PRODUCT NAME

INVEGA TRINZA® (175 mg paliperidone as 273 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.
INVEGA TRINZA® (263 mg paliperidone as 410 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.
INVEGA TRINZA® (350 mg paliperidone as 546 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.
INVEGA TRINZA® (525 mg paliperidone as 819 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

DOSAGE FORMS AND STRENGTHS

INVEGA TRINZA® contains 175, 263, 350, or 525 mg paliperidone (as 273, 410, 546, or 819 mg of paliperidone palmitate, respectively).

The chemical name is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate.

Prolonged-release suspension in prefilled syringes. The suspension is white to off-white.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

INVEGA TRINZA®, a 3-month injection, is indicated for the treatment of schizophrenia in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months.

Dosage and Administration

INVEGA TRINZA® is to be used only after the 1-month paliperidone palmitate injectable product 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 the 1-month injection be the same dosage strength before starting INVEGA TRINZA®.

Dosage

Initiate INVEGA TRINZA® at the time when the next 1-month paliperidone palmitate dose was to be scheduled with a INVEGA TRINZA® dose based on the previous 1-month injection 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. Conversion From the Last Paliperidone Palmitate 1-Month Injectable Product Dose To the Paliperidone Palmitate 3-Month Injectable Product (INVEGA TRINZA®) Dose Using 3.5 as a Multiplier

If the last 1-month paliperidone palmitate injection dose is:	Initiate INVEGA TRINZA® at the following dose:
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

Conversion from the 25 mg 1-month paliperidone palmitate injectable product 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 175 mg to 525 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 *Pharmacokinetic Properties*).

Missed dose(s)

Dosing Window. Missing doses of INVEGA TRINZA® should be avoided. However, on exceptional occasions, patients may be given the injection up to 2 weeks before or after the 3-month time point.

Missed Dose > 3½ Months up to 4 Months. If more than 3½ months (up to 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 up to 9 Months. If more than 4 months (up to 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 up to 9 months of INVEGA TRINZA®

Last INVEGA TRINZA® 3-Month Injectable Product Dose	Administer Paliperidone Palmitate 1-Month Injectable Product, two doses one week apart (into deltoid muscle)		Then administer INVEGA TRINZA® 3-Month Injectable Product Dose (into deltoid[a] or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
175 mg	50 mg	50 mg	175 mg
263 mg	75 mg	75 mg	263 mg
350 mg	100 mg	100 mg	350 mg
525 mg	100 mg	100 mg	525 mg

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

Missed Dose > 9 Months. If more than 9 months have elapsed since the last injection of INVEGA TRINZA®, re-initiate treatment with the 1-month paliperidone palmitate injectable product 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 injectable product for at least 4 months.

Administration information

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **Within 5 minutes prior to administration of INVEGA TRINZA® to the patient, it is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension** (see *Instructions for Use and Handling and Disposal*).

INVEGA TRINZA® is intended for intramuscular use only. Do not administer intravascularly or subcutaneously. Avoid inadvertent injection into a blood vessel. Each injection must be administered only by a health care professional. 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. Needles from the 1-month paliperidone palmitate injectable product pack or other commercially-available needles are not to be used when administering INVEGA TRINZA®.

The recommended needle size for administration of INVEGA TRINZA® into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg (≥ 200 lbs), the 1½-inch, 22 gauge thin wall needle is recommended. For those < 90 kg (< 200 lbs), the 1-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.

The recommended needle size for administration of INVEGA TRINZA® into the gluteal muscle regardless of body weight 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.

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

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 (see *Instructions for Use and Handling and Disposal*). 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. Closely monitor and treat the patient appropriately until the next scheduled 3-month injection of INVEGA TRINZA®.

Special populations

Pediatrics (less than 18 years of age)

Safety and effectiveness of INVEGA TRINZA® in patients < 18 years of age have not been studied.

Elderly (65 years of age and older)

In general, recommended dosing of INVEGA TRINZA® for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. As elderly patients may have reduced renal function, see *Renal impairment* below for dosing recommendations in patients with renal impairment. Efficacy and safety in elderly >65 years of have not been established.

