INVEGA TRINZA- paliperidone palmitate injection, suspension, extended release
Janssen Pharmaceuticals, Inc

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)

INDICATIONS AND USAGE

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)

DOSAGE AND ADMINISTRATION

- Use INVEGA TRINZA® only after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (2.2)
- INVEGA TRINZA® should be administered once every 3 months. (2.1)
- For intramuscular injection only. (2.1)
- Each injection must be administered only by a health care professional. (2.1)
- For deltoid injection: For patients weighing less than 90 kg, use the 1-inch 22 gauge thin wall needle. For patients weighing 90 kg or more, use the 1½-inch 22 gauge thin wall needle.
- For gluteal injection: Regardless of patient weight, use the1½-inch 22 gauge thin wall needle.
- Prior to administration, shake the prefilled syringe vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension. (2.1)
- 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 as shown below. (2.2)

INVEGA TRINZA® Doses for Adult Patients Adequately Treated with INVEGA SUSTENNA®

If the Last Dose of INVEGA SUSTENNA® is:	Initiate INVEGA TRINZA® at the Following Dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

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)

DOSAGE FORMS AND STRENGTHS

Extended-release injectable suspension: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, or 819

mg/2.625 mL (3)

CONTRAINDICATIONS

Known hypersensitivity to paliperidone, risperidone, or to any excipients in INVEGA TRINZA®. (4)

WARNINGS AND PRECAUTIONS

- *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/cere**b**rovascular 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)

USE IN SPECIFIC POPULATIONS

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

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

Revised: 2/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: 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. INVEGA TRINZA® is not approved for use in patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)].*

1 INDICATIONS AND USAGE

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)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

INVEGA TRINZA® should be administered once every 3 months.

Each injection must be administered only by a health care 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 to ensure a homogeneous suspension. 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.

Administer into the center of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

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-outer 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.

Table 1. INVEGA TRINZA® Doses for Adult Patients Adequately Treated with INVEGA SUSTENNA®

If the Last Dose of INVEGA SUSTENNA® is:	Initiate INVEGA TRINZA® at the Following Dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

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

Following the initial INVEGA TRINZA® dose, INVEGA TRINZA® should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of INVEGA TRINZA®, the patient's response to an adjusted dose may not be apparent for several months *[see Clinical Pharmacology (12.3)]*.

2.3 Missed Doses

Dosing Window

Missing 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®

If the Last Dose of INVEGA TRINZA® was:	Administer INVEGA SUSTENNA®, two doses one week apart (into deltoid muscle)		Then administer INVEGA TRINZA® (into deltoid* or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

* 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®

If the Last Dose of INVEGA TRINZA® is:	Initiate* INVEGA SUSTENNA® 3 Months Later at the Following Dose:
273 mg	78 mg
410 mg	117 mg
546 mg	156 mg

819 mg	234 mg

* The initiation dosing as described in the prescribing information for INVEGA SUSTENNA® is not required.

2.7 Switching from INVEGA TRINZA® to Oral Paliperidone Extended-Release Tablets

For switching from INVEGA TRINZA® to oral paliperidone extended-release tablets, the daily dosing of the paliperidone extended-release tablets should be started 3 months after the last INVEGA TRINZA® dose and transitioned over the next several months following the last INVEGA TRINZA® dose as described in Table 4. Table 4 provides dose conversion regimens to allow patients previously stabilized on different doses of INVEGA TRINZA® to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

Table 4. INVEGA TRINZA® Doses and Once-Daily Paliperidone Extended-Release Conversion Regimens Needed to Attain Similar Paliperidone Exposures

	Weeks Since Last INVEGA TRINZA® Dose		
	3 months to 18 weeks	**Longer than 18 weeks to 24 weeks**	**Longer than 24 weeks**
Last INVEGA TRINZA® Dose	**Doses of oral paliperidone extended-release tablets**		
273 mg	3 mg	3 mg	3 mg
410 mg	3 mg	3 mg	6 mg
546 mg	3 mg	6 mg	9 mg
819 mg	6 mg	9 mg	12 mg

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

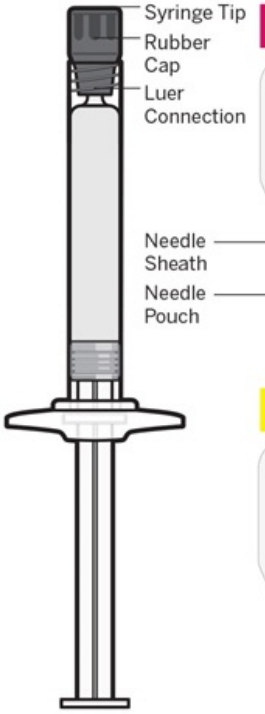
Peel off tab label from the syringe and place in patient record.

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**.

Dose pack contents

Prefilled Syringe	**Thin Wall Safety Needles**
	

1 Select needle

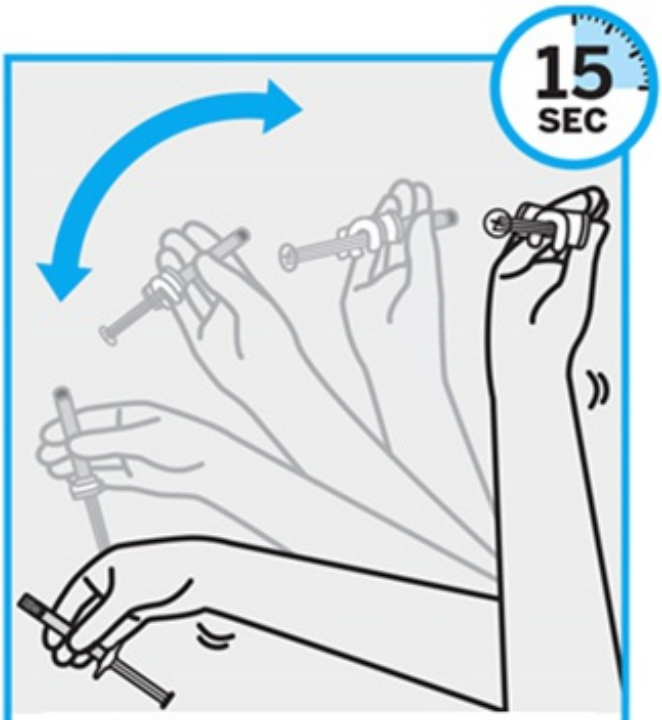
Needle selection is determined by injection area and patient weight.

