INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA SUSTENNA® safely and effectively. See full prescribing information for INVEGA SUSTENNA®. INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Initial U.S. Approval: 2006

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis. (5.1)

------------------------ INDICATIONS AND USAGE ------------------------

INVEGA SUSTENNA® is an atypical antipsychotic indicated for

• Treatment of schizophrenia in adults. (1)
• Treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants. (1)

---DOSE AND ADMINISTRATION---

• For intramuscular injection only. (2.1)
• Each injection must be administered only by a healthcare professional. (2.1)
• For deltoid injection, use 1-inch 22G needle for patients weighing less than 90 kg or 1 ½-inch 22G needle for patients weighing 90 kg or more. For gluteal injection, use 1 ½-inch 22G needle regardless of patient weight. (2.1)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initiation Dosing (deltoid)</th>
<th>Monthly Maintenance Dose a (deltoid or gluteal)</th>
<th>Maximum Monthly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (2.2)</td>
<td>234 mg</td>
<td>39-234 mg b</td>
<td>234 mg</td>
</tr>
<tr>
<td>Schizoaffective disorder (2.2)</td>
<td>234 mg</td>
<td>78-234 mg c</td>
<td>234 mg</td>
</tr>
</tbody>
</table>

a Administered 5 weeks after the first injection.

b The recommended maintenance dose for treatment of schizophrenia is 117 mg.

Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).

c Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

• For patients naïve to oral paliperidone or oral or injectable risperidone, establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®. (2.2)
• Missed Doses: To manage either a missed second initiation dose or a missed monthly maintenance dose, refer to the Full Prescribing Information. (2.3)
• Moderate to severe renal impairment (creatinine clearance < 50 mL/min): INVEGA SUSTENNA® is not recommended. (2.5)
• Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Administer 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Follow with monthly injections of 78 mg in either the deltoid or gluteal muscle. (2.5)

---ADVERSE REACTIONS---

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---DRUG INTERACTIONS---

• Drugs that may cause orthostatic hypotension: An additive effect may occur when co-administered with INVEGA SUSTENNA®. (7.1)
• Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John’s Wort) during a dosing interval for INVEGA SUSTENNA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (2.5, 7.1, 12.3)

---USE IN SPECIFIC POPULATIONS---

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2018
INVEGA SUSTENNA® (paliperidone palmitate)
extended-release injectable suspension, for intramuscular use

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE

INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:
- Schizophrenia in adults [see Clinical Studies (14.1)].
- Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Each injection must be administered only by a healthcare professional. Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration, whenever product and container permit.

INVEGA SUSTENNA® is intended for intramuscular use only. Do not administer by discoloration prior to administration, whenever product and container permit.

2.2 Schizophrenia and Schizoaffective Disorder

For patients who have never taken oral risperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®. The recommended dosing of INVEGA SUSTENNA® for each approved indication is displayed in Table 1. The recommended initiation of INVEGA SUSTENNA® is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Table 1: Recommended Dosing of INVEGA SUSTENNA® for Adults with Schizophrenia or Schizoaffective Disorder

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Initiation Dosing (deltoid)</th>
<th>Monthly Maintenance Dose* (deltoid or gluteal)</th>
<th>Maximum Monthly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>234 mg</td>
<td>156 mg</td>
<td>234 mg</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>234 mg</td>
<td>156 mg</td>
<td>234 mg</td>
</tr>
</tbody>
</table>

*Administered 5 weeks after the first injection.

a The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).

b Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA SUSTENNA® should be considered [see Clinical Pharmacology (12.3)], as the full effect of the dose adjustment may not be evident for several months.

2.3 Missed Doses

Avoiding Missed Doses

It is recommended that the second initiation dose of INVEGA SUSTENNA® be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.
**INVEGA SUSTENNA**® (paliperidone palmitate)
extended-release injectable suspension, for intramuscular use

**Management of a Missed Second Initiation Dose**
If the target date for the second INVEGA SUSTENNA injection (one week ± 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection. In case of a missed second initiation dose follow the dosing instructions provided in Table 2.

Table 2: Management of a Missed Second Initiation Dose

<table>
<thead>
<tr>
<th>TIMING OF MISSED SECOND INITIATION DOSE</th>
<th>DOSING</th>
</tr>
</thead>
</table>
| Less than 4 weeks since first injection | 1. Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible.  
2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle. |
| 4 to 7 weeks since first injection     | 1. Administer a deltoid injection as soon as possible.  
2. Administer a second deltoid injection 1 week later.  
3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle. |
| More than 7 weeks since first injection| Restart with recommended initiation (see Section 2.2, Table 1):  
1. Administer a 234 mg deltoid injection on Day 1.  
2. Administer a 156 mg deltoid injection 1 week later.  
3. Thereafter, resume regular monthly dosing 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) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

**2.4 Use with Risperidone or with Oral Paliperidone**
Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA SUSTENNA® is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA SUSTENNA® with other antipsychotics is limited.

**2.5 Dosage Adjustments**

**Renal Impairment**
INVEGA SUSTENNA® has not been systematically studied in patients with renal impairment [see Clinical Pharmacology (12.3)]. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), initiate INVEGA SUSTENNA® with a dose of 156 mg on treatment day 1 and 117 mg one week later. Administer both doses in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

**2.6 Switching from Other Antipsychotics**
For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®. Extended-release antipsychotics can be gradually discontinued at the time of initiation of treatment with INVEGA SUSTENNA®. Recommended initiation of INVEGA SUSTENNA® is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle [see Dosage and Administration (2.2)]. Patients previously stabilized on different doses of INVEGA® Extended-Release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA SUSTENNA® monthly doses as depicted in Table 4.

