INVEGA TRINZA® (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 TRINZA® safely and effectively. See full prescribing information for INVEGA TRINZA®.

INVEGA TRINZA® (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 TRINZA® is not approved for use in patients with dementia-related psychosis. (5.1)

---------------------------- RECENT MAJOR CHANGES ---------------------------- 2/2021

INVEGA TRINZA®, a 3-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) for at least four months. (1)

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

Warnings and Precautions (5.3, 5.5) 2/2021

INVEGA TRINZA® is not approved for use in patients with dementia-related psychosis. (5.1)

INVEGA TRINZA® is not recommended. (2.5)

Hyperprolactinemia: Evaluate prolactin levels at baseline and periodically during treatment with INVEGA TRINZA®. (4)

-------------------------- DOSAGE FORMS AND STRENGTHS ------------------------

INVEGA TRINZA® (paliperidone palmitate)

Extended-release injectable suspension: 273 mg/0.88 mL, 410 mg/1.32 mL, 546 mg/1.75 mL, or 819 mg/2.63 mL (3)

CONTRAINDICATIONS

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities). INVEGA TRINZA® is not approved for use in patients with dementia-related psychosis (5.2)

Neuroleptic Malignant Syndrome: Manage with immediate discontinuation of drug and close monitoring (5.3)

QT Prolongation: Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)

Tardive Dyskinesia: Discontinue drug if clinically appropriate (5.5)

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
- Hyperglycemia and Diabetes Mellitus: Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
- Dyslipidemia: Undesirable alterations have been observed. (5.6)
- Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.6)

Orthostatic Hypotension and Syncope: Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)

Leukopenia, Neutropenia, and Agranulocytosis: Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.9)

Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration (5.10)

Potential for Cognitive and Motor Impairment: Use caution when operating machinery (5.11)

Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. (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

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 TRINZA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (7.2, 12.3)

USING 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: 8/2021

If the Last Dose of INVEGA SUSTENNA® is:

<table>
<thead>
<tr>
<th>Dosage</th>
<th>INVEGA TRINZA® at the Following Dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 mg</td>
<td>273 mg</td>
</tr>
<tr>
<td>117 mg</td>
<td>410 mg</td>
</tr>
<tr>
<td>156 mg</td>
<td>546 mg</td>
</tr>
<tr>
<td>234 mg</td>
<td>819 mg</td>
</tr>
</tbody>
</table>

Conversion from the INVEGA SUSTENNA® 39 mg dose was not studied.

- Missed Doses: Missing doses of INVEGA TRINZA® should be avoided. To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): INVEGA TRINZA® is not recommended. (2.5)
- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Adjust dosage and stabilize the patient using INVEGA SUSTENNA®, then transition to INVEGA TRINZA®. See above table. (2.5)
INVEGA TRINZA® (paliperidone palmitate) | INVEGA TRINZA® (paliperidone palmitate)

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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INVEGA TRINZA® (paliperidone palmitate), a 3-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) for at least four months [see Dosage and Administration (2.2) and Clinical Studies (14)].

INVEGA TRINZA® should be administered once every 3 months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of INVEGA SUSTENNA® be the same dosage strength before starting INVEGA TRINZA®.

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. It is important to shake the syringe vigorously for at least 15 seconds within 5 minutes prior to injection. Inject INVEGA TRINZA® within 5 minutes of shaking vigorously [see Dosage and Administration (2.8)].

INVEGA TRINZA® is intended for intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.

INVEGA TRINZA® must be administered using only the thin wall needles that are provided in the INVEGA TRINZA® pack. Do not use needles from the 1-month paliperidone palmitate extended-release injectable suspension pack or other commercially-available needles to reduce the risk of blockage.

Deltoid Injection
The recommended needle size for administration of INVEGA TRINZA® into the deltoid muscle is determined by the patient’s weight:
- For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

Gluteal Injection
Regardless of patient weight, the recommended needle size for administration of INVEGA TRINZA® into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle. Administer into the upper-outter quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

Incomplete Administration
To avoid an incomplete administration of INVEGA TRINZA®, ensure that the prefilled syringe is shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection [see Dosage and Administration (2.8)].

However, in the event of an incompletely administered dose, do not re-inject the dose remaining in the syringe and do not administer another dose of INVEGA TRINZA®. Closely monitor and treat the patient with oral supplementation as clinically appropriate until the next scheduled 3-month injection of INVEGA TRINZA®.

2.2 Schizophrenia
Adults
INVEGA TRINZA® is to be used only after INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of INVEGA SUSTENNA® be the same dosage strength before starting INVEGA TRINZA®.

Initiate INVEGA TRINZA® when the next 1-month paliperidone palmitate dose is scheduled with an INVEGA TRINZA® dose based on the previous 1-month injection dose, using the equivalent 3.5-fold higher dose as shown in Table 1. INVEGA TRINZA® may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.
2.3 Missed Doses

Dosing Window

Missed doses of INVEGA TRINZA® should be avoided. If necessary, patients may be given the injection up to 2 weeks before or after the 3-month time point.

Missed Dose 3½ Months to 4 Months Since Last Injection

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of INVEGA TRINZA®, the previously administered INVEGA TRINZA® dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

Missed Dose 4 Months to 9 Months Since Last Injection

If 4 months up to and including 9 months have elapsed since the last injection of INVEGA TRINZA®, do NOT administer the next dose of INVEGA TRINZA®. Instead, use the re-initiation regimen shown in Table 2.

Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of INVEGA TRINZA®

<table>
<thead>
<tr>
<th>If the Last Dose of INVEGA TRINZA® was:</th>
<th>Administer INVEGA SUSTENNA®, two doses one week apart (into deltoid or gluteal muscle)</th>
<th>Then administer INVEGA TRINZA® extended-release injectable suspension (into deltoid or gluteal muscle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
<td>1 month after Day 8</td>
</tr>
<tr>
<td>273 mg</td>
<td>78 mg</td>
<td>78 mg</td>
</tr>
<tr>
<td>410 mg</td>
<td>117 mg</td>
<td>117 mg</td>
</tr>
<tr>
<td>546 mg</td>
<td>156 mg</td>
<td>156 mg</td>
</tr>
<tr>
<td>819 mg</td>
<td>156 mg</td>
<td>156 mg</td>
</tr>
</tbody>
</table>

a See Instructions for Use for deltoid injection needle selection based on body weight.

Missed Dose Longer than 9 Months Since Last Injection

If more than 9 months have elapsed since the last injection of INVEGA TRINZA®, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. INVEGA TRINZA® can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

2.4 Use with Risperidone or with Oral Paliperidone

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

2.5 Dosage Adjustment in Renal Impairment

INVEGA TRINZA® 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], adjust dosage and stabilize the patient using the 1-month paliperidone palmitate extended-release injectable suspension, then transition to INVEGA TRINZA® [see Table 1, Dosage and Administration (2.2)]. [See also Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

INVEGA TRINZA® 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 INVEGA TRINZA® to the 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension

For switching from INVEGA TRINZA® to INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension), the 1-month paliperidone palmitate extended-release injectable suspension should be started 3 months after the last INVEGA TRINZA® dose, using the equivalent 3.5-fold lower dose as shown in Table 3. The 1-month paliperidone palmitate extended-release injectable suspension should then continue, dosed at monthly intervals.

Table 3. Conversion From INVEGA TRINZA® to INVEGA SUSTENNA®

<table>
<thead>
<tr>
<th>If the Last Dose of INVEGA TRINZA® is:</th>
<th>3 Months Later at the Following Dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>273 mg</td>
<td>78 mg</td>
</tr>
<tr>
<td>410 mg</td>
<td>117 mg</td>
</tr>
<tr>
<td>546 mg</td>
<td>156 mg</td>
</tr>
<tr>
<td>819 mg</td>
<td>234 mg</td>
</tr>
</tbody>
</table>

Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of INVEGA TRINZA®

2.8 Instructions for Use

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

For intramuscular injection only. Do not administer by any other route.

Important

INVEGA TRINZA® should be administered by a healthcare professional as a single injection. DO NOT divide dose into multiple injections.

INVEGA TRINZA® is intended for intramuscular use only. Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.

Read complete instructions prior to use.

Dosing

This medication should be administered once every 3 months.

Preparation

Peel off tab label from the syringe and place in patient record.

INVEGA TRINZA® requires longer and more vigorous shaking than INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension). Shake the syringe vigorously, with the syringe tip pointing up, for at least 15 seconds within 5 minutes prior to administration (see Step 2).

Thin Wall Safety Needle Selection

Thin wall safety needles are designed to be used with INVEGA TRINZA®. Therefore, it is important to only use the needles provided in the INVEGA TRINZA® kit.
INVEGA TRINZA® (paliperidone palmitate)

Dose pack contents

<table>
<thead>
<tr>
<th>Prefilled Syringe</th>
<th>Thin Wall Safety Needles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syringe Tip</td>
<td>Rubber Cap</td>
</tr>
<tr>
<td>Rubber Cap</td>
<td>Luer Connection</td>
</tr>
<tr>
<td>Needle Sheath</td>
<td></td>
</tr>
<tr>
<td>Needle Pouch</td>
<td></td>
</tr>
</tbody>
</table>

1 Select needle

Needle selection is determined by injection area and patient weight.

If administering a Deltoid injection

- If patient weighs: Less than 90 kg pink hub
  - 22G×1”
- 90 kg or more yellow hub
  - 22G×1½”

If administering a Gluteal injection

- If patient weighs: Less than 90 kg yellow hub
  - 22G×1½”
- 90 kg or more yellow hub
  - 22G×1½”

Immediately discard the unused needle in an approved sharps container. Do not save for future use.

2 Prepare for injection

SHAKE VIGOROUSLY for at least 15 seconds

With the syringe tip pointing up, SHAKE VIGOROUSLY with a loose wrist for at least 15 seconds to ensure a homogeneous suspension.

NOTE: This medication requires longer and more vigorous shaking than the 1-month paliperidone palmitate extended-release injectable suspension.

Proceed to the next step immediately after shaking. If more than 5 minutes pass before injection, shake vigorously, with the syringe tip pointing up, again for at least 15 seconds to re-suspend the medication.

Check suspension

After shaking the syringe for at least 15 seconds, check the liquid in the viewing window. The suspension should appear uniform and milky white in color. It is also normal to see small air bubbles.
Open needle pouch and remove cap

First, open needle pouch by peeling the cover back half way. Place on a clean surface. Then, holding the syringe upright, twist and pull the rubber cap to remove.

Grasp needle pouch

Fold back needle cover and plastic tray. Then, firmly grasp the needle sheath through the pouch, as shown.

Attach needle

With your other hand, hold the syringe by the luer connection and attach it to the safety needle with a gentle clockwise twisting motion.

Do not remove the pouch until the syringe and needle are securely attached.