Renal impairment

INVEGA TRINZA® has not been systematically studied in patients with renal impairment (see *Pharmacokinetic Properties*). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), dose adjustment is done when initiating treatment with the 1-month paliperidone palmitate injectable product; no dose adjustment of INVEGA TRINZA® is required. Transition to INVEGA TRINZA® is with a dose in a 3.5 to 1 ratio to the previous stabilized 1-month paliperidone palmitate injectable product as described in *Dosage* above. The maximum recommended dose of INVEGA TRINZA® in patients with mild renal impairment is 350 mg.

INVEGA TRINZA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

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 *Pharmacokinetic Properties*)

Other populations

No dose adjustment for INVEGA TRINZA® is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see *Pregnancy and Breast-feeding*.)

Switching from other antipsychotic agents

INVEGA TRINZA® is to be used only after the patient has been adequately treated with the 1-month paliperidone palmitate injectable product for at least 4 months (see *Indications* and *Dosage and Administration*).

If INVEGA TRINZA® is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

Switching from INVEGA TRINZA® to the 1-Month Paliperidone Palmitate Injectable Product

For switching from INVEGA TRINZA® to the 1-month paliperidone palmitate injectable product, the 1-month paliperidone palmitate injectable product should be administered at the time the next INVEGA TRINZA® dose was to be administered using the equivalent 3.5-fold lower dose as shown in Table 3. The 1-month paliperidone palmitate injectable product should then continue dosed at monthly intervals.

Table 3. Conversion From the Last Paliperidone Palmitate 3-Month Injectable Product (INVEGA TRINZA®) Dose To the Paliperidone Palmitate 1-Month Injectable Product Dose Using 3.5 as a conversion factor

If the last INVEGA TRINZA® dose is:	Administer 1-Month Paliperidone Palmitate at the following dose:
175 mg	50 mg
263 mg	75 mg
350 mg	100 mg
525 mg	150 mg

The initiation dosing as described in the prescribing information for the 1-month paliperidone palmitate injectable product is not required.

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	> 18 weeks to ≤ 24 weeks	> 24 weeks
Last INVEGA TRINZA® Dose	**Daily dose of oral paliperidone extended-release tablets**		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

* Doses of oral paliperidone extended-release tablets should be individualized taking into consideration the reason for switching, response to previous paliperidone treatment, severity of psychotic symptoms, and/or tolerability.

Contraindications

INVEGA TRINZA® is contraindicated in patients with a known hypersensitivity to paliperidone or to any of the components in the formulation. Since paliperidone is an active metabolite of risperidone, INVEGA TRINZA® is contraindicated in patients with a known hypersensitivity to risperidone.

Warnings and Precautions

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotic drugs, including paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotic drugs, including INVEGA TRINZA®, should be discontinued. Consideration should be given to the long-acting nature of INVEGA TRINZA®.

Tardive dyskinesia/extrapyramidal symptoms

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs, including INVEGA TRINZA®, should be considered. Consideration should be given to the long-acting nature of INVEGA TRINZA®.

Extrapyramidal symptoms and psychostimulants

Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or

both medications. Gradual withdrawal of one or both treatments should be considered (see *Interactions*).

QT interval

As with other antipsychotics, caution should be exercised when INVEGA TRINZA® is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval (see *Pharmacodynamic Properties: Effect on QT/QTc interval and cardiac electrophysiology*).

Hypersensitivity reactions

Anaphylactic reactions in patients who have previously tolerated oral risperidone or oral paliperidone have been very rarely reported during post marketing experience with the 1-month paliperidone palmitate injectable product (see *Dosage and Administration* and *Adverse Reactions*).

If hypersensitivity reactions occur, discontinue use of INVEGA TRINZA®; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve (see *Contraindications* and *Adverse Reactions*).

Hyperglycemia and diabetes mellitus

Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with antipsychotic drugs. 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. Any patient treated with atypical antipsychotics, including INVEGA TRINZA® should be monitored for symptoms of hyperglycemia and diabetes mellitus (see also *Adverse Reactions*). 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.

Weight gain

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

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-adrenergic blocking activity. INVEGA TRINZA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, 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).

Seizures

As with 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.

Elderly patients with dementia

INVEGA TRINZA® has not been studied in elderly patients with dementia.
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® (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis.