Table 4: Doses of INVEGA® and INVEGA SUSTENNA® Needed to Attain Similar Steady-State Paliperidone Exposure During Maintenance Treatment

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosing Frequency</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVEGA®</td>
<td>Once Daily</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Once every 4 weeks</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>INVEGA SUSTENNA®</td>
<td>Once Daily</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td></td>
<td>156</td>
</tr>
<tr>
<td></td>
<td></td>
<td>117</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39-78</td>
</tr>
</tbody>
</table>

**Switching from Long-Acting Injectable Antipsychotics**
For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®.

When switching patients currently at steady-state on a long-acting injectable antipsychotic, initiate INVEGA SUSTENNA® therapy in place of the pre-scheduled injection. INVEGA SUSTENNA® should then be continued at monthly intervals. The one-week initiation dosing regimen as described in Section 2.2 is not required. See Table 1 above for recommended monthly maintenance dosing. Based on previous clinical history of tolerability and/or efficacy, some patients may benefit from lower or higher maintenance doses within the available strengths (39 mg, 78 mg, 117 mg, 156 mg, and 234 mg). The 39 mg strength was not studied in the long-term schizophrenia disorder study. Monthly maintenance doses can be administered in either the deltoid or gluteal muscle [see Dosage and Administration (2.2)].

If INVEGA SUSTENNA® is discontinued, its prolonged-release characteristics may not be apparent immediately. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

**2.7 Instructions for Use**
Each injection must be administered only by a healthcare professional. The kit contains a prefilled syringe and 2 safety needles (a 1½-inch 22 gauge needle and a 1-inch 22 gauge needle) for intramuscular injection.
a. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.

b. Select the appropriate needle.
   For DELTOID injection:
   • If the patient weighs less than 90 kg, use the 1-inch 23 gauge needle (needle with blue colored hub).
   • If the patient weighs 90 kg or more, use the 1 ½-inch 22 gauge needle (needle with gray colored hub).
   For GLUTEAL injection:
   Use the 1 ½-inch 22 gauge needle (needle with gray colored hub) regardless of patient’s weight.

c. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.

d. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.

e. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.

f. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.

g. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. Do not administer by any other route.
h. After the injection is complete, use either thumb or finger of one hand (h1, h2) or a flat surface (h3) to activate the needle protection system. The needle protection system is fully activated when a ‘click’ is heard. Discard the syringe with needle appropriately.

3 DOSAGE FORMS AND STRENGTHS
INVEGA SUSTENNA® is available as a white to off-white aqueous extended-release injectable suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate.

4 CONTRAINDICATIONS
INVEGA SUSTENNA® is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA SUSTENNA® formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone.

5 WARNINGS AND PRECAUTIONS
5.1 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 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 SUSTENNA® is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning and Warnings and Precautions (5.2)).

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse
5.3 Neuroleptic Malignant Syndrome
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregularities of blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient appears to require antipsychotic drug treatment after recovery from NMS, the drug therapy should be closely monitored, since recurrences of NMS have been reported.

5.4 QT Prolongation
Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antidepressants (e.g., fluoxetine, mianserin), or any other class of medications known to prolong the 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, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 1.23 msec (90% CI: 0.3; 2.2) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release (Cmax ss = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA SUSTENNA® administered in the dextrotole muscle (predicted median Cmax ss = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. In the three fixed-dose efficacy studies of oral paliperidone extended release in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). In the four fixed-dose efficacy studies of INVEGA SUSTENNA® in subjects with schizophrenia and in the long-term study in subjects with schizoaffective disorder, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study in subjects with schizophrenia, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett’s QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute. 5.5 Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.
Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Table 6: Change in Fasting Lipids from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

Table 7: Change from Baseline in Lipid Values during the Initial 25-Week Open-Label Period and at the Endpoint of the Subsequent 15-Month Double-Blind Period in Subjects with Schizophrenia

Table 8: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizoaffective Disorder

Table 9: Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Gain in Body Weight from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

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

Orthostatic Hypotension and Syncope
Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in <1% (4/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg.

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5.8 Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA SUSTENNA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate this effect, assess the risk of antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including INVEGA SUSTENNA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia include: pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count < 1000/mm³) and follow their WBC until recovery.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D₂ receptors, paliperidon elevates prolactin levels and the elevation persists during chronic administration. Paliperidon has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in a decrease in gonadal steroidogenesis. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypergonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancer cells are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats [see Nonclinical Toxicology (12.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorogenesis in humans, but the available evidence is too limited to be conclusive.

Prolactin data from two long-term, double-blind, placebo-controlled studies with INVEGA SUSTENNA® are presented below; one study was in a population of patients with schizophrenia; the second study was in patients with schizoaffective disorder.

Schizophrenia

In a long-term maintenance trial of INVEGA SUSTENNA® in schizophrenia patients (Study PSY-3001), see Clinical Studies (14.1), elevations of prolactin to above the reference range (> 18 ng/mL in males and > 30 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in a higher percentage of patients in the INVEGA SUSTENNA® group than those in the placebo group (N=488; amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced adverse reaction of blood prolactin increased. Prior to the 15-month double-blind phase (during the 25-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.6 (14.0) ng/mL in males (N=352) and 39.1 (44.6) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) serum prolactin values were 22.8 (17.2) ng/mL in males (N=275) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase, 48.3% of females and 53.3% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (10.0% vs. 9.0%). Amenorrhea (5.8%) and galactorrhea (2.9%) in males and libido decrease (2.8%) and erectile dysfunction (2.5%) in males were observed with a rate greater than 2%.