Remove needle sheath

Pull the needle sheath away from the needle in a straight motion.

Do not twist the sheath, as this may loosen the needle from the syringe.

INVEGA TRINZA® (paliperidone palmitate)

Remove air bubbles

Hold the syringe upright and tap gently to make any air bubbles rise to the top. Remove air by pressing the plunger rod upward carefully until a drop of liquid comes out of the needle tip.

3 Inject

Inject dose

Slowly inject the entire contents of the syringe intramuscularly, deep into the selected deltoid or gluteal muscle. Do not administer by any other route.

4 After injection

Secure needle

After the injection is complete, use your thumb or a flat surface to secure the needle in the safety device. The needle is secure when a “click” sound is heard.

INVEGA TRINZA® (paliperidone palmitate)
INVEGA TRINZA® (paliperidone palmitate)

Dispose properly

Dispose of the syringe and unused needle in an approved sharps container.

INVEGA TRINZA® (paliperidone palmitate)

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 or sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), 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 paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study with oral paliperidone in adult patients, and in four fixed-dose efficacy studies and one maintenance study of the 1-month paliperidone palmitate injectable product. In the Through 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 (QT interval corrected for heart rate using the population specified linear method) of 12.3 msec (90% CI: 8.9; 15.6) 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 (CmaxSS=113 ng/mL) was approximately 2-fold the exposure with the maximum recommended 819 mg dose of INVEGA TRINZA® administered in the deltoid muscle (predicted median CmaxSS=56 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which CmaxSS=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 four fixed-dose efficacy studies of the 1-month paliperidone palmitate injectable product, no subject had 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, 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.

In the long-term maintenance trial of INVEGA TRINZA® in subjects with schizophrenia, an increase in QTcLD exceeding 60 msec was observed in 1 subject (< 1%) in the open-label phase, no subject had an increase in QTcLD exceeding 60 msec after treatment with INVEGA TRINZA® in the double-blind phase, and no subject had a QTcLD value of >480 msec at any point in the study.

3 DOSAGE FORMS AND STRENGTHS

INVEGA TRINZA® is available as a white to off-white aqueous extended-release injectable suspension for intramuscular injection in dose strengths of 273 mg/0.88 mL, 410 mg/1.32 mL, 546 mg/1.75 mL, and 819 mg/2.63 mL paliperidone palmitate in single-dose prefilled syringes.

4 CONTRAINDICATIONS

INVEGA TRINZA® is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA TRINZA® 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 45%, 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 TRINZA® 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 reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, the 1-month paliperidone palmitate extended-release injectable suspension, or INVEGA TRINZA® in elderly patients with dementia. These medications are not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.1)].

5.3 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue INVEGA TRINZA® and provide symptomatic treatment and monitoring.

INVEGA TRINZA® (paliperidone palmitate)

INVEGA TRINZA® is not approved for the treatment and monitoring.

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If NMS is suspected, immediately discontinue INVEGA TRINZA® and provide symptomatic treatment and monitoring.
5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoadosis or hypoglycemic coma or death, have been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials. Hyperglycemia and diabetes have been reported in trial subjects treated with INVEGA TRINZA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Data from the long-term maintenance trial with INVEGA TRINZA® in subjects with schizophrenia are presented in Table 5.

Table 5. Change in Fasting Glucose from the Long-Term Maintenance Trial with INVEGA TRINZA® in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Paliperidone Palmitatea</th>
<th>Placebo</th>
<th>INVEGA TRINZA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-Label Phase (relative to open-label baseline)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>n=397</td>
<td>n=120</td>
</tr>
<tr>
<td>Serum Glucose Change from baseline</td>
<td>-1.2</td>
<td>-1.6</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Paliperidone Palmitatea</th>
<th>Placebo</th>
<th>INVEGA TRINZA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-Blind Phase (relative to double-blind baseline)</td>
<td>Proportion of Patients with Shifts</td>
<td>n=397</td>
<td>n=128</td>
</tr>
<tr>
<td>Serum Glucose Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>2.3%</td>
<td>2.3%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

- During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA® [see Clinical Studies (14)].

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Data from the long-term maintenance trial with INVEGA TRINZA® in subjects with schizophrenia are presented in Table 6.

Table 6. Change in Fasting Lipids from the Long-Term Maintenance Trial with INVEGA TRINZA® in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Paliperidone Palmitatea</th>
<th>Placebo</th>
<th>INVEGA TRINZA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-Label Phase (relative to open-label baseline)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>n=400</td>
<td>n=120</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2.0%</td>
<td>3.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>LDL Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>0.3%</td>
<td>0.8%</td>
<td>0%</td>
</tr>
<tr>
<td>HDL Normal to Low (&lt;40 mg/dL to ≥160 mg/dL)</td>
<td>8.6%</td>
<td>9.4%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Triglycerides Normal to High (&lt;150 mg/dL to ≥200 mg/dL)</td>
<td>4.5%</td>
<td>1.6%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

- During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA® [see Clinical Studies (14)].

Weight Gain

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

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥7% of body weight from the long-term maintenance trial with INVEGA TRINZA® in subjects with schizophrenia are presented in Table 7.

Table 7. Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Gain in Body Weight from the Long-Term Maintenance Trial with INVEGA TRINZA® in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Paliperidone Palmitatea</th>
<th>Placebo</th>
<th>INVEGA TRINZA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-Label Phase (relative to open-label baseline)</td>
<td>Weight (kg) Change from baseline</td>
<td>n=466</td>
<td>n=142</td>
</tr>
<tr>
<td>Weight Gain ≥7% increase from baseline</td>
<td>15.2%</td>
<td>0.7%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

- During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA® [see Clinical Studies (14)].