If administering a **Deltoid**	If administering a **Gluteal**

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

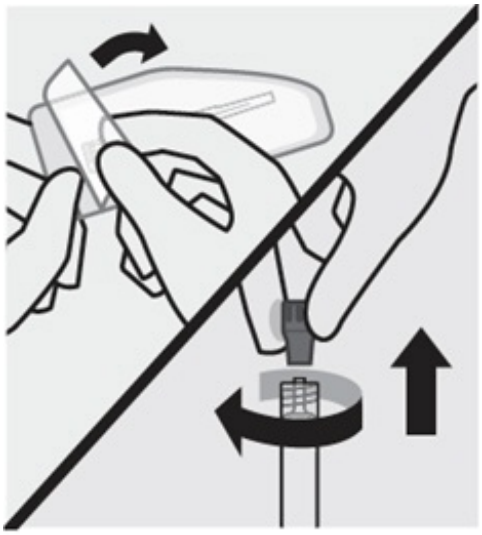
NOTE: This medication requires longer and more vigorous shaking than the 1-month paliperidone palmitate extended-release injectable suspension.

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

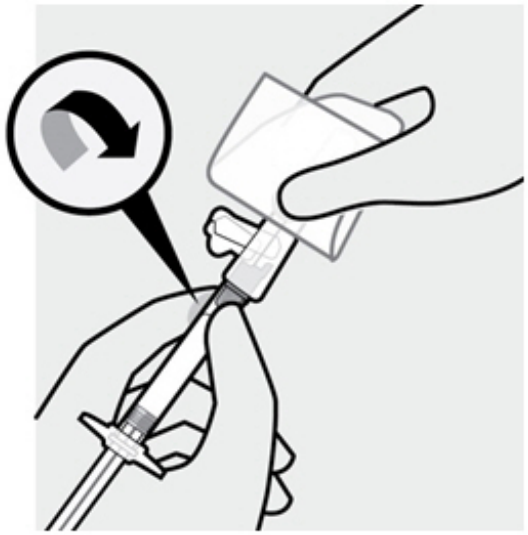


First, open needle pouch by peeling the cover back half way. Place on a clean surface.
Then, holding the syringe upright, twist and pull the rubber cap to remove.

Grasp needle pouch

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

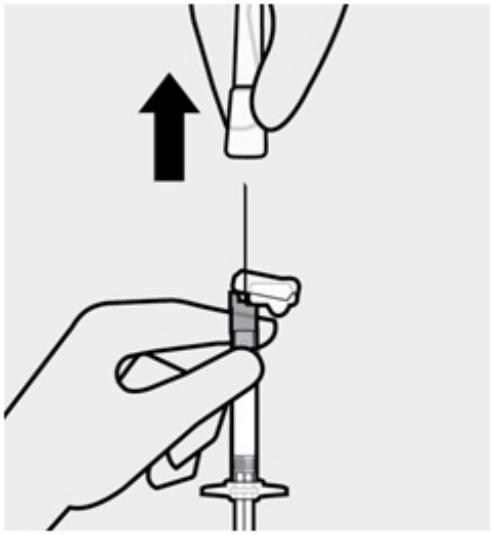
Attach needle



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.

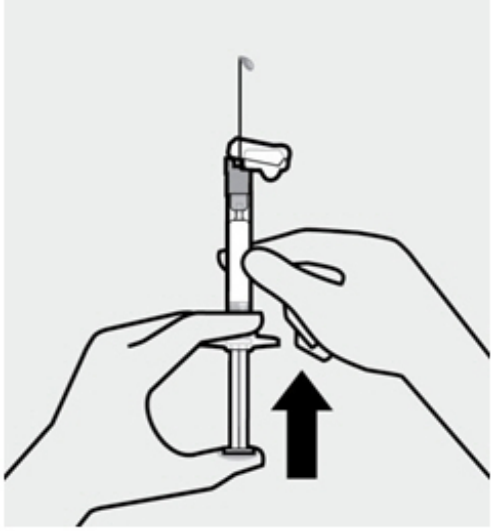
Remove needle sheath



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.

Remove air bubbles

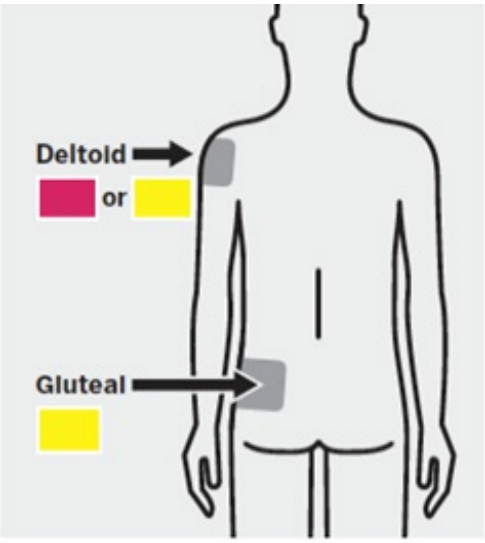


Hold the syringe upright and tap gently to make any air bubbles rise to the top.