5.11 Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in patients treated with INVEGA SUSTENNA® [see Adverse Reactions (6.1)]. Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.12 Seizures

In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion. Like other antipsychotic drugs, INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA SUSTENNA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.14 Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA SUSTENNA®, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

5.15 Disruption of Body Temperature Regulation

Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA SUSTENNA® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

• Increased mortality in elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
• Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis [see Warnings and Precautions (5.2)]
• Neuroleptic malignant syndrome [see Warnings and Precautions (5.3)]
• QT prolongation [see Warnings and Precautions (5.4)]
• Tardive dyskinesia [see Warnings and Precautions (5.5)]
• Metabolic changes [see Warnings and Precautions (5.6)]
• Orthostatic hypotension [see Warnings and Precautions (5.7)]
• Falls [see Warnings and Precautions (5.8)]
• Leukopenia, neutropenia, and agranulocytosis [see Warnings and Precautions (5.9)]
• Hyperprolactinemia [see Warnings and Precautions (5.10)]
• Potential for cognitive and motor impairment [see Warnings and Precautions (5.11)]
• Seizures [see Warnings and Precautions (5.12)]
• Dysphagia [see Warnings and Precautions (5.13)]
• Priapism [see Warnings and Precautions (5.14)]
• Disruption of body temperature regulation [see Warnings and Precautions (5.15)]
**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Patient Exposure**

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects (approximately 1705 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA® in the four fixed-dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA SUSTENNA®-treated subjects, 1293 received INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA SUSTENNA® in the maintenance trial (median exposure 229 days during the initial 33-week open-label phase of this study, of whom 205 continued to receive INVEGA SUSTENNA® during the double-blind placebo-controlled phase of this study [median exposure 171 days]), and 1675 received INVEGA SUSTENNA® in five non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 667 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 147 days); 164 subjects continued to receive INVEGA SUSTENNA® during the 15-month double-blind placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently in the INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

**Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials**

**Commonly Observed Adverse Reactions**: The most common (at least 5% in any INVEGA SUSTENNA® group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials in subjects with schizophrenia were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. No occurrences of adverse events reached this threshold in the long-term double-blind, placebo-controlled study in subjects with schizoaffective disorder.

**Discontinuation of Treatment Due to Adverse Events**: The percentage of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled schizophrenia trials were similar for INVEGA SUSTENNA® and placebo-treated subjects.

The percentage of subjects who discontinued due to adverse events in the open-label period of the long-term study in subjects with schizoaffective disorder was 7.5%. During the double-blind, placebo-controlled period of that study, the percentages of subjects who discontinued due to adverse events were 5.5% and 1.8% in INVEGA SUSTENNA® and placebo-treated subjects, respectively.

**Dose-Related Adverse Reactions**: Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, among the adverse reactions that occurred with ≥ 2% incidence in the subjects treated with INVEGA SUSTENNA®, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA SUSTENNA®-treated subjects from the four fixed-dose studies.

**Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA SUSTENNA®-Treated Patients**: Table 10 lists the adverse reactions reported in 2% or more of INVEGA SUSTENNA®-treated subjects and at a greater proportion than in the placebo group with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.
The results across all phases of the maintenance trial in subjects with schizophrenia exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA SUSTENNA® 156 mg group (48% and 11%, respectively) than in the placebo group (4% and 5%, respectively). In the 13-week study in subjects with schizophrenia involving 234 mg initiation dosing, the incidence of any EPS was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 8%, 10%, and 11% in the INVEGA SUSTENNA® 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.5%) and INVEGA SUSTENNA® 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

In the long-term study in subjects with schizoaffective disorder, EPS reported during the 25-week open-label INVEGA SUSTENNA® treatment included hyperkinesia (12.2%), parkinsonism (8.7%), tremor (3.4%), dyskinesia (2.5%), and dystonia (2.1%). During the 15-month double-blind treatment, the incidence of any EPS was similar to that of the placebo group (8.5% and 7.1%, respectively). The most commonly reported treatment-emergent EPS-related adverse events (>2%) in any treatment group in the double-blind phase of the study (INVEGA SUSTENNA® versus placebo) were hyperkinesia (3.7% vs. 2.9%), parkinsonism (3.0% vs. 1.8%), and tremor (1.2% vs. 2.4%).

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials in adult subjects with schizophrenia provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale scores which evaluates dyskinesia, and (4) use of anticholinergic medications to treat EPS (Table 11), and (5) incidence of spontaneous reports of EPS (Table 12).

Table 11: Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>Percentage of Subjects</th>
<th>INVEGA SUSTENNA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale</td>
<td>N=262</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=130)</td>
</tr>
<tr>
<td></td>
<td>39 mg</td>
</tr>
<tr>
<td></td>
<td>78 mg</td>
</tr>
<tr>
<td></td>
<td>156 mg</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>9</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>3</td>
</tr>
<tr>
<td>Use of Anticholinergic Medications</td>
<td>12</td>
</tr>
</tbody>
</table>

- For parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)
- For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint
- For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint
- Percent of subjects who received anticholinergic medications to treat EPS

Table 12: Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>Percentage of Subjects</th>
<th>INVEGA SUSTENNA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS Group</td>
<td>Placebo (N=262)</td>
</tr>
<tr>
<td></td>
<td>39 mg (N=130)</td>
</tr>
<tr>
<td></td>
<td>78 mg (N=223)</td>
</tr>
<tr>
<td></td>
<td>156 mg (N=228)</td>
</tr>
<tr>
<td>Overall percentage of subjects with EPS-related adverse events</td>
<td>10</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>2</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0</td>
</tr>
</tbody>
</table>

- Parkinsonism group includes: Extrapyramidal disorder, hypertonias, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia
- Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness
- Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia
- Dystonia group includes: Dystonia, muscle spasms

The following is a list of additional adverse reactions that have been reported in clinical trials with oral paliperidone:
- Cardiac disorders: bundle branch block left, sinus arrhythmia
- Gastrointestinal disorders: abdominal pain, small intestinal obstruction
- General disorders and administration site conditions: edema, edema peripheral
- Immune system disorders: anaphylactic reaction
- Infections and infestations: rhinitis
- Musculoskeletal and connective tissue disorders: musculoskeletal pain, toothache, trismus
- Nervous system disorders: grand mal convulsion, parkinsonian gait, transient ischemic attack
- Psychiatric disorders: sleep disorder
- Reproductive system and breast disorders: breast engorgement

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of paliperidone; because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: angioedema, ileus, tachycardia, swollen tongue, thrombotic thrombocytopenic purpura, urinary incontinence, and urinary retention.