Overall mortality

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotic drugs, including risperidone, aripiprazole, olanzapine, and quetiapine, had an increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

Cerebrovascular adverse events

In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone, aripiprazole, and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including paliperidone. Agranulocytosis has been reported very rarely (< 1/10000 patients) during postmarketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of INVEGA TRINZA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue INVEGA TRINZA® and have their WBC followed until recovery.

Consideration should be given to the long-acting nature of INVEGA TRINZA®.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA TRINZA® and preventive measures undertaken.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotic drugs, including INVEGA TRINZA®, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during postmarketing surveillance (see *Adverse Reactions*).

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.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Administration

Care must be taken to avoid inadvertent injection of INVEGA TRINZA® into a blood vessel.

Intraoperative floppy iris syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as INVEGA TRINZA® (see *Adverse Reactions*).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Interactions

Caution is advised when prescribing INVEGA TRINZA® with drugs known to prolong the QT interval.

Since paliperidone palmitate is hydrolyzed to paliperidone (see *Pharmacokinetic Properties*), results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Potential for INVEGA TRINZA® to affect other drugs

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed 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-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Given the primary CNS effects of paliperidone (see *Adverse Reactions*), INVEGA TRINZA® should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension (see *Warnings and Precautions: Orthostatic hypotension*), an additive effect may be observed when INVEGA TRINZA® is administered with other therapeutic agents that have this potential.

Co-administration of oral paliperidone extended-release tablets at steady-state (12 mg once daily) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

Pharmacokinetic interaction between INVEGA TRINZA® and lithium is unlikely.

Potential for other drugs to affect INVEGA TRINZA®

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone

metabolism, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Paliperidone is metabolized to a limited extent by CYP2D6 (see *Pharmacokinetic Properties: Metabolism and excretion*). In an interaction study in healthy subjects in which oral paliperidone was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA TRINZA® should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA TRINZA® should be re-evaluated and decreased if necessary. Consideration should be given to the long-acting nature of INVEGA TRINZA®.

Paliperidone, a cation under physiological pH, is primarily excreted unchanged by the kidneys, approximately half via filtration and half via active secretion. Concomitant administration of trimethoprim, a drug known to inhibit active renal cation drug transport, did not influence the pharmacokinetics of paliperidone.

Co-administration of a single dose of an oral paliperidone extended-release tablet 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone, likely the result of an increased oral absorption. Since no significant effect on the systemic clearance was observed, a clinically significant interaction would not be expected between divalproex sodium extended-release tablets and INVEGA TRINZA® intramuscular injection. This interaction has not been studied with INVEGA TRINZA®.

Pharmacokinetic interaction between lithium and INVEGA TRINZA® is unlikely.

Concomitant use of INVEGA TRINZA® with risperidone or with oral paliperidone

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

Concomitant use of INVEGA TRINZA® with psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with paliperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see *Warnings and Precautions*).

Pregnancy and Breast-feeding

Pregnancy

The safety of intramuscularly-injected paliperidone palmitate or orally-dosed paliperidone for use during human pregnancy has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. Paliperidone, the active metabolite of risperidone, was not specifically evaluated in this study. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

No teratogenic effect was noted in any animal study. Laboratory animals treated with a high dose of oral paliperidone showed a slight increase in fetal deaths. Pregnancy parameters were not affected in rats given the intramuscular injection of the 1-month paliperidone palmitate injectable product. The high doses were toxic to the mothers. The offspring was not affected at oral exposures 20- to 22-fold the maximum human dose of oral paliperidone or at intramuscular exposures 6-fold the maximum human dose of the 1-month paliperidone palmitate injectable product.

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA TRINZA®, consideration should be given to the long-acting nature of INVEGA TRINZA® as neonates may be at risk from INVEGA TRINZA® administration before pregnancy or during first and second trimesters as well.

INVEGA TRINZA® should only be used during pregnancy if the benefits outweigh the risks. The effect of INVEGA TRINZA® on labor and delivery in humans is unknown.

Breast-feeding

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA TRINZA® should not breast-feed

infants. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA TRINZA®, consideration should be given to the long-acting nature of INVEGA TRINZA® as nursing infants may be at risk even from INVEGA TRINZA® administration long before nursing.