Remove air by pressing the plunger rod upward carefully until a drop of liquid comes out of the needle tip.

3 Inject

Inject dose

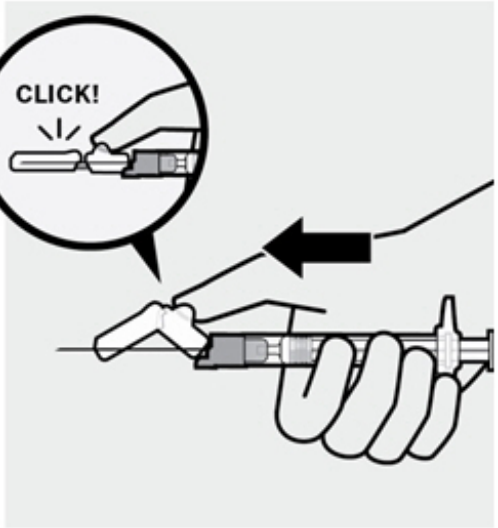


Slowly inject the entire contents of the syringe intramuscularly, deep into the selected deltoid or gluteal muscle.

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.

Dispose properly

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

Thin wall safety needles are designed specifically for use with INVEGA TRINZA®. Unused needle should be discarded and not saved for future use.

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/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, and 819 mg/2.625 mL paliperidone palmitate.

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 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA 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

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

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. Consideration should be given to the long-acting nature of INVEGA TRINZA®. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS

have been reported.

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), 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 Thorough 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 Thorough 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 derived 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 ($C_{max\ ss}$=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 $C_{max\ ss}$=56 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$=35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the 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.

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome

appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA TRINZA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA TRINZA®, drug discontinuation should be considered. Consideration should be given to the long-acting nature of INVEGA TRINZA®. However, some patients may require treatment with INVEGA TRINZA® despite the presence of the syndrome.

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 ketoacidosis or hyperosmolar 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

	Open-Label Phase (relative to open-label baseline)	**Double-Blind Phase (relative to double-blind baseline)**	
	Paliperidone Palmitate*	**Placebo**	**INVEGA TRINZA®**
	Mean change from baseline (mg/dL)		
	n=397	**n=120**	**n=138**
Serum Glucose Change from baseline	1.2	-1.6	-1.2
	Proportion of Patients with Shifts		
	n=397	**n=128**	**n=148**
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	2.3% (9/397)	2.3% (3/128)	4.1% (6/148)

* 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

	Open-Label Phase (relative to open-label	**Double-Blind Phase (relative to double-blind baseline)**

	baseline)		
	Paliperidone Palmitate*	**Placebo**	**INVEGA TRINZA®**
	Mean change from baseline (mg/dL)		
Cholesterol	**n=400**	**n=120**	**n=138**
Change from baseline	0.5	-0.4	0.9
LDL	**n=396**	**n=119**	**n=138**
Change from baseline	1.1	-0.4	1.1
HDL	**n=397**	**n=119**	**n=138**
Change from baseline	-0.2	-0.5	-1.3
Triglycerides	**n=400**	**n=120**	**n=138**
Change from baseline	0.1	-2.0	5.1
	Proportion of Patients with Shifts		
Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	2.0% (8/400)	3.9% (5/128)	1.4% (2/148)
LDL Normal to High (<100 mg/dL to ≥160 mg/dL)	0.3% (1/396)	0.8% (1/127)	0% (0/148)
HDL Normal to Low (≥40 mg/dL to <40 mg/dL)	8.6% (34/397)	9.4% (12/127)	13.5% (20/148)
Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	4.5% (18/400)	1.6% (2/128)	8.1% (12/148)

* 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

	Open-Label Phase (relative to open-label baseline)	Double-Blind Phase (relative to double-blind baseline)	
	Paliperidone Palmitate*	Placebo	INVEGA TRINZA®
	n=466	n=142	n=157
Weight (kg) Change from baseline	1.42	-1.28	0.94
Weight Gain ≥ 7% increase from baseline	15.2%	0.7%	9.6%

* 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® 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/mm^3) and follow their WBC until recovery.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 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 Toxicology (13.1)]*. 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 (13.55) ng/mL and 51.6 (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 (40.23) 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 trial 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 Warnings and Precautions (5.1)]*
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic changes *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension 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.

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

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence 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

	--- Open Label-----	---------- Double Blind --- ----------	
System Organ Class Adverse Reaction†	**Paliperidone Palmitate* (N=506) %‡**	**Placebo (N=145) %‡**	**INVEGA TRINZA® (N=160) %‡**
General disorders and administration site conditions			
Injection site reaction	12	0	3
Infections and infestations			
Upper respiratory tract infection	5	4	10
Urinary tract infection	<1	1	3
Metabolism and nutrition disorders			
Weight increased	10	3	9
Nervous system disorders			
Akathisia	5	2	5
Headache	7	4	9
Parkinsonism	5	0	4

Table includes adverse reactions that were reported in 2% or more of subjects in the INVEGA TRINZA® group during the double-blind phase and which occurred at greater incidence than in the placebo group.

* 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® prior to randomization to either placebo or INVEGA TRINZA® in the subsequent double-blind phase *[see Clinical Studies (14)].*

† The following terms were combined:
Injection site reaction includes Injection site reaction, Injection site erythema, Injection site extravasation, Injection site induration, Injection site inflammation, Injection site mass, Injection site nodule, Injection site pain, Injection site swelling.
Weight increased includes Weight increased, Waist circumference increased.
Upper respiratory tract infection includes Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Rhinitis.
Akathisia includes Akathisia, Restlessness.
Parkinsonism includes Parkinsonism, Cogwheel rigidity, Drooling, Extrapyramidal disorder, Hypokinesia, Muscle rigidity, Muscle tightness, Musculoskeletal stiffness, Salivary hypersecretion.
‡ Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Demographic Differences

An examination of population subgroups in the long-term maintenance trial did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects 65 years of age and older.