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.
Clinical Pharmacology (12.3). Results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Table 13: Clinically Important Drug Interactions with INVEGA SUSTENNA®

<table>
<thead>
<tr>
<th>Drugs with Potential for Inducing Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact</td>
</tr>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>Examples</td>
</tr>
<tr>
<td>Strong Inducers of CYP3A4 and P-gp</td>
</tr>
<tr>
<td>Clinical Impact</td>
</tr>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>Examples</td>
</tr>
</tbody>
</table>

Dopamine Agonist

Clinical Impact | Paliperidone may antagonize the effect of levodopa and other dopamine agonist |
| Intervention | Monitor and manage patient as clinically appropriate |
| Examples | Levodopa, bromocriptine, ropinirole and pramipexole |

7.2 Drugs Having No Clinically Important Interactions with INVEGA SUSTENNA®: Clinically meaningful pharmacokinetic interaction between INVEGA SUSTENNA® and valproate (including valproic acid and divalproex sodium) is not expected. Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA SUSTENNA® is required when administered with valproate [see Clinical Pharmacology (12.3)]. Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA SUSTENNA® [see Clinical Pharmacology (12.3)].

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA® is also unlikely.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence in vivo that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2D6; an interaction with inhibitors or inducers of these isozymes is unlikely. [see Clinical Pharmacology (12.3)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including INVEGA SUSTENNA®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see Clinical Considerations). Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA SUSTENNA®, during pregnancy (see Clinical Considerations).

Paliperidone has been detected in plasma in adult subjects up to 128 days after a single-dose administration of INVEGA SUSTENNA® [see Clinical Pharmacology (12.3)], and the clinical significance of INVEGA SUSTENNA® administered before pregnancy or anytime during pregnancy is not known. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

In animal reproduction studies, 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 10 times the maximum recommended human dose (MRHD) of 234 mg paliperidone based on mg/m² body surface area. There were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg paliperidone based on mg/m² body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia, including increases in risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including INVEGA SUSTENNA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates exhibiting extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 5 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR= 1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

In animal reproduction studies, there were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 10 times MRHD of 234 mg paliperidone based on mg/m² body surface area. In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m² body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m² body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.
9.1 Controlled Substance

INVEGA SUSTENNA® (paliperidone) is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

9.3 Dependence

Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10. OVERDOSAGE

10.1 Human Experience

No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA®. Because INVEGA SUSTENNA® is to be administered by healthcare professionals, the potential for overdosage 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. Thrombocytopenia and venous fibrillation have been reported in a patient in the setting of overdose with oral paliperidone.

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.

10.2 Management of Overdosage

Contact a Certified Poison Control Center for the most up to date information on the management of INVEGA SUSTENNA® overdose (1-800-222-1222 or www.poison.org). Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose and ensure adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. There is no specific antidote to paliperidone.

Consider the prolonged-release characteristics of INVEGA SUSTENNA® and the long apparent half-life of paliperidone when assessing treatment needs and recording dosages.

11. DESCRIPTION

INVEGA SUSTENNA® contains paliperidone palmitate. The active ingredient, paliperidone, is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. INVEGA SUSTENNA® contains a racemic mixture of (+)- and (-)-paliperidone palmitate. The chemical name is (9R,3S)-3-[2-[4-[(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-d]pyrimidin-1-yl]hexadecanoate. Its molecular formula is C_{39}H_{57}FN_{4}O_{4} and its molecular weight is 664.89. The structural formula is:

\[
\text{Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.}
\]

INVEGA SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in the following dose strengths of paliperidone palmitate (and deliverable volumes of the prefilled syringes): 39 mg (0.25 mL), 78 mg (0.5 mL), 117 mg (0.75 mL), 156 mg (1.0 mL), and 234 mg (1.5 mL). The drug product hydrates to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20 (12 mg/mL), polyethylene glycol 4000 (30 mg/mL), citric acid monohydrate (5 mg/mL), disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

INVEGA SUSTENNA® is provided in a prefilled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The kit also contains 2 safety needles (a ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolized to paliperidone [see Clinical Pharmacology (12.3)]. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone is unclear. However, the drug’s therapeutic effect in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_{2}) and serotonin Type 2 (5HT_{2A}) receptor antagonism.
12.2 Pharmacodynamics

In vitro, paliperidone acts as an antagonist at the central dopamine Type 2 (D₂) and serotonin Type 2 (5HT₁A) receptors with binding affinities (Ki values) of 1.6-2.8 nM for D₂ and 0.8-1.2 nM for 5HT₁A receptors. Paliperidone is also active as an antagonist at the α₁ and α₂ adrenergic receptors and H₁ histaminergic receptors. No specific drug interaction studies have been performed with paliperidone. In vitro studies suggest a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, but no evidence in vivo that inhibitors of these enzymes significantly affect the metabolism of paliperidone; they contribute to only a small fraction of total body clearance. In vitro studies demonstrated that paliperidone is a substrate of P-glycoprotein (P-gp) [see Drug Interactions (7.2)].

