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 26 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 56% (CV: 40), 30 higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance of this finding 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 each) resulted in an increase of approximately 50% in the Cmax 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 administered paliperidone extended-release for the period of organogenesis at dosages up to 160 mg/kg, which is 10 times the maximum recommended human dose 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-limiting. 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]. 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 deltid muscle. Thereafter, follow with monthly injections of 78 mg either in 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 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.

**OVERDOSE**

**Human Experience:** No cases of overdose were reported in premarking studies with INVEGA** SUSTENNA™. Because INVEGA** SUSTENNA™ is to be administered by health care professionals, the potential for overdose by patients is low. INVEGA** SUSTENNA™ is a relatively low exposure product as it contains only 12 mg paliperidone. While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with paliperidone INVEGA*, ingestion of greater than 10 mg of oral paliperidone extended-release on more than one occasion caused confusion, drowsiness, sedation, hyperthermia, agitation, and tachycardia, panic reaction, and increased blood pressure. Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the package insert. Hypotension, tachycardia, and QT prolongation are exaggerated of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypertension, and QT prolongation.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with paliperidone INVEGA*, ingestion of greater than 10 mg of oral paliperidone extended-release on more than one occasion caused confusion, drowsiness, sedation, hyperthermia, agitation, and tachycardia, panic reaction, and increased blood pressure. Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the package insert. Hypotension, tachycardia, and QT prolongation are exaggerated of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypertension, and QT prolongation.

In an acute overdose study, 160 mg/kg, which is 10 times the maximum recommended human dose of 234 mg dose of INVEGA** SUSTENNA™ on a mg/m² basis. When administered paliperidone [INVEGA**] on a mg/m² basis.

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 at 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 involved in combined behavioral and medication alcoholism treatment, especially in terms of the newer medications: naltrexone and acamprosate.”

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 psychology. “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 the 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 included 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 Inven- tory of Consequences, compared to measured 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 signifi- cant 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 an 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-