5.7 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. In the long-term maintenance trial, syncope was reported in <1% (1/506) of subjects treated with the 1-month paliperidone palmitate extended-release injectable suspension during the open-label phase; there were no cases reported during the double-blind phase in either treatment group. In the long-term maintenance trial, orthostatic hypotension was reported as an adverse event by <1% (1/506) of subjects treated with the 1-month paliperidone palmitate extended-release injectable suspension and <1% (1/379) of subjects after receiving a single-dose of INVEGA TRINZA® during the open-label phase; there were no cases reported during the double-blind phase in either treatment group.
INVEGA TRINZA® (paliperidone palmitate)

INVEGA TRINZA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.8 Falls
Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA TRINZA®, 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 these effects, assess the risk of falls when initiating 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 TRINZA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia 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 TRINZA® 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 treated promptly if such symptoms or signs occur. Discontinue INVEGA TRINZA® 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, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone 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 reduced pituitary gonadotrophin secretion. 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 hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers 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 Pharmacology). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

In a long-term maintenance trial of INVEGA TRINZA®, elevations of prolactin to above the reference range (13.13 ng/mL in males and >26.72 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in a higher percentage of males in the INVEGA TRINZA® group than in the placebo group (46% vs. 25%) and in a higher percentage of females in the INVEGA TRINZA® group than in the placebo group (32% vs. 15%). During the double-blind phase, 1 female (2.4%) in the INVEGA TRINZA® group experienced an adverse reaction of amenorrhea, while no potentially prolactin-related adverse reactions were noted among females in the placebo group. There were no potentially prolactin-related adverse reactions among males in either group.

Prior to the double-blind phase (during the 29-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline in males (N=368) were 17.1 ± 12.6 (40.85 ng/mL in females (N=122). Twelve weeks after a single injection of INVEGA TRINZA® at the end of the open-label phase, mean (SD) prolactin values were 25.8 ± 13.49 ng/mL in males (N=322) and 70.6 ± 20.23 ng/mL in females (N=107). During the open-label phases 27% of females and 42% 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 (7.9% vs. 3.7%). Amenorrhea (4.7%) and galactorrhea (3.1%) were the most commonly observed (≥3%) potentially prolactin-related adverse reactions in females. Among males in the open-label phase, no potentially prolactin-related adverse reaction was observed with a rate greater than 3%.

5.11 Potential for Cognitive and Motor Impairment
Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA TRINZA® [see Adverse Reactions (6.1)]. Antipsychotics, including INVEGA TRINZA®, 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 long-term maintenance trials there were no reports of seizures or convulsions. In the pivotal clinical studies with the 1-month paliperidone palmitate extended-release injectable suspension which included four fixed-dose, double-blind, placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with the 1-month injection 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 TRINZA® 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 TRINZA® 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 TRINZA®, 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 TRINZA® 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 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 and syncope [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 include data from two clinical trials. One is a long-term maintenance trial, in which 506 subjects with schizophrenia received several doses of the 1-month paliperidone palmitate extended-release injectable suspension during the open-label phase, of which 379 subjects continued to receive a single injection of INVEGA TRINZA® during the open-label phase, and 160 subjects were subsequently randomized to receive at least one dose of INVEGA TRINZA® and 145 subjects received placebo during the double-blind placebo-controlled phase. The mean (SD) duration of exposure during the double-blind phase was 150 (79) days in the placebo group and 175 (90) days in the INVEGA TRINZA® group. The other is a Phase 1 study (N=308), which included patients with schizophrenia who received a single injection of INVEGA TRINZA® concomitantly with other oral antipsychotics.
INVEGA TRINZA® (paliperidone palmitate)

Adverse Reactions in a Double-Blind, Placebo-Controlled (Long-Term Maintenance) Clinical Trial

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence of at least 5% in the open-label phase, or in the INVEGA TRINZA® group and at least twice the incidence in the placebo group during the double-blind phase) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism.

Discontinuation of Treatment Due to Adverse Events: The percentages of subjects who discontinued due to adverse events in the long-term maintenance trial were 5.1% during the open-label phase. During the double-blind phase, no INVEGA TRINZA®-treated subject and one placebo-treated subject discontinued due to adverse events.

Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA TRINZA®-Treated Patients: The safety profile of INVEGA TRINZA® was similar to that seen with the 1-month paliperidone extended-release injectable suspension. Table 8 lists the adverse reactions reported in a long-term maintenance trial in subjects with schizophrenia.

Table 8. Incidences of Adverse Reactions 2% or More of INVEGA TRINZA®-Treated Patients (and Greater Than Placebo) for the Open-Label and Double-Blind Phases of a Long-Term Maintenance Trial in Patients with Schizophrenia

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
<th>Percentage of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction</td>
<td>Placebo (N=506)</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Double Blind (N=145)</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>INVEGA TRINZA® (N=160)</td>
<td>3%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Placebo (N=506)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Double Blind (N=145)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>INVEGA TRINZA® (N=160)</td>
<td>10%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Placebo (N=506)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Double Blind (N=145)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>INVEGA TRINZA® (N=160)</td>
<td>9%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Placebo (N=506)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Double Blind (N=145)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>INVEGA TRINZA® (N=160)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 9. Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication

<table>
<thead>
<tr>
<th>EPS Group</th>
<th>Open-label Phase</th>
<th>Placebo</th>
<th>INVEGA TRINZA®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paliperidone Palmitatea</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>(N=506)</td>
<td>(N=145)</td>
<td>(N=160)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Akathisiaa</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Dyskinesiaa</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Use of Anticholinergic Medicationsa</td>
<td>11</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

a During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA®.
Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the Adverse Reactions (6) sections of the package inserts for those products.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with INVEGA TRINZA®

Because paliperidone palmitate is hydrolyzed to paliperidone [see Clinical Pharmacology (12.3)], results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential. In addition, consider the 3-month dosing interval and long half-life of INVEGA TRINZA® [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)].