In vitro studies in human liver microsomes demonstrated that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isoforms, including CYP1A2, CYP2A6, CYP2C9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Long-Acting Paliperidone Palmitate Injection versus Oral Extended-Release Paliperidone

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

12.3 Pharmacokinetics

Absorption and Distribution

Due to its extremely low water solubility, the 1-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tₘₚₐ of 13 days. The release of the drug is rapid, with ≤28% higher Cₘₚₐ observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 234 mg on day 1 and 156 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA SUSTENNA® results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA SUSTENNA® administration was dose-proportional over a 39 mg-234 mg dose range, and less than dose-proportional for Cₘₚₐ for doses exceeding 78 mg. The mean steady-state peak-trough ratio for an INVEGA SUSTENNA® dose of 156 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6-1.8.

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

No specific drug interaction studies have been performed with INVEGA SUSTENNA® extended-release injectable suspension, for intramuscular use.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

12.4 Other Drugs on Paliperidone Pharmacokinetics

Clinically meaningful pharmacokinetic interaction between INVEGA SUSTENNA® and valproate (including valproic acid and divalproex sodium) is not expected. Oral administration of divalproex sodium extended-release tablets (two 500 mg tablets once daily at steady-state) with oral paliperidone extended-release tablets resulted in an increase of approximately 50% in the Cₘₚₐ and AUC of paliperidone.

Effects of other drugs on the exposures of paliperidone are summarized in Figure 1. After oral administration of 20 mg/day of paroxetine (a potent CYP2D6 inhibitor), an increase in mean Cₘₚₐ and AUC values at steady-state was observed (see Figure 1). Higher doses of paroxetine have not been studied. The clinical relevance is unknown. After oral administration, a decrease in mean Cₘₚₐ and AUC values at steady state is expected when patients are treated with carbamazepine, a strong inducer of both CYP3A4 and P-gp [see Drug Interactions (7.1)]. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Figure 1: The effects of other drugs on paliperidone pharmacokinetics.
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed. There was an increase in mammary gland adenomas in female rats at 16, 47, and 94 mg/kg/month, which is 0.6, 2, and 4 times, respectively, the MRHD of 234 mg of INVEGA SUSTENNA® based on mg/m² body surface area. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 2 and 4 times the MRHD based on mg/m² body surface area. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies with risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone based on mg/m² body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D₂ antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear [see Warnings and Precautions (5.7)].

Mutagenesis

Paliperidone palmitate showed no genotoxicity in the in vitro Ames bacterial reverse mutation test or the mouse lymphoma assay. Paliperidone was not genotoxic in the in vitro Ames bacterial reverse mutation test, the mouse lymphoma assay, or the in vivo rat bone marrow micronucleus test.

Impairment of Fertility

No fertility studies were conducted with paliperidone palmitate.

In an oral paliperidone study of fertility, the percentage of treated female rats that became pregnant was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day which is 2 times the MRHD based on mg/m² body surface area. However, the number of post-implantation losses was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the MRHD based on mg/m² body surface area.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2 times the MRHD of 12 mg/day based on mg/m² body surface area, although sperm count and sperm viability studies were not conducted with paliperidone.

In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration by 4 to 10 times the MRHD of 16 mg/day for risperidone, based on mg/m² body surface area. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

13.2 Animal Toxicology and/or Pharmacology

Injection site toxicity was assessed in minipigs injected intramuscularly with the 3-month paliperidone palmitate extended-release injectable suspension at doses up to 819 mg, which is equal to the MRHD. Injection site inflammatory reactions were not examined. For INVEGA SUSTENNA® at 78 mg and 156 mg doses, injection site reactions were mild and consistent with the site of injection.

14 CLINICAL STUDIES

14.1 Schizophrenia

Short-Term Monotherapy (Studies 1, 2, 3, 4)

The efficacy of INVEGA SUSTENNA® in the acute treatment of schizophrenia was evaluated in four short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia. The fixed doses of INVEGA SUSTENNA® in these studies were given on days 1, 8, and 26 of the 9-week study, and additionally on day 64 of the 13-week studies, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance.

Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210.

In Study 1 (PSY-3007), a 13-week study (n=636) comparing three fixed doses of INVEGA SUSTENNA® (initial deltoid injection of 234 mg followed by 3 gluteal or deltoid deltoid injections of either 78 mg/4 weeks, 156 mg/4 weeks or 234 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA® were superior to placebo in improving the PANSS total score.

In Study 2 (PSY-3003), another 13-week study (n=349) comparing three fixed doses of INVEGA SUSTENNA® (78 mg/4 weeks, 156 mg/4 weeks, and 234 mg/4 weeks) to placebo, only 156 mg/4 weeks of INVEGA SUSTENNA® was superior to placebo in improving the PANSS total score.

In Study 3 (PSY-3004), a third 12-week study (n=513) comparing three fixed doses of INVEGA SUSTENNA® (39 mg/4 weeks, 78 mg/4 weeks, and 156 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA® were superior to placebo in improving the PANSS total score.

In Study 4 (SCS-201), the 9-week study (n=197) comparing two fixed doses of INVEGA SUSTENNA® (78 mg and 156 mg) to placebo, both doses of INVEGA SUSTENNA® were superior to placebo in improving PANSS total score.

A summary of the mean baseline PANSS scores along with the mean changes from baseline in the four short-term acute schizophrenia studies are provided in Table 14.

