

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

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].

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 overdose 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

© Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2009

36348B

POLICY & PRACTICE

**CAN'T GET ENOUGH POLICY & PRACTICE?
CHECK OUT OUR NEW PODCAST EACH MONDAY.**
egmnblog.wordpress.com

Hard Times and Mental Stress

No surprise here: A national survey found that the unemployed are far more likely than others to report severe mental distress. Mental Health America and the National Alliance on Mental Illness (NAMI) surveyed 1,002 adults (half men, half women) nationwide in mid-September. About 13% of those without jobs said they'd had thoughts of harming themselves—four times the rate of people with jobs. Unemployed people were also twice as likely to say they were concerned about their mental health or had used alcohol or drugs in the past 6 months. Among those who had not consulted a health provider about their concerns, 42% said that lack of insurance coverage or cost was the main impediment.

Phone Intervention Effective

A structured phone intervention appears to be as effective as in-office primary care visits when it comes to managing patients receiving antidepressant therapy, according to a study from the Group Health Cooperative's Center for Health Studies in Seattle. Patients starting antidepressants were invited to be randomized into a trial comparing two telephone-support programs with standard care (Arch. Gen. Psychiatry 2009;66:1081-9). One telephone group received up to five brief calls or personalized mailings from care managers with bachelor's degree-level training. The second group got up to 12 calls, which included care management and structured cognitive-behavioral psychotherapy delivered by clinicians with master's degree-level training and psychotherapy experience. For effectiveness assessment, patients were contacted 1 month after entering the study and every 3 months thereafter, for a year and half. Each time, they were assessed on the Symptom Checklist 90 depression scale. Both phone programs had long-term clinical benefits but a greater impact was seen from the intervention that included therapy.

Gene Centers of Excellence

The National Human Genome Research Institute and the National Institute of Mental Health are awarding \$45 million in grants to establish two new Centers of Excellence in Genomic Science in Wisconsin and North Carolina and to support existing centers at the University of Southern California, Los Angeles, and Johns Hopkins University, Baltimore. The Medical College of Wisconsin, Milwaukee, and the University of Wisconsin, Madison, will codirect a center, and the University

of North Carolina, Chapel Hill, will establish the other new center. In North Carolina, researchers are developing new approaches to identifying genetic and environmental factors that may contribute to psychiatric disorders. The Johns Hopkins researchers plan to study in bipolar disorder, aging, and autism.

Levamisole-Laced Cocaine

The Drug Enforcement Administration and the Substance Abuse and Mental Health Services Administration are warning health providers and treatment centers that "substantial levels" of cocaine may be adulterated with levamisole, a veterinary drug. SAMHSA said there have been 20 confirmed or probable cases of agranulocytosis, including 2 deaths, in people who had ingested cocaine that was mixed with the antiparasite agent, which can suppress white blood cell counts. Levamisole was once used in human chemotherapy but is no longer approved for that indication. The DEA reported that levamisole has been found in cocaine samples since 2002. An analysis in July concluded that 70% of cocaine samples contained levamisole. SAMHSA, the DEA, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Office of National Drug Control Policy are gathering case reports from state health departments. So far, there has been no uptick in cases of cocaine-related agranulocytosis, but reporting probably lags behind occurrences.

Practice Revenues Decline

Medical practice revenues fell in 2008, possibly because of declining patient volumes and payments from people in financial hardship, according to the Medical Group Management Association. Medical practices responded by trimming overhead costs more than 1%, but that wasn't enough to offset shrinking revenues, the MGMA found in its yearly practice-cost survey. Multispecialty group practices saw a 1.9% decline in total medical revenue in 2008, with substantial drops in both the number of procedures and the number of patients. Bad debt in multispecialty group practices from fee-for-service charges increased 13% from 2006 to 2008. Practices trimmed their expenses mostly by cutting support-staff costs. However, total worker count remained constant, suggesting that practices might have eliminated raises and bonuses or even cut pay, the MGMA said.

—Alicia Ault