Table 11. Clinically Important Drug Interactions with INVEGA TRINZA®

<table>
<thead>
<tr>
<th>Concomitant Drug Name or Drug Class</th>
<th>Clinical Rationale</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally Acting Drugs and Alcohol</td>
<td>Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA TRINZA®.</td>
<td>INVEGA TRINZA® should be used with caution in combination with other centrally acting drugs and alcohol [see Adverse Reactions (6.1, 6.2)].</td>
</tr>
<tr>
<td>Drugs with Potential for Inducing Orthostatic Hypotension</td>
<td>Because INVEGA TRINZA® has the potential for inducing orthostatic hypotension, an additive effect may occur when INVEGA TRINZA® is administered with other therapeutic agents that have this potential [see Warnings and Precautions (5.7)].</td>
<td>Monitor orthostatic vital signs in patients who are vulnerable to hypotension [see Warnings and Precautions (5.7)].</td>
</tr>
<tr>
<td>Strong Inducers of CYP3A4 or P-gp (e.g., carbamazepine, rifampin, or St. John’s Wort)</td>
<td>The concomitant use of paliperidone and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone [see Clinical Pharmacology (12.3)].</td>
<td>Avoid using CYP3A4 and/or P-gp inducers with INVEGA TRINZA® during the 3-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets [see Dosage and Administration (2.7)].</td>
</tr>
<tr>
<td>Levodopa and Other Dopamine Agonists</td>
<td>Paliperidone may antagonize the effect of levodopa and other dopamine agonists.</td>
<td>Monitor and manage patient as clinically appropriate.</td>
</tr>
</tbody>
</table>

7.2 Drugs Having No Clinically Important Interactions with INVEGA TRINZA®

Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA TRINZA® is required when administered concomitantly with valproate [see Clinical Pharmacology (12.3)]. Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA TRINZA® [see Clinical Pharmacology (12.3)]. Pharmacokinetic interaction between lithium and INVEGA TRINZA® is unlikely. Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 enzymes. 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 CYP2C19; an interaction with inhibitors or inducers of these isoforms is unlikely. [see Clinical Pharmacology (12.3)].
18 months after a single-dose administration of INVEGA TRINZA® [see Clinical Pharmacology (12.3)], and the clinical significance of INVEGA TRINZA® 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, loss, 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 of 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 increased risk of relapse, hospitalization, and suicide. Schizophrenia is 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, hyperactivity, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including INVEGA TRINZA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for 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 6 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 risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformations rates.

Animal Data

No developmental toxicity studies were conducted with the 3-month paliperidone palmitate extended-release injectable suspension. There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with 1-month paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 3 times the MRHD of 819 mg of the 3-month paliperidone palmitate extended-release injectable suspension 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 for 7 days after birth, 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.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m² body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or, to effects on the dams (see RISPERDAL® package insert).

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant, or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone’s parent compound, risperidone (see Clinical Considerations). Paliperidone has been detected in plasma in adult subjects up to 10 months after a single-dose administration of INVEGA TRINZA®, and the clinical significance on the breastfed infant is not known [see Clinical Pharmacology (12.3)].

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for INVEGA TRINZA® and any potential adverse effects on the breastfed child from INVEGA TRINZA® or from the mother’s underlying condition.

Clinical Considerations

Infants exposed to INVEGA TRINZA® through breast milk should be monitored for excess jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of paliperidone (D₂ receptor antagonism), treatment with INVEGA TRINZA® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see Warnings and Precautions (5.10)].

8.4 Pediatric Use

Safety and effectiveness of INVEGA TRINZA® in patients less than 18 years of age have not been established. Use of INVEGA TRINZA® is not recommended in pediatric patients because of the potential longer duration of an adverse event compared to shorter-acting products. In clinical trials of oral paliperidone, there were notably higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescent population as compared to the adult studies.

Juvenile Animal Studies

No juvenile animal studies were conducted with the 3-month paliperidone palmitate extended-release injectable suspension.

In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents dosed at 12 mg/day. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, and at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels of risperidone 2-3 times those in adolescents.

8.5 Geriatric Use

Clinical studies of INVEGA TRINZA® 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)], who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, monitor renal function and adjust dosage [see Dosage and Administration (2.5)].

8.6 Renal Impairment

Use of INVEGA TRINZA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Use of INVEGA TRINZA® in patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min) is based on the previous dose of the 1-month paliperidone palmitate extended-release injectable suspension that the patient was stabilized on prior to initiation of INVEGA TRINZA® [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

INVEGA TRINZA® 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 [see Clinical Pharmacology (12.3)].
8.8 Patients with Parkinson’s Disease or Lewy Body Dementia
Patients with Parkinson’s Disease or Lewy Body Dementia may experience increased sensitivity to INVEGA TRINZA®. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
INVEGA TRINZA® (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 premarking studies with paliperidone palmitate injection. Because INVEGA TRINZA® 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 premarking 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. Torsade de points and ventricular 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 Overdose
Contact a Certified Poison Control Center for the most up to date information on the management of paliperidone and INVEGA TRINZA® 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 overdose with any drug. Consider the possibility of multiple drug overdose. Ensure an 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 TRINZA® and the long apparent half-life of paliperidone when assessing treatment needs and recovery.