Table 14: Schizophrenia Short-Term Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: PANSS Total Score</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>INVEGA SUSTENNA®</td>
<td>-13.3 (2.21)</td>
<td>(-11.2 (1.69), -15.5 (2.21))</td>
<td>(-12.62, -4.78)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>86.8 (10.31)</td>
<td>-6.1 (1.69)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>INVEGA SUSTENNA®</td>
<td>-11.2 (2.47)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>90.1 (11.66)</td>
<td>-10.4 (2.47)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>INVEGA SUSTENNA®</td>
<td>-10.76 (1.07)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>91.2 (12.02)</td>
<td>-12.2 (2.19)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>INVEGA SUSTENNA®</td>
<td>-14.0 (4.33)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>89.9 (10.78)</td>
<td>-6.9 (2.50)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval. * Difference (drug minus placebo) in least-squares mean change from baseline. Because an insufficient number of subjects received the 224 mg/4 weeks dose, results from this group are not included.</td>
<td>p&lt;0.05 (Doses statistically significantly superior to placebo).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maintenance Monotherapy Treatment (Study 5: PSY-3001)

The efficacy of INVEGA SUSTENNA® in maintaining symptomatic control in schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia. This study included a minimum 12-week, fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of INVEGA SUSTENNA® they received during the stabilization phase, i.e., 39 mg, 79 mg, or 156 mg administered every 4 weeks, or to placebo. A total of 410 stabilized patients were randomized to either INVEGA SUSTENNA® or to placebo until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in the total PANSS score, or ≥ 5 (if the maximum baseline score was ≤ 5) or ≥ 6 (if the maximum baseline score was >5) in total PANSS score on two consecutive assessments, or ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in the total PANSS score on two consecutive assessments.

The primary efficacy variable was time to relapse. A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA SUSTENNA® compared to placebo, and the study was stopped early because maintenance of efficacy was demonstrated. Thirty-four percent (34%) of subjects in the placebo group and 10% of subjects in the INVEGA SUSTENNA® group experienced a relapse event. There was a statistically significant difference between the treatment groups in favor of INVEGA SUSTENNA®.
The efficacy of INVEGA SUSTENNA® in delaying time to treatment failure compared with selected oral antipsychotic medications was established in a long-term, randomized, flexible-dose study in subjects with schizophrenia and a history of incarceration. Subjects were screened for up to 14 days followed by a 15-month treatment phase during which they were observed for treatment failure. The primary endpoint was time to first treatment failure. Treatment failure was defined as one of the following: arrest and/or incarceration; psychiatric hospitalization; discontinuation of antipsychotic treatment because of safety or tolerability; treatment supplementation with another antipsychotic because of inadequate efficacy; need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization; discontinuation of antipsychotic treatment because of inadequate efficacy; or suicide. Treatment failure was determined by an Event Monitoring Board (EMB) that was blinded to treatment assignment. A total of 444 subjects were randomly assigned to either INVEGA SUSTENNA® (N = 226; median dose 156 mg) or one of up to seven pre-specified, flexibly-dosed, commonly prescribed oral antipsychotic medications (N = 218; aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone). The selection of the oral antipsychotic medication was determined to be appropriate for the patient by the investigator. A statistically significantly longer time to first treatment failure was seen for INVEGA SUSTENNA® compared with oral antipsychotic medications. The median time to treatment failure was 416 days and 226 days for INVEGA SUSTENNA® and antipsychotic medications, respectively. A Kaplan-Meier plot of time to first treatment failure is shown in Figure 4. The frequencies of first treatment failure events by type are shown in Table 15. The time to first arrest and/or incarceration or psychiatric hospitalization was also statistically significantly longer for the INVEGA SUSTENNA® group compared to the oral antipsychotic group.

Table 15: Components of Composite Endpoint in a Long-Term, Randomized, Flexible-Dose Study in Subjects with Schizophrenia and a History of Incarceration (Schizophrenia Study 6)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>INVEGA SUSTENNA® (N=226) frequency (%)</th>
<th>Oral Antipsychotics (N=218) frequency (%)</th>
<th>Hazard Ratioa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Treatment Failures</td>
<td>90 (39.8%)</td>
<td>117 (53.7%)</td>
<td>0.70 [0.53, 0.92]</td>
</tr>
<tr>
<td>First Treatment Failure Component Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Arrest and/or incarceration</td>
<td>48 (21.2%)</td>
<td>64 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>• Psychiatric hospitalization</td>
<td>18 (8.0%)</td>
<td>26 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>• Discontinuation of antipsychotic treatment because of safety or tolerability</td>
<td>15 (6.6%)</td>
<td>8 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>• Treatment supplementation with another antipsychotic because of inadequate efficacy</td>
<td>5 (2.2%)</td>
<td>6 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>• Need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization</td>
<td>3 (1.3%)</td>
<td>4 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>• Discontinuation of antipsychotic treatment because of inadequate efficacy</td>
<td>1 (0.4%)</td>
<td>9 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>• Suicide</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

| Arrest and/or Incarceration or Psychiatric Hospitalization Events, regardless of whether they were first eventsb | 76 (33.6%) | 98 (45.0%) | 0.70 [0.52, 0.94] |

* Median time to first treatment failure: 416 days with INVEGA SUSTENNA®; 226 days with oral antipsychotics

a Hazard ratio of INVEGA SUSTENNA® to Oral Antipsychotics based on Cox regression model for time-to-event analysis. Note that the hazard ratio did not appear constant throughout the trial.

b Analysis results, which incorporated relevant events collected after discontinuation for those who discontinued, were consistent with the results from the pre-specified analysis of this secondary endpoint.