Effects on Ability to Drive and Use Machines

INVEGA TRINZA® may interfere with activities requiring mental alertness and may have visual effects (see *Adverse Reactions*). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone palmitate based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone palmitate cannot be reliably established in individual cases. Further, 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.

Clinical trial data

The data described in this section include data from 3 clinical trials. One was a long-term relapse-prevention/randomized withdrawal trial, in which 506 subjects with schizophrenia received the 1-month paliperidone palmitate injectable product 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 (Standard Deviation [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 second trial was a long-term double-blind, active-controlled noninferiority study, in which 1429 acutely ill subjects were enrolled into the open-label phase and treated with the 1-month paliperidone palmitate injectable product. Subjects who met the randomization criteria were randomized in a 1:1 ratio to continue on monthly injections of the 1-month paliperidone palmitate injectable product (n=512) or to switch to INVEGA TRINZA® (n=504) for 48 weeks. The mean (SD) duration of exposure during the double-blind phase was 295 (88) days in the INVEGA TRINZA® group and 287 (96) days in the 1-month paliperidone palmitate injectable product group.

The third trial was a Phase 1 study, in which 308 subjects with schizophrenia or schizoaffective disorder received a single injection of INVEGA TRINZA® concomitantly with other oral

antipsychotics.

The majority of adverse reactions were mild to moderate in severity.

Adverse reactions reported in the long-term relapse-prevention trial are shown in Table 5.

Table 5. Incidences of Adverse Reactions Identified for INVEGA TRINZA® Summarized by Grouped Term for the Open-Label and Double-Blind Phases of a Long-Term Relapse Prevention Trial in Subjects with Schizophrenia

	--- Open Label-----	---------- Double Blind ----------	
	Paliperidone Palmitate[a]	**Placebo**	**INVEGA TRINZA®**
System Organ Class Adverse Reaction[b]	**(N=506) n (%)[c]**	**(N=145) n (%)[c]**	**(N=160) n (%)[c]**
Infections and infestations			
Upper respiratory tract infection	26 (5.1)	6 (4.1)	16 (10.0)
Urinary tract infection	2 (0.4)	2 (1.4)	5 (3.1)
Metabolism and nutrition disorders			
Hyperglycemia	0	7 (4.8)	3 (1.9)
Hyperinsulinemia	0	1 (0.7)	1 (0.6)
Weight increased	52 (10.3)	5 (3.4)	14 (8.8)
Psychiatric disorders			
Anxiety	44 (8.7)	16 (11.0)	13 (8.1)
Nervous system disorders			
Akathisia	23 (4.5)	3 (2.1)	8 (5.0)
Dyskinesia	1 (0.2)	2 (1.4)	1 (0.6)
Dystonia	6 (1.2)	0	1 (0.6)
Headache	33 (6.5)	6 (4.1)	14 (8.8)
Parkinsonism	23 (4.5)	0	7 (4.4)
Somnolence	20 (4.0)	0	1 (0.6)
Cardiac disorders			
Tachycardia	8 (1.6)	1 (0.7)	1 (0.6)
Vascular disorders			
Orthostatic hypotension	2 (0.4)	0	0
Gastrointestinal disorders			
Nausea	11 (2.2)	0	2 (1.3)
Vomiting	9 (1.8)	0	0

Table 5. Incidences of Adverse Reactions Identified for INVEGA TRINZA® Summarized by Grouped Term for the Open-Label and Double-Blind Phases of a Long-Term Relapse Prevention Trial in Subjects with Schizophrenia

	--- Open Label-----	---------- Double Blind ----------	
	Paliperidone Palmitate[a]	**Placebo**	**INVEGA TRINZA®**
System Organ Class	**(N=506)**	**(N=145)**	**(N=160)**
Adverse Reaction[b]	**n (%)[c]**	**n (%)[c]**	**n (%)[c]**
Reproductive system and breast disorders			
Amenorrhea	6 (1.2)	0	1 (0.6)
Galactorrhea	4 (0.8)	0	0
General disorders and administration site conditions			
Injection site reaction	62 (12.3)	0	5 (3.1)

[a] During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate injectable product followed by a single dose of INVEGA TRINZA® prior to randomization to either placebo or INVEGA TRINZA® in the subsequent double-blind phase (see *Pharmacodynamic Properties: Clinical efficacy*).

