

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 dose [234 mg dose of INVEGA® SUSTENNA™ on a mg/m^2 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/m^2 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/m^2 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.

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Social Support Lowers Dependence on Alcohol

VITALS

Major Finding: Participants with supportive significant others had a higher percentage of alcohol-abstinent days.

Data Source: COMBINE, a multisite, double-blind clinical trial of combinations of medications and behavioral therapies in treating alcohol dependence.

Disclosures: The National Institute on Alcohol Abuse and Alcoholism sponsored the study. Dr. Berger had no conflicts to disclose.

BY DOUG BRUNK

SAN DIEGO — Alcohol-dependent patients with a supportive significant other have a greater reduction in drinking-related consequences over time, compared with those without such support, results from an exploratory analysis demonstrate.

The finding underscores the importance of social support in treatment and recovery from alcohol problems, Lisa Berger, Ph.D., said during the annual scientific conference of the Research Society on Alcoholism.

“There is a body of literature that positively supports the involvement of family members—in particular, spouses or cohabiting partners—in the treatment of individuals with alcoholism,” said Dr. Berger, a scientist in the University of Wisconsin, Milwaukee’s Center for Addiction and Behavioral Health Research. “Yet to date, not as much work has been done on family member or supportive significant other involvement in combined behavioral and medication alcoholism treatments, especially in terms of the newer medications: naltrexone and acamprostate.”

She and her associates explored the effects of a supportive significant other (SSO) on drinking behavior in a cohort of patients from the Combined Pharmacotherapies and Behavioral Interventions study (COMBINE). For the current study, participants were treatment seeking, and the involvement of an SSO was a component of the combined behavioral intervention psychotherapy.

“A supportive significant other did not necessarily have to be a spouse or a partner, although we believe most were,” Dr. Berger said. “An ideal SSO candidate was an individual who supported a participant’s sobriety and their treatment, an individual who the participant sees regularly, and an individual who is important to the participant.”

The mean age of the 619 study participants was 45 years, and 69% were men. Most (89%) had at least a high school education, 44% were married, 76% were white and 24% reported being black, Hispanic, or of another racial identity.

Alcohol outcome study measures in-

cluded percentage of days abstinent and drinks per drinking day as derived from Form 90, a structured assessment interview for drinking and related behaviors. They used the Drinker Inventory of Consequences to measure alcohol-related problems.

Dr. Berger said that 161 study participants (26%) had an SSO involved in their treatment. Slightly more than half of SSOs (54%) attended one combined behavioral intervention session, 22% attended 2-3 sessions, and 24% attended 4 or more sessions.

Mixed-model repeated measures of variance revealed a significant main effect for time in the study and a significant three-way interaction effect for naltrexone, by SSO, and by time in the reduction of the number of drinks per drinking day.

“Participants who did not receive naltrexone but had SSO involvement had a higher average number of drinks per drinking day over time than the group with no SSO involvement,” Dr. Berger said. “Participants who did receive naltrexone experienced fluctuations of high-



An ideal significant other supports the participant's sobriety and treatment.

DR. BERGER

er and lower average number of drinks per drinking day over time relative to those participants without SSO involvement. So it appears that there is some support for naltrexone in terms of helping those with SSO involvement reduce their average number of drinks per drinking day.”

The researchers also found that study participants with involvement of an SSO had more alcohol-related problems at baseline, compared with their counterparts who did not have involvement from an SSO. However, those with an SSO had fewer problems halfway through the 4-month combined treatment period and had fewer problems thereafter, compared with the participants without an SSO.

“The results suggest that SSO involvement alone and in combination with naltrexone may positively impact patient alcohol use and alcohol-related problems,” Dr. Berger said.

The SSO main effect on percentage of days abstinent “may have been in part due to the SSO’s role in supporting abstinence,” she explained.

“In the present study, however, this is a tentative notion, because we do not know what was stated in [the behavioral intervention] session about abstinence and the role of the SSO. Nor do we know to what fidelity this may have even occurred.”