14.2 Schizoaffective Disorder

Maintenance Treatment – Monotherapy and as Adjunct to Mood Stabilizer or Antidepressant (SAff Study 1: SCA-3004)

The efficacy of INVEGA SUSTENNA® in maintaining symptom control in schizoaffective disorder was established in a long-term double-blind, placebo-controlled, flexible-dose randomized-withdrawal study designed to delay relapse in adult subjects who met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders. The population included subjects with schizoaffective bipolar and depressive types. Subjects received INVEGA SUSTENNA® either as monotherapy or as an adjunct to stable doses of antidepressant or mood stabilizers.

This study included a 13-week, open-label, flexible-dose (INVEGA SUSTENNA® 78 mg, 117 mg, 156 mg, or 234 mg) lead-in period which enrolled a total of 667 subjects who had 1) acute exacerbation of psychotic symptoms; 2) score ≥4 on ≥3 PANSS items of delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, tension, and poor impulse control; and 3) prominent mood symptoms ≥16 on the Young Mania Rating Scale (YMRS) and/or the Hamilton Rating Scale for Depression, 21-item version (HAM-D-21). Subjects were 19 to 66 years old (mean 39.5 years) and 53.5% were male. The mean scores at open-label enrollment of PANSS total was 85.8 (range 42 to 128), HAM-D-21 was 20.4 (range 3 to 43), YMRS was 18.6 (range 0 to 50), and CGI-S-SCA was 4.4 (range 2 to 6).

After the 13-week open-label flexible-dose INVEGA SUSTENNA® treatment, 432 subjects met stabilization criteria (PANSS total score ≤70, YMRS ≤12, and HAM-D-21 ≤12) and continued into the 12-week open-label fixed-dose stabilization period.

A total of 234 subjects who met stabilization criteria for 12 consecutive weeks were randomized (1:1) to continue the same dose of INVEGA SUSTENNA® or placebo in the 15-month, double-blind, maintenance period. For the 164 subjects who were randomized to INVEGA SUSTENNA®, dose distribution was 78 mg (4.9%), 117 mg (8.8%), 156 mg (47.0%), and 234 mg (38.4%). The primary efficacy variable was time to relapse. Relapse was defined as the first occurrence of one or more of the following: 1) psychiatric hospitalization; 2) intervention employed to avert hospitalization; 3) clinically significant self-injury, suicidal or homicidal ideation or violent behavior; 4) a score of ≥8 (if the score was ≤4 at randomization) of any of the individual PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, or poor impulse control; 5) on two consecutive assessments within 7 days: ≥25% increase (if the score at
randomization was >45 or ≥10-point increase (if the score at randomization was ≤45) in total PANSS score; a score of ≥5 (if the score was ≤3 at randomization) of any of the individual PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, or poor impulse control; an increase of ≥2 points (if the score was 1 [not ill] to 2 [mildly ill] at randomization) or increase of ≥1 point (if the score was ≥4 [moderately ill or worse] at randomization) in CGI-S-SCA overall score.

There was a statistically significant difference in time to relapse between the treatment groups in favor of INVEGA SUSTENNA®. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 5.

**Figure 5: Kaplan-Meier Plot of Cumulative Proportion of Subjects with Relapse Over Time (SAff Study 1)**

Table 16 summarizes the number of subjects with relapse in the overall population, by subgroup (monotherapy vs. adjunctive therapy), and by symptom type at the first occurrence of relapse.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All Subjects</th>
<th>Monotherapy subset</th>
<th>Adjunct to Antidepressants or Mood Stabilizer subset</th>
<th>Psychotic Symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=170</td>
<td>57 (33.5%)</td>
<td>24 (32.9%)</td>
<td>33 (34.0%)</td>
<td>53 (31.2%)</td>
</tr>
<tr>
<td>INVEGA SUSTENNA® N=164</td>
<td>25 (15.2%)</td>
<td>9 (11.5%)</td>
<td>16 (18.6%)</td>
<td>21 (12.8%)</td>
</tr>
</tbody>
</table>

* 8 subjects experienced a relapse without psychotic symptoms.
* 16 subjects experienced a relapse without any mood symptoms.

16 **HOW SUPPLIED/STORAGE AND HANDLING**

INVEGA SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular use in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The kit contains a prefilled syringe and 2 safety needles (a 1-inch 23 gauge safety needle and a 1½-inch 22 gauge safety needle).

**Table 16: Summary of Relapse Rates (SAff Study 1).**

### INVEGA SUSTENNA® (paliperidone palmitate)

extended-release injectable suspension, for intramuscular use

to the emergency room if they experience the following signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia [see Warnings and Precautions (5.3)].

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur [see Warnings and Precautions (5.5)].

Orthostatic Hypotension

Counsel patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose [see Warnings and Precautions (5.6)].

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia they should have their CBC monitored while taking INVEGA SUSTENNA® [see Warnings and Precautions (5.9)].

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of INVEGA SUSTENNA®. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males [see Warnings and Precautions (5.10)].

Interference with Cognitive and Motor Performance

As INVEGA SUSTENNA® has the potential to impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA SUSTENNA® therapy does not affect them adversely [see Warnings and Precautions (5.11)].

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism [see Warnings and Precautions (5.14)].

Heat Exposure and Dehydration

Counsel patients on the importance of avoiding overheating and dehydration [see Warnings and Precautions (5.15)].

Concomitant Medication

Advise patients to inform their healthcare providers if they are taking, or plan to take any prescription or over-the-counter drugs as there is a potential for interactions [see Drug Interactions (7)].

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with INVEGA SUSTENNA®. Advise patients that INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to INVEGA SUSTENNA® during pregnancy [see Use in Specific Populations (8.1)].

Lactation

Advise breastfeeding women using INVEGA SUSTENNA® to monitor infants for somnolence, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs [see Use in Specific Populations (8.2)].