Extrapyramidal Symptoms (EPS)

Data from the long-term maintenance trial provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale scores which evaluates dyskinesia, and (4) use of anticholinergic medications to treat EPS (Table 9), and (5) incidence of spontaneous reports of EPS (Table 10).

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

	Percentage of Subjects		
	Open-label Phase	**Double-blind Phase**	
	Paliperidone Palmitate*	**Placebo**	**INVEGA TRINZA®**
Scale	**(N=506) %**	**(N=145) %**	**(N=160) %**
Parkinsonism†	6	3	6
Akathisia‡	3	1	4
Dyskinesia§	1	3	3
Use of Anticholinergic Medications¶	11	9	11

* 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)]*.
† For Parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at any time (Global score defined as total sum of items score divided by the number of items)
‡ For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at any time
§ For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary

Movement Scale at any time
¶ Percent of subjects who received anticholinergic medications to treat EPS

Table 10. Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term

	Percentage of Subjects		
	Open-label Phase	Double-blind Phase	
	Paliperidone Palmitate* (N=506)	Placebo (N=145)	INVEGA TRINZA® (N=160)
EPS Group	**%**	**%**	**%**
Overall percentage of subjects with EPS-related adverse events	10	3	8
Parkinsonism	4	0	4
Hyperkinesia	5	2	5
Tremor	2	0	1
Dyskinesia	<1	1	1
Dystonia	1	0	1

Parkinsonism group includes: Cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonism

Hyperkinesia group includes: Akathisia, restlessness

Dystonia group includes: Blepharospasm, dystonia, muscle spasms

* 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)]*.

After injection of INVEGA TRINZA® in the open-label phase, 12 (3.2%) subjects had EPS that were new or worsened in severity, with events under the groupings of hyperkinesia (1.6%) and parkinsonism (1.3%) being the most common. After injection of INVEGA TRINZA® in the open-label or double-blind phases, one subject discontinued from the open-label phase due to restlessness.

An examination of the time to EPS during the double-blind phase showed no clustering of these events at visits that would be expected to correspond to median peak plasma concentrations of paliperidone for subjects randomized to INVEGA TRINZA®.

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Pain Assessment and Local Injection Site Reactions

Investigator ratings of injection site. Redness and swelling were observed in 2% or less of subjects in the INVEGA TRINZA® and placebo groups during the double-blind phase of the long-term maintenance study, and were rated mild based on investigator ratings using a 4-point scale (0=absent; 1=mild; 2=moderate; 3=severe). There were no reports of induration in either group during the double-blind phase, and no subjects discontinued due to INVEGA TRINZA® injection.

Subject ratings of injection site pain. Subject evaluations of injection pain during the double-blind phase also were similar for placebo and INVEGA TRINZA®.

Subject ratings of injection site pain in the single-dose Phase 1 study allowed for assessment of the temporal course of injection site pain. Residual injection pain peaked 1 or 6 hours after injection, and trended downward 3 days after the injection. Deltoid injections were numerically more painful than gluteal injections, although most pain ratings were below 10 mm on a 100-mm scale.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA TRINZA®

The following additional adverse reactions were identified in the long-term maintenance trial. The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) occurred at an incidence lower than that of placebo-treated patients.

Cardiac disorders: tachycardia

Gastrointestinal disorders: nausea, vomiting

Metabolism and nutrition disorders: hyperinsulinemia

Psychiatric disorders: anxiety

Additional Adverse Reactions Reported in Clinical Trials with the 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension

The following is a list of additional adverse reactions that have been reported in clinical trials with the 1-month paliperidone palmitate extended-release injectable suspension:

Cardiac disorders: atrioventricular block first degree, bradycardia, bundle branch block, palpitations, postural orthostatic tachycardia syndrome

Ear and labyrinth disorders: vertigo

Eye disorders: eye movement disorder, eye rolling, oculogyric crisis, vision blurred

Gastrointestinal disorders: abdominal discomfort/abdominal pain upper, diarrhea, dry mouth, toothache

General disorders and administration site conditions: asthenia, fatigue

Immune system disorders: hypersensitivity

Investigations: electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, increased appetite

Musculoskeletal and connective tissue disorders: back pain, myalgia, pain in extremity, joint stiffness, muscle spasms, muscle twitching, nuchal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, convulsion, dizziness, dizziness postural, dysarthria, hypertonia, lethargy, oromandibular dystonia, psychomotor hyperactivity, syncope

Psychiatric disorders: agitation, nightmare

Reproductive system and breast disorders: breast discharge, erectile dysfunction, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: drug eruption, pruritus, pruritus generalized, rash, urticaria

Vascular disorders: hypertension

Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

The following is a list of additional adverse reactions that have been reported in clinical trials with oral paliperidone:

Cardiac disorders: bundle branch block left, sinus arrhythmia

Gastrointestinal disorders: abdominal pain, constipation, flatulence, small intestinal obstruction

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, torticollis, trismus

Nervous system disorders: grand mal convulsion, parkinsonian gait, transient ischemic attack

Psychiatric disorders: sleep disorder

Reproductive system and breast disorders: breast engorgement, breast tenderness/breast pain, retrograde ejaculation

Respiratory, thoracic and mediastinal disorders: nasal congestion, pharyngolaryngeal pain, pneumonia aspiration

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: hypotension, ischemia

6.2 Postmarketing Experience

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

Cases of anaphylactic reaction after injection with the 1-month paliperidone palmitate

extended-release suspension have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

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®

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Drugs with Potential for Inducing Orthostatic Hypotension	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)]*.	Monitor orthostatic vital signs in patients who are vulnerable to hypotension *[see Warnings and Precautions (5.7)]*.
Strong Inducers of CYP3A4 and P-gp (e.g., carbamazepine, rifampin, or St. John's Wort)	The concomitant use of paliperidone and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone *[see Clinical Pharmacology (12.3)]*.	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)]*.
Levodopa and Other Dopamine Agonists	Paliperidone may antagonize the effect of levodopa and other dopamine agonists.	Monitor and manage patient as clinically appropriate.