11 DESCRIPTION
INVEGA TRINZA® contains paliperidone palmitate. The active ingredient, paliperidone, is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives.

INVEGA TRINZA® contains a racemic mixture of (+)- and (-)- paliperidone palmitate. The chemical name is (SRS)-3-(2-[4-(6-Fuoro-1,2-benzisoxazol-3-yl)pyridin-1-yl]ethyl)-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate. Its molecular formula is C_{95}H_{146}N_{11}O_{21} and its molecular weight is 664.89. The structural formula is:

\[
\text{INVEGA TRINZA® (paliperidone palmitate)}
\]

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 TRINZA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in single-dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate in single-dose prefilled syringes. The drug product is a suspension of the free base of paliperidone palmitate in water for injection containing sodium hydroxide (5.4 mg/mL used as an alkalizing agent to set the pH at 7), and polysorbate 20 (10 mg/mL), polyethylene glycol 4000 (75 mg/mL), citric acid monohydrate (7.5 mg/mL), sodium dihydrogen phosphate monohydrate (6 mg/mL), sodium hydroxide (5.4 mg/mL used as an alkalizing agent to set the pH at 7), and water for injection.

INVEGA TRINZA® is provided in a single-dose prefilled syringe (cyclic-olefin-copolymer) with either 175 mg (0.875 mL), 263 mg (1.315 mL), 350 mg (1.75 mL), or 525 mg (2.625 mL) paliperidone (as 273 mg, 410 mg, 546 mg, or 819 mg paliperidone palmitate) dissolved with a plunger and a top cap (borosilicate rubber), a backstop, and 2 types of commercially available needles: a thin walled 22G, 1 ½-inch safety needle and a thin walled 22G, 1-inch safety needle.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Paliperidone palmitate is hydrolyzed 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 (D₂) and serotonin Type 2 (5HT₂A) receptor antagonism.

12.2 Pharmacodynamics
In vitro, paliperidone acts as an antagonist at the central dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂A) receptors with binding affinities (Ki values) of 1.6-2.8 nM for D₂ and 0.8-1.2 nM for 5HT₂A receptors. Paliperidone is also active as an antagonist at the α₁ and α₂ adrenergic receptors and H₁ histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β₁- and β₂-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar in vitro.

12.3 Pharmacokinetics
Absorption and Distribution
Due to its extremely low water solubility, the 3-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection and may show variable absorption before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug starts as early as 1 day and lasts for as long as 18 months.

Following a single intramuscular dose of INVEGA TRINZA®, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 30-33 days. Following intramuscular injection of INVEGA TRINZA® at doses of 273-819 mg in the deltoid muscle, on average, an 11-12% higher C_{max} was observed compared with injection in the gluteal muscle. The release profile and dosing regimen of INVEGA TRINZA® results in sustained therapeutic concentrations over 3 months. The total and peak exposure of paliperidone following INVEGA TRINZA® administration was dose-proportional over a 273-819 mg dose range. The mean steady-state peak:trough ratio for a INVEGA TRINZA® dose was 1.6 following gluteal administration and 1.7 following deltoid administration. Following administration of INVEGA TRINZA®, the apparent volume of distribution of paliperidone is 1960 L.

The plasma protein binding of racemic paliperidone is 74%. Following administration of INVEGA TRINZA®, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.7-1.8.

Metabolism and Elimination
In a study with oral immediate-release ¹⁴C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ¹⁴C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified in vivo, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence in vivo that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

The median apparent half-life of paliperidone following INVEGA TRINZA® administration over the dose range of 273-819 mg ranged from 84-95 days following deltoid injections and 118-139 days following gluteal injections. The half-life of paliperidone remaining in the circulation 18 months after dosing of 819 mg INVEGA TRINZA® is estimated to be 3% (following deltoid injection) or 7% (following gluteal injection) of the average steady-state values.

Long-acting 3-month paliperidone palmitate injection versus other paliperidone formulations
INVEGA TRINZA® is designed to deliver paliperidone over a 3-month period, while 1-month paliperidone palmitate injection is administered on a monthly basis. INVEGA TRINZA®, when administered at doses that are 3.5-fold higher than the corresponding dose of 1-month paliperidone palmitate injection, results in paliperidone exposures similar to those obtained with corresponding monthly doses of 1-month paliperidone palmitate injection and corresponding once daily doses of paliperidone extended-release tablets. The exposure range for INVEGA TRINZA® is encompassed within the exposure range for the approved dose strengths of paliperidone extended-release tablets.
The between-subject variability for paliperidone pharmacokinetics following delivery from INVEGA TRINZA® was similar to the variability for paliperidone extended-release tablets. Because of the difference in median pharmacokinetic profiles among the three formulations, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

**Drug Interaction Studies**

No specific drug interaction studies have been performed with INVEGA TRINZA®. The information below is obtained from studies with oral paliperidone.

**Effects of other drugs on the exposures of INVEGA TRINZA®** are summarized in Figure 1. After oral administration of 20 mg/day of paroxetine (a potent CYP2D6 inhibitor), an increase in mean C_{max} 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 C_{max} 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.