[b] The following terms were combined:
Tachycardia includes Tachycardia, Sinus tachycardia.
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.
Somnolence includes Somnolence, Sedation.
Akathisia includes Akisthisia, Restlessness.
Parkinsonism includes Parkinsonism, Cogwheel rigidity, Drooling, Extrapyramidal disorder, Hypokinesia, Muscle rigidity, Muscle tightness, Musculoskeletal stiffness, Salivary hypersecretion.
Dystonia includes Dystonia, Blepharospasm.

[c] Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Other clinical trial data

Paliperidone palmitate is hydrolyzed to paliperidone. Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. This subsection includes additional adverse reactions reported with paliperidone and/or risperidone in clinical trials.

Additional adverse reactions reported in clinical trials of INVEGA TRINZA®, not included in Table 5, are shown in Table 6a.

Table 6a. Additional Adverse Reactions Reported in Clinical Trials of INVEGA TRINZA®

System/Organ Class Adverse Reaction
Infections and infestations Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Ear infection, Eye infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Subcutaneous abscess, Tonsillitis
Blood and lymphatic system disorders Anemia, Neutropenia, White blood cell count decreased
Immune system disorders Hypersensitivity
Endocrine disorders Glucose urine present, Hyperprolactinemia
Metabolism and nutritional disorders Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Increased appetite, Polydipsia, Weight decreased[a]
Psychiatric disorders Agitation, Anorgasmia, Blunted affect, Confusional state, Depression[a], Insomnia[a], Libido decreased, Nervousness, Nightmare, Sleep disorder
Nervous system disorders Cerebral ischemia, Disturbance in attention, Dizziness, Dizziness postural, Dysarthria, Hypoesthesia, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia, Tremor[a]
Eye disorders Conjunctivitis, Dry eye, Glaucoma, Lacrimation increased, Vision blurred
Ear and labyrinth disorders Ear pain, Tinnitus, Vertigo
Cardiac disorders Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations, Postural orthostatic tachycardia syndrome
Vascular disorders Hypertension[a], Hypotension
Respiratory, thoracic and mediastinal disorders Cough, Dyspnea, Epistaxis, Nasal congestion, Pharyngolaryngeal pain, Respiratory tract congestion
Gastrointestinal disorders Abdominal discomfort, Abdominal pain, Cheilitis, Constipation[a], Diarrhea[a], Dry mouth, Dyspepsia, Dysphagia, Flatulence, Gastroenteritis, Toothache[a]

Table 6a. Additional Adverse Reactions Reported in Clinical Trials of INVEGA TRINZA®

System/Organ Class Adverse Reaction
Hepatobiliary disorders Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased
Skin and subcutaneous tissue disorder Acne, Drug eruption, Dry skin, Eczema, Erythema, Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders Arthralgia, Back pain[a], Blood creatine phosphokinase increased, Joint stiffness, Joint swelling, Muscle spasms, Muscular weakness, Musculoskeletal pain[a], Neck pain
Renal and urinary disorders Dysuria, Pollakiuria, Urinary incontinence
Reproductive system and breast disorders Breast discomfort, Breast enlargement, Breast pain, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder[b], Sexual dysfunction
General disorders and administration site conditions Asthenia, Body temperature increased, Chest discomfort, Chest pain, Chills, Drug withdrawal syndrome, Face edema, Fatigue[a], Gait abnormal, Malaise, Edema[b], Pyrexia
Injury, poisoning and procedural complications Fall

[a] Reported by ≥2% of subjects treated with INVEGA TRINZA® or 1-month paliperidone palmitate injectable product.

[b] **Edema includes:** generalized edema, edema peripheral, pitting edema. **Menstrual disorder includes:** menstruation irregular, oligomenorrhea.

Additional adverse reactions reported in other clinical trials of paliperidone and risperidone are shown in Table 6b.

Table 6b. Additional Adverse Reactions Reported in other Clinical Trials of Paliperidone and Risperidone.