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 isozymes. *In vitro* studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely. *[See Clinical Pharmacology (12.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA TRINZA® during pregnancy *(see Clinical Considerations)*. Paliperidone has been detected in plasma in adult subjects up to 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/m^2 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/m^2 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, hypertonia, 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 the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

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/m^2 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/m^2 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/m^2 body surface area; maternal toxicity occurred at 4 times the MHRD. 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/m^2 body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m^2 body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m^2 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 18 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 breastmilk should be monitored for excess sedation, failure to thrive, 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, 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 (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of INVEGA TRINZA® on growth and sexual maturation have not been fully evaluated in children and 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 Dementia with Lewy Bodies can 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 premarketing studies with paliperidone palmitate injection. Because INVEGA TRINZA® is to be administered by health care professionals, the potential for overdosage by patients is low.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation. Torsades de pointes 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 Overdosage

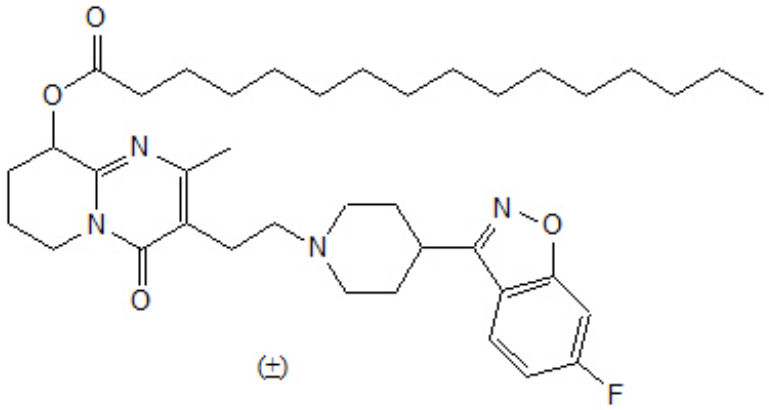
Contact a Certified Poison Control Center for the most up to date information on the management of paliperidone and INVEGA TRINZA® overdosage (1-800-222-1222 or

www.poison.org). Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. 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 (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimadin-9-yl hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



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 dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 175 mg, 263 mg, 350 mg, and 525 mg of paliperidone, respectively. The inactive ingredients are 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 prefilled syringe (cyclic-olefin-copolymer) prefilled 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) suspension with a plunger stopper and tip cap (bromobutyl 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 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

In vitro, paliperidone acts as an antagonist at the central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptors with binding affinities (Ki values) of 1.6–2.8 nM for D_2 and 0.8–1.2 nM for $5HT_{2A}$ receptors. Paliperidone is also active as an antagonist at the α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-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 before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug starts as early as day 1 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 ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C-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 concentration of paliperidone remaining in the circulation 18 months after dosing of 819 mg INVEGA TRINZA® is stopped is estimated to be 3% (following deltoid injection) or 7% (following gluteal injection) of the average steady-state levels.

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.

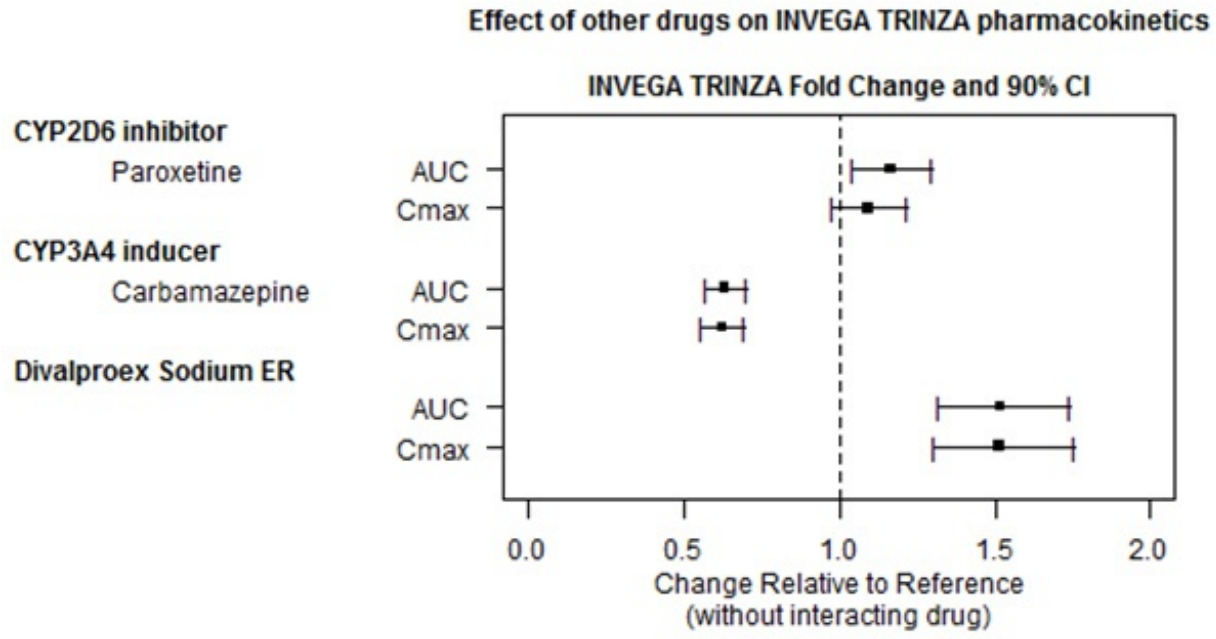
The between-subject variability for paliperidone pharmacokinetics following delivery from INVEGA TRINZA® was similar to the variability for paliperidone extended-release tablets. Because of the difference in median pharmacokinetic profiles among the three formulations, caution should be exercised when 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.