**Figure 1:** The effects of other drugs on INVEGA TRINZA® pharmacokinetics.

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Drug} & \text{CYP2D6} & \text{CYP3A4} & \text{Divalproex Sodium ER} \\
\hline
\text{Paroxetine} & \text{Cmax} & \text{AUC} & \text{Cmax} \\
\text{Carbamazepine} & \text{Cmax} & \text{AUC} & \text{Cmax} \\
\text{Divalproex Sodium ER} & \text{Cmax} & \text{AUC} & \text{Cmax} \\
\hline
\end{array}
\]

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; they contribute to only a small fraction of total drug 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 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, 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. Paliperidone is a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available, and the clinical relevance is unknown.

The effects of INVEGA TRINZA® on the exposures of other drugs are summarized in Figure 2.

After oral administration of paliperidone, the steady-state C_{max} and AUC of valproate were not affected in 13 patients stabilized on valproate. In a clinical study, subjects on stable doses of valproate had comparable valproate average plasma concentrations when oral paliperidone extended-release tablets 3-15 mg/day was added to their existing valproate treatment [see Drug Interactions (7.1)].

**Figure 2:** The effects of INVEGA TRINZA® on pharmacokinetics of other drugs.

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Drug} & \text{INVEGA TRINZA Fold Change and 90% CI} \\
\hline
\text{Paroxetine} & \text{Cmax} & \text{AUC} & \text{Cmax} \\
\text{Carbamazepine} & \text{Cmax} & \text{AUC} & \text{Cmax} \\
\text{Divalproex Sodium ER} & \text{Cmax} & \text{AUC} & \text{Cmax} \\
\hline
\end{array}
\]

In *vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Slower absorption was observed in females in a population pharmacokinetic analysis. At apparent steady-state with INVEGA TRINZA®, the trough concentrations were similar between males and females.

Lower C_{max} was observed in overweight and obese subjects. At apparent steady-state with INVEGA TRINZA®, the trough concentrations were similar among normal, overweight, and obese subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity studies were conducted with the 3-month paliperidone palmitate extended-release injectable suspension.

The carcinogenic potential of intramuscularly injected 1-month paliperidone palmitate extended-release injectable suspension was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg/kg/month, which is 0.2, 0.6, and 1 times, respectively, the MRHD of 819 mg of INVEGA TRINZA® 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 0.6 and 1 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 to rodents to human risk is unclear [see Warnings and Precautions (5.7)].

Mutagenesis

No mutagenesis studies were conducted with the 3-month paliperidone palmitate extended-release injectable suspension.

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 the 3-month paliperidone palmitate extended-release injectable suspension. 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, pre- and post-implantation loss 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/kg 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 (0.6 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. When injected subcutaneously, the MRHD. Injection site inflammatory reactions were greater and more advanced than reactions to the 1-month paliperidone palmitate extended-release injectable suspension. Reversibility of these findings was not examined.

14 CLINICAL STUDIES

The efficacy of INVEGA TRINZA® for the treatment of schizophrenia in patients who have been adequately treated for at least 4 months with INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) was evaluated in a long-term double-blind, placebo-controlled randomized-withdrawal trial designed to evaluate time to relapse involving adult subjects who met DSM-IV-TR criteria for schizophrenia.

Patients could enter the study with acute symptoms (if previously treated with oral antipsychotics) or be clinically stable (if treated with long-acting injectable antipsychotics [LAI]). All patients who previously received oral antipsychotics received the paliperidone palmitate 1-month initiation regimen (deltoid injections of 234 mg and 156 mg one week apart), while those patients switching from LAI medication were treated with the 1-month paliperidone palmitate extended-release injectable suspension in place of the next scheduled injection. Specifically:

- For patients entering the study who were already being treated with the 1-month paliperidone palmitate extended-release injectable suspension, their dosing remained unchanged. Patients who were currently receiving the 39 mg dose of 1-month paliperidone palmitate were not eligible to enroll in the study.
- Patients entering the study who were being treated with 25 mg, 37.5 mg, or 50 mg of RISPERDAL CONSTRA® (risperidone long-acting injection) were switched to 78 mg, 117 mg, or 156 mg, respectively, of the 1-month paliperidone palmitate administered in the deltoid muscle.
- Patients entering the study who were being treated with any other LAI product were switched to 234 mg of the 1-month paliperidone palmitate administered in the deltoid muscle.

This study consisted of the following three treatment periods:

- A 17-week flexible-dose open-label period with the 1-month paliperidone palmitate (first part of a 29-week open-label stabilization phase). A total of 506 patients entered this phase of the study. Dosing of the 1-month paliperidone palmitate was individualized based on symptom response, tolerability, and previous medication history. Specifically, the dose could be adjusted at the week 5 and 9 injections and the injection site could be deltoid or gluteal. The week 13 dose had to be the same as the week 9 dose. Patients had to be clinically stable at the end of this period before receiving INVEGA TRINZA® at the week 17 visit. Clinical stability was defined as achieving a PANSS total score <70 at week 17. 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.

- A 23% of patients in the placebo group and 7.4% of patients in the INVEGA TRINZA® group experienced a relapse event. The time to relapse was statistically significantly longer than the placebo group in the INVEGA TRINZA® group (N=148) and the placebo group (N=135).

The primary efficacy variable was time to first relapse. Relapse was pre-defined as 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 total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items.