Infertility

Advise females of reproductive potential that INVEGA SUSTENNA® may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible [see Use in Specific Populations (8.3)].

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

Product of Ireland

Manufactured by: Janssen Pharmaceutical NV, Beerse, Belgium

Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560

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What is the most important information I should know about INVEGA SUSTENNA®?
INVEGA SUSTENNA® can cause serious side effects, including:
- Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis). INVEGA SUSTENNA® is not for treating dementia-related psychosis.

What is INVEGA SUSTENNA®?
INVEGA SUSTENNA® is a prescription medicine given by injection by a healthcare professional and used to treat:
- schizophrenia in adults
- schizoaffective disorder in adults either alone or with other medicines such as mood stabilizers or antidepressants
It is not known if INVEGA SUSTENNA® is safe and effective in children under 18 years of age.

Who should not receive INVEGA SUSTENNA®?
Do not receive INVEGA SUSTENNA® if you:
- are allergic to paliperidone, paliperidone palmitate, risperidone, or any of the ingredients in INVEGA SUSTENNA®. See the end of this Patient Information leaflet for a complete list of ingredients in INVEGA SUSTENNA®.

What should I tell my healthcare provider before receiving INVEGA SUSTENNA®?
Before you receive INVEGA SUSTENNA®, tell your healthcare provider about all your medical conditions, including if you:
- have had Neuroleptic Malignant Syndrome (NMS)
- have or have had heart problems, including a heart attack, heart failure, abnormal heart rhythm, or long QT syndrome
- have or have had low levels of potassium or magnesium in your blood
- have or have had uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)
- have or have had kidney or liver problems
- have diabetes or have a family history of diabetes
- have had a low white blood cell count
- have had problems with dizziness or fainting or are being treated for high blood pressure
- have or have had seizures or epilepsy
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if INVEGA SUSTENNA® will harm your unborn baby.
  - If you become pregnant while taking INVEGA SUSTENNA®, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
  - Infants born to women who are treated with INVEGA SUSTENNA® may experience symptoms such as tremors, irritability, excessive sleepiness, eye twitching, muscle spasms, decreased appetite, difficulty breathing, or abnormal movement of arms and legs. Let your healthcare provider know if these symptoms occur.
- are breastfeeding or plan to breastfeed. INVEGA SUSTENNA® can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive INVEGA SUSTENNA®.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show to your healthcare provider or pharmacist when you get a new medicine.
How will I receive INVEGA SUSTENNA®?

- Follow your INVEGA SUSTENNA® treatment schedule exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much INVEGA SUSTENNA® you will receive and when you will receive it.
- INVEGA SUSTENNA® is given as an injection by your healthcare provider into the muscle (intramuscularly) of your arm or your buttocks.
- When you receive your first dose of INVEGA SUSTENNA® you will need to get a second dose 1 week later. After that you will only need to get a dose 1 time a month.

What should I avoid while receiving INVEGA SUSTENNA®?

- INVEGA SUSTENNA® may affect your ability to make decisions, think clearly, or react quickly. Do not drive, operate heavy machinery, or do other dangerous activities until you know how INVEGA SUSTENNA® affects you.
- Avoid getting overheated or dehydrated.

What are the possible side effects of INVEGA SUSTENNA®?

INVEGA SUSTENNA® may cause serious side effects, including:

- See “What is the most important information I should know about INVEGA SUSTENNA®”
- stroke in elderly people (cerebrovascular problems) that can lead to death
- Neuroleptic Malignant Syndrome (NMS). NMS is a rare but very serious problem that can happen in people who receive INVEGA SUSTENNA®, NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have any of these symptoms:
  - high fever
  - severe muscle stiffness
  - confusion
  - loss of consciousness
  - changes in your breathing, heartbeat and blood pressure
- problems with your heartbeat. These heart problems can cause death. Call your healthcare provider right away if you have any of these symptoms:
  - passing out or feeling like you will pass out
  - dizziness
  - feeling as if your heart is pounding or missing beats
- uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)
- metabolic changes. Metabolic changes may include high blood sugar (hyperglycemia), diabetes mellitus and changes in the fat levels in your blood (dyslipidemia), and weight gain.
- low blood pressure and fainting
- changes in your blood cell counts
- high level of prolactin in your blood (hyperprolactinemia). INVEGA SUSTENNA® may cause a rise in the blood levels of a hormone called prolactin (hyperprolactinemia) that may cause side effects including missed menstrual periods, leakage of milk from the breasts, development of breasts in men, or problems with erection.
- problems thinking clearly and moving your body
- seizures
- difficulty swallowing that can cause food or liquid to get into your lungs
- prolonged or painful erection lasting more than 4 hours. Call your healthcare provider or go to your nearest emergency room right away if you have an erection that lasts more than 4 hours.
- problems with control of your body temperature especially when you exercise a lot or spend time doing things that make you warm. It is important for you to drink water to avoid dehydration.
The most common side effects of INVEGA SUSTENNA® include: injection site reactions, sleepiness or drowsiness, dizziness, feeling restlessness or needing to be constantly moving, abnormal muscle movements including tremor (shaking), shuffling, uncontrolled involuntary movements, and abnormal movements of your eyes.

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of INVEGA SUSTENNA®. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

<table>
<thead>
<tr>
<th>What are the ingredients in INVEGA SUSTENNA®?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredient:</strong> paliperidone palmitate</td>
</tr>
<tr>
<td><strong>Inactive ingredients:</strong> polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection</td>
</tr>
</tbody>
</table>

Revised: 07/2018

Manufactured by: Janssen Pharmaceutica NV, Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560
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