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 body clearance. *In vitro* studies demonstrated that paliperidone is a substrate of P-glycoprotein (P-gp) *[see Drug Interactions (7.2)]*.

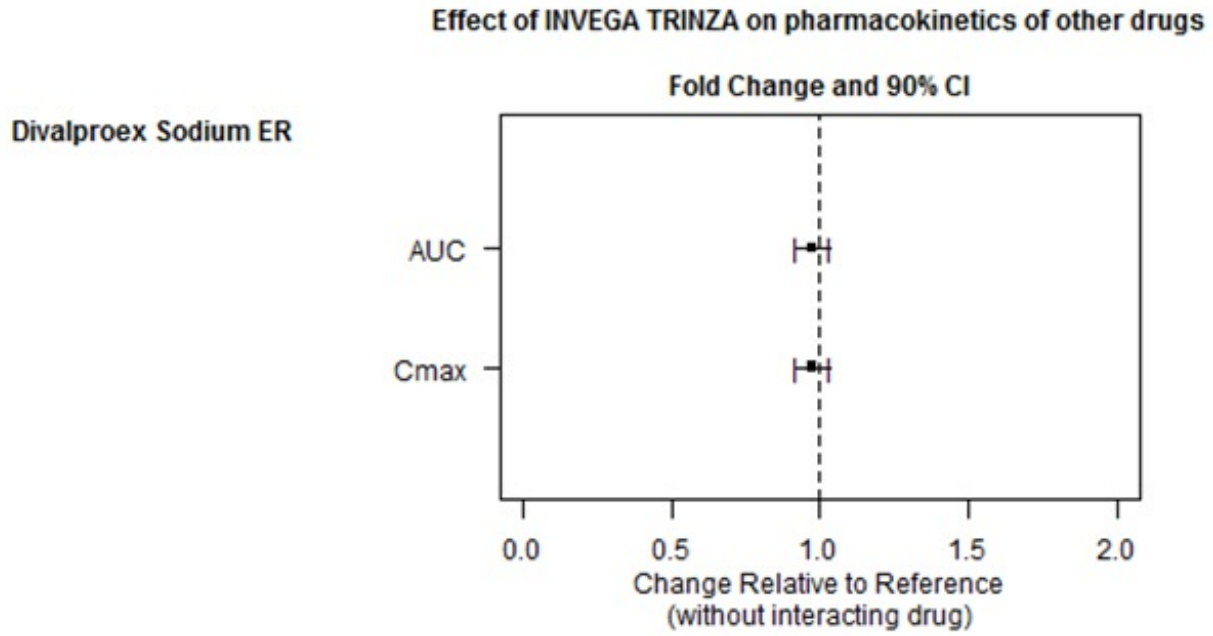
In vitro studies in human liver microsomes demonstrated that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance 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.



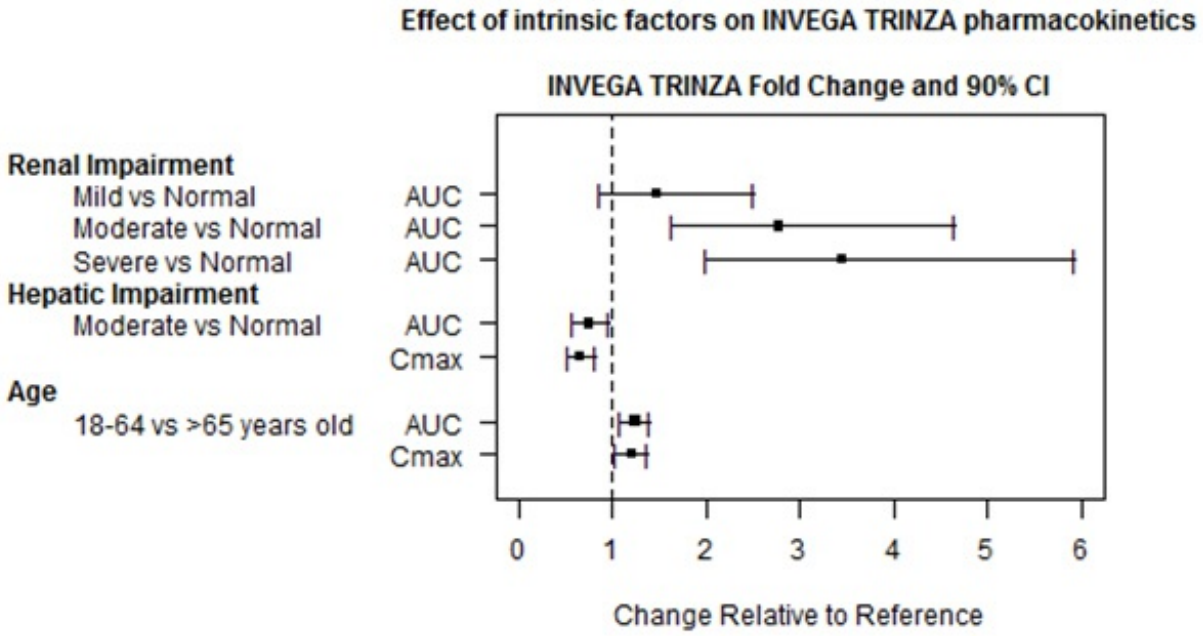
Studies in Specific Populations

No specific pharmacokinetic studies have been performed with INVEGA TRINZA® in specific populations. All the information is obtained from studies with oral paliperidone or is based on the population pharmacokinetic modelling of oral paliperidone and INVEGA TRINZA®. Exposures of paliperidone in specific populations (renal impairment, hepatic impairment and elderly) are summarized in Figure 3 *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*.