A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA TRINZA® compared to placebo, and the study was stopped early because efficacy was demonstrated. The most common reason for relapse observed across both treatment groups was increase in the PANSS total score value, followed by psychiatric hospitalization.

Twenty-three percent (23%) of patients in the placebo group and 7.4% of patients in the INVEGA TRINZA® group experienced a relapse event. The time to relapse was statistically significantly longer in patients randomized to the INVEGA TRINZA® group than compared to placebo-treated patients. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 4.

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

Figure 4: Kaplan-Meier Plot of Cumulative Proportion of Patients with Relapse Over Time – Interim Analysis.

The median time to relapse in the placebo group was 274 days. The median time to relapse in the INVEGA TRINZA® group could not be estimated due to low percentage (7.4%) of subjects with relapse.

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA TRINZA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 273 mg/0.88 mL, 410 mg/1.32 mL, 546 mg/1.75 mL, and 819 mg/2.63 mL paliperidone palmitate in single-dose prefilled syringes. The single-use kit contains a prefilled syringe and 2 safety needles (a thin walled 22G, 1-inch safety needle and a thin walled 22G, 1½-inch safety needle).

- 273 mg paliperidone palmitate kit (NDC 50458-606-01)
- 410 mg paliperidone palmitate kit (NDC 50458-607-01)
- 546 mg paliperidone palmitate kit (NDC 50458-608-01)
- 819 mg paliperidone palmitate kit (NDC 50458-609-01)

Storage and Handling

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F and 86°F) are permitted. Do not mix with any other product or diluent.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact their healthcare provider or report to the emergency room if they experience signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status including delirium, 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)].

Metabolic Changes
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight [see Warnings and Precautions (5.6)].

Orthostatic Hypotension
Educate patients about the risk of orthostatic hypotension and syncope, particularlly at the time of initiating treatment, re-initiating treatment, or increasing the dose [see Warnings and Precautions (5.7)].

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

Hyperprolactinemia
Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of INVEGA TRINZA®. 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
Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery, or operating a motor vehicle until they are reasonably certain that INVEGA TRINZA® 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 [Warnings and Precautions (5.14)]

Heat Exposure and Dehydration
Counsel patients regarding appropriate care in 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 medications, because there is a potential for clinically significant interactions [see Drug Interactions (7)].

Alcohol
Advise patients to avoid alcohol during treatment with INVEGA TRINZA® [see Drug Interactions (7.1)].

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with INVEGA TRINZA®. Advise patients that INVEGA TRINZA® 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 TRINZA® during pregnancy [see Use in Specific Populations (8.1)].

Lactation
Advise breastfeeding women using INVEGA TRINZA® 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 TRINZA® 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 TRINZA® (paliperidone palmitate) Extended-Release Injectable Suspension
INVEGA SUSTENNA®, RISPERDAL®, and RISPERDAL CONSTA® are trademarks of Janssen Pharmaceuticals, Inc.

Product of Ireland
Manufactured by:
Janssen Pharmaceutica 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 TRINZA®?

INVEGA TRINZA® 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 TRINZA® is not for treating dementia-related psychosis.

What is INVEGA TRINZA®?

INVEGA TRINZA® is a prescription medicine given by injection by a healthcare professional and used to treat schizophrenia.

INVEGA TRINZA® is used in people who have been treated with INVEGA SUSTENNA® 1 time a month injections for at least 4 months.

It is not known if INVEGA TRINZA® is safe and effective in children under 18 years of age.

Who should not receive INVEGA TRINZA®?

Do not receive INVEGA TRINZA® if you:

- are allergic to paliperidone palmitate, risperidone, or any of the ingredients in INVEGA TRINZA®. See the end of this Patient Information leaflet for a complete list of ingredients in INVEGA TRINZA®.

What should I tell my healthcare provider before receiving INVEGA TRINZA®?

Before you receive INVEGA TRINZA®, 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 or have had 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 TRINZA® will harm your unborn baby.
  - If you become pregnant while taking INVEGA TRINZA®, 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 TRINZA® 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 TRINZA® can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive INVEGA TRINZA®.

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 TRINZA®?

- Follow your INVEGA TRINZA® treatment schedule exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much INVEGA TRINZA® you will receive and when you will receive it.
- INVEGA TRINZA® is given as an injection by your healthcare provider into the muscle (intramuscularly) of your arm or your buttocks, 1 time every 3 months.

What should I avoid while receiving INVEGA TRINZA®?

- INVEGA TRINZA® 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 TRINZA® affects you.
- Avoid getting overheated or dehydrated.
What are the possible side effects of INVEGA TRINZA®?

INVEGA TRINZA® may cause serious side effects, including:

- See “What is the most important information I should know about INVEGA TRINZA®?”
- 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 TRINZA®. 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 TRINZA® 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 TRINZA® include: injection site reactions, weight gain, headache, upper respiratory tract infections, feeling restlessness or difficulty sitting still, slow movements, tremors, stiffness and shuffling walk.

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 TRINZA®. 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.

General information about the safe and effective use of INVEGA TRINZA®.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INVEGA TRINZA® for a condition for which it was not prescribed. Do not give INVEGA TRINZA® to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about INVEGA TRINZA® that is written for health professionals.

This Patient Information leaflet summarizes the most important information about INVEGA TRINZA®. If you would like more information, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for more information that is written for healthcare professionals. For more information, go to www.invegatrinzahcp.com or call 1-800-526-7736.

What are the ingredients in INVEGA TRINZA®?

Active ingredient: paliperidone palmitate

Inactive ingredients: polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection

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