It may be necessary to decrease the dose when a CYP3A4 strong inducer is discontinued.
- **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 (greater than or equal to 5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

Please see full Prescribing Information including Boxed Warning for INVEGA® SUSTENNA® (paliperidone palmitate) available at http://www.invegasustenna.com/important-product-information

About Janssen Research & Development, LLC

Janssen Research & Development, LLC is headquartered in Raritan, N.J. and has affiliated facilities in Europe, the United States and Asia. Janssen Research & Development is leveraging a combination of internal and external innovation to discover and develop novel medicines and solutions in five distinct therapeutic areas: Neuroscience, Oncology, Immunology, Infectious Diseases and Vaccines, and Cardiovascular and Metabolism. For more information about Janssen Research & Development, LLC visit www.janssenrnd.com.

Janssen Research & Development is part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Driven by our commitment to patients, we work together to bring innovative ideas, products, services and solutions to address serious unmet medical needs around the world.

(This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding products in development. The reader is cautioned not to rely on these forward-looking statements. 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 Research & Development, LLC and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges inherent in new product development, including obtaining regulatory approvals; competition, including technological advances, new products and patents attained by competitors; challenges to patents; changes in behavior and spending patterns or financial distress of purchasers of health care products and services; changes to governmental laws and regulations and domestic and foreign health care reforms; and general industry conditions including trends toward health care cost containment. A further list and description of these 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 our subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.)

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