After oral administration of paliperidone in patients with moderate hepatic impairment, the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Paliperidone has not been studied in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

After oral administration of paliperidone in elderly subjects, the C_{max} and AUC increased 1.2-fold compared to young subjects. However, there may be age-related decreases in creatinine clearance *[see Dosage and Administration (2.5) and Use in Specific Populations (8.5)]*.

Figure 3: Effects of intrinsic factors on paliperidone pharmacokinetics.



Based on *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/m^2 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/m^2 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/m^2 body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear *[see Warnings and Precautions (5.7)].*

Mutagenesis

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/m^2 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/m^2 body surface area.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2 times the MRHD of 12 mg/day based on mg/m^2 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/m^2 body surface area). Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

13.2 Animal Toxicology and/or Pharmacology

Injection site toxicity was assessed in minipigs injected intramuscularly with the 3-month paliperidone palmitate extended-release injectable suspension at doses up to 819 mg, which is equal to the MRHD. Injection site inflammatory reactions were 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 CONSTA® (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 12-week open-label treatment period with INVEGA TRINZA® (second part of a 29-week open-label stabilization phase). A total of 379 patients received a single-dose of INVEGA TRINZA® which was a 3.5 multiple of the last dose of the 1-month paliperidone palmitate. Patients had to remain clinically stable before entry into the next period (double-blind). Clinical stability was defined as achieving a PANSS total score <70 and scores of ≤ 4 for seven specific PANSS items.
- A variable length double-blind treatment period. In this period, 305 stabilized patients were randomized 1:1 to continue treatment with INVEGA TRINZA® or placebo until relapse, early withdrawal, or the end of study. Patients were randomized to the same dose of INVEGA TRINZA® they received during the open-label phase (i.e., 273 mg, 410 mg, 546 mg, or 819 mg) or to placebo administered every 12 weeks. The numbers (%) of patients entering double-blind on each of the dose levels were 6 (4%) for 273 mg, 15 (9%) for 410 mg, 78 (49%) for 546 mg, and 61 (38%) for 819 mg.

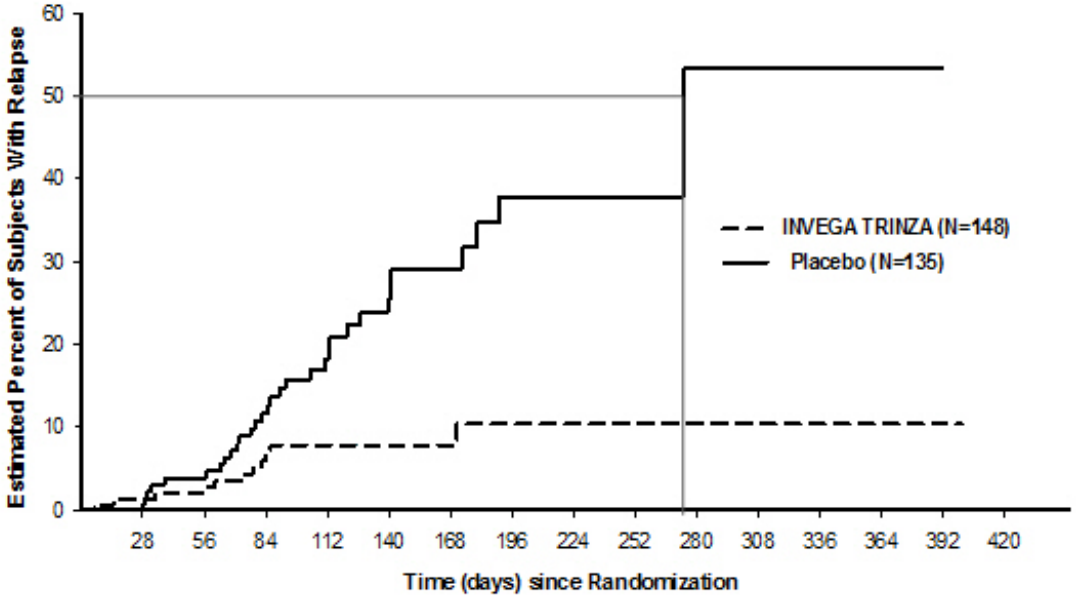
The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, 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/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, and 819 mg/2.625 mL paliperidone palmitate. The 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 side effect referred to as Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Patients should contact their health care provider or report to the emergency room if they experience the following signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia *[see Warnings and Precautions (5.3)].*

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care 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 (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness), 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, particularly 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 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

As INVEGA TRINZA® has the potential to impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA 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 on the importance of avoiding overheating and dehydration *[see Warnings and Precautions (5.15)]*.

Concomitant Medication

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

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with INVEGA 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 N.V.
Beerse, Belgium

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

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PATIENT INFORMATION
INVEGA TRINZA® (in-VAY-guh TRIN-zuh)
(paliperidone palmitate)
Extended-Release Injectable Suspension

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 health care 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 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
Revised: 07/2018
Manufactured by: Janssen Pharmaceutica N.V. Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560
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PRINCIPAL DISPLAY PANEL - 273 mg Syringe Carton

3
MONTHS

Administer
every
3 months

Shake syringe
vigorously for at
least 15 seconds

273 mg

Each 0.875 mL prefilled syringe contains
273 mg paliperidone palmitate.

NDC 50458-606-01
For Single Use Only - Use Entire Content of Syringe

INVEGA TRINZA® 273 mg
paliperidone palmitate
extended-release injectable suspension

FOR INTRAMUSCULAR INJECTION ONLY
Each injection must be administered only by
a health care professional.
Shake before using

CONTENTS: 1 prefilled syringe and 2 needles
(a 22G, 1-inch thin wall safety needle and a 22G,
1½-inch thin wall safety needle)

For recommended dosing instructions, please see
accompanying full Package Insert.
Rx only

Store at room temperature
(20°C to 25°C; 68°F to 77°F).

janssen

PRINCIPAL DISPLAY PANEL - 410 mg Syringe Carton

3
MONTHS

Administer
every
3 months

Shake syringe
vigorously for at
least 15 seconds

410 mg

Each 1.315 mL prefilled syringe contains
410 mg paliperidone palmitate.

NDC 50458-607-01
For Single Use Only - Use Entire Content of Syringe

INVEGA TRINZA® 410 mg
paliperidone palmitate
extended-release injectable suspension

FOR INTRAMUSCULAR INJECTION ONLY
Each injection must be administered only by
a health care professional.
Shake before using

CONTENTS: 1 prefilled syringe and 2 needles
(a 22G, 1-inch thin wall safety needle and a 22G,
1½-inch thin wall safety needle)

For recommended dosing instructions, please see
accompanying full Package Insert.
Rx only

Store at room temperature
(20°C to 25°C; 68°F to 77°F).

janssen

PRINCIPAL DISPLAY PANEL - 546 mg Syringe Carton

3

MONTHS

**Administer
every
3 months**

**Shake syringe
vigorously for at
least 15 seconds**

546 mg

**Each 1.75 mL prefilled syringe contains
546 mg paliperidone palmitate.**

**NDC 50458-608-01
For Single Use Only - Use Entire Content of Syringe**

**INVEGA TRINZA® 546 mg
paliperidone palmitate
extended-release injectable suspension**

FOR INTRAMUSCULAR INJECTION ONLY
Each injection must be administered only by
a health care professional.
Shake before using

CONTENTS: 1 prefilled syringe and 2 needles
(a 22G, 1-inch thin wall safety needle and a 22G,
1½-inch thin wall safety needle)

For recommended dosing instructions, please see
accompanying full Package Insert.
Rx only

**Store at room temperature
(20°C to 25°C; 68°F to 77°F).**

janssen

PRINCIPAL DISPLAY PANEL - 819 mg Syringe Carton

3
MONTHS

Administer
every
3 months

Shake syringe
vigorously for at
least 15 seconds

819 mg

Each 2.625 mL prefilled syringe contains
819 mg paliperidone palmitate.

NDC 50458-609-01
For Single Use Only - Use Entire Content of Syringe

INVEGA TRINZA® 819 mg
paliperidone palmitate
extended-release injectable suspension

FOR INTRAMUSCULAR INJECTION ONLY
Each injection must be administered only by
a health care professional.
Shake before using

CONTENTS: 1 prefilled syringe and 2 needles
(a 22G, 1-inch thin wall safety needle and a 22G,
1½-inch thin wall safety needle)

For recommended dosing instructions, please see
accompanying full Package Insert.
Rx only

Store at room temperature
(20°C to 25°C; 68°F to 77°F).

janssen

INVEGA TRINZA

paliperidone palmitate injection, suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-606
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
paliperidone palmitate (UNII: R8P8USM8FR) (paliperidone - UNII:838F01T721)	paliperidone palmitate	273 mg in 0.875 mL

Inactive Ingredients

Ingredient Name	Strength
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-606-01	1 in 1 KIT	05/19/2015	
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207946	05/19/2015	

INVEGA TRINZA

paliperidone palmitate injection, suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-607
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
paliperidone palmitate (UNII: R8P8USM8FR) (paliperidone - UNII:838F01T721)	paliperidone palmitate	410 mg in 1.315 mL

Inactive Ingredients

Ingredient Name	Strength
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-607-01	1 in 1 KIT	05/19/2015	
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207946	05/19/2015	

INVEGA TRINZA

paliperidone palmitate injection, suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-608
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
paliperidone palmitate (UNII: R8P8USM8FR) (paliperidone - UNII:838F01T721)	paliperidone palmitate	546 mg in 1.75 mL

Inactive Ingredients

Ingredient Name	Strength
POLYSORBATE 20 (UNII: 7T1F30V5YH)	

POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-608-01	1 in 1 KIT	05/19/2015	
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207946	05/19/2015	

INVEGA TRINZA

paliperidone palmitate injection, suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-609
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
paliperidone palmitate (UNII: R8P8USM8FR) (paliperidone - UNII:838F01T721)	paliperidone palmitate	819 mg in 2.625 mL

Inactive Ingredients

Ingredient Name	Strength
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:50458-609-01	1 in 1 KIT	05/19/2015	
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207946	05/19/2015	

Labeler - Janssen Pharmaceuticals, Inc (063137772)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Pharmaceutica NV		370005019	MANUFACTURE(50458-606, 50458-607, 50458-608, 50458-609) , PACK(50458-606, 50458-607, 50458-608, 50458-609) , ANALYSIS(50458-606, 50458-607, 50458-608, 50458-609)

Establishment

Name	Address	ID/FEI	Business Operations
Phast		331156161	ANALYSIS(50458-606, 50458-607, 50458-608, 50458-609)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Pharmaceuticals, Inc		063137772	ANALYSIS(50458-606, 50458-607, 50458-608, 50458-609)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen-Cilag Manufacturing, LLC		963971374	ANALYSIS(50458-606, 50458-607, 50458-608, 50458-609)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Pharmaceutical Sciences Unlimited Company		985639841	API MANUFACTURE(50458-606, 50458-607, 50458-608, 50458-609)

Revised: 5/2021 Janssen Pharmaceuticals, Inc