System/Organ Class Adverse Reaction
Blood and lymphatic system disorders Eosinophil count increased
Immune system disorders Anaphylactic reaction
Metabolism and nutritional disorders Anorexia
Nervous system disorders

Table 6b. Additional Adverse Reactions Reported in other Clinical Trials of Paliperidone and Risperidone.

System/Organ Class Adverse Reaction
Balance disorder, Convulsion[a], Coordination abnormal, Depressed level of consciousness, Diabetic coma, Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Unresponsive to stimuli
Eye disorders Eye movement disorder, Eye rolling, Ocular hyperemia, Photophobia
Cardiac disorders Sinus arrhythmia
Vascular disorders Flushing, Ischemia
Respiratory, thoracic and mediastinal disorders Dysphonia, Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Rales, Wheezing
Gastrointestinal disorders Fecal incontinence, Fecaloma, Intestinal obstruction, Swollen tongue
Skin and subcutaneous tissue disorder Dandruff, Hyperkeratosis, Seborrheic dermatitis, Skin discoloration
Musculoskeletal and connective tissue disorders Posture abnormal, Rhabdomyolysis
Reproductive system and breast disorders Breast engorgement, Vaginal discharge
General disorders and administration site conditions Body temperature decreased, Induration, Thirst

[a] **Convulsion includes:** grand mal convulsion.

Events of particular interest to the class

Extrapyramidal symptoms (EPS). Data from the double-blind placebo-controlled phase of the long-term relapse prevention trial (see *Pharmacodynamic Properties: Clinical efficacy*) showed that the incidence of EPS-related AEs was higher in the INVEGA TRINZA® group (13 subjects [8.1%]) than in the placebo group (5 subjects [3.4%]). Evaluation of EPS included a pooled analysis of the following EPS groups: dyskinesia, dystonia, hyperkinesia, parkinsonism, and tremor.

Weight gain. In the double-blind placebo-controlled phase of the long-term relapse prevention trial, abnormal increases of ≥7% in body weight from double-blind baseline to double-blind end point were reported for 15 subjects (10%) in the INVEGA TRINZA® group and 1 subject (1%) in

the placebo group. Conversely, abnormal decreases in body weight (≥ 7%) from double-blind baseline to double-blind end point were reported for 2 subjects (1%) in the INVEGA TRINZA® group and 12 subjects (8%) in the placebo group. The mean changes in body weight from double-blind baseline to double-blind end point were +0.94 kg and -1.28 kg for the INVEGA TRINZA® and placebo groups, respectively.

Laboratory tests: serum prolactin. During the double-blind placebo-controlled phase of the long-term relapse prevention trial, elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) were noted in a higher percentage of males and females in the INVEGA TRINZA® group than in the placebo group (9% vs. 3% and 5% vs. 3%, respectively). In the INVEGA TRINZA® group, the mean change from double-blind baseline to double-blind end point was +2.90 ng/mL for males (vs. -10.26 ng/mL in the placebo group) and +7.48 ng/mL for females (vs. -32.93 ng/mL in the placebo group). One 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.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience with paliperidone and/or risperidone (Table 7). In Table 7, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports
Not known	Cannot be estimated from the available data.

Table 7. Adverse Reactions Identified During Postmarketing Experience with Paliperidone and/or Risperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Paliperidone

Blood and lymphatic system disorders	
Very rare	Agranulocytosis, Thrombocytopenia
Endocrine disorders	
Not known	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia
Not known	Water intoxication
Psychiatric disorders	
Very rare	Catatonia, Mania, Somnambulism
Not known	Sleep-related eating disorder
Nervous system disorders	
Very rare	Dysgeusia
Eye disorders	
Not known	Floppy iris syndrome (intraoperative)
Cardiac disorders	
Very rare	Atrial fibrillation
Vascular disorder	
Very rare	Venous thrombosis, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal disorders	
Very rare	Pancreatitis
Very rare	Ileus
Hepatobiliary disorders	
Not known	Jaundice
Skin and subcutaneous tissue disorders	
Rare	Angioedema
Very rare	Alopecia
Not known	Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders	
Very rare	Urinary retention
Pregnancy, puerperium and perinatal conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	
Very rare	Priapism
General disorders and administration site conditions	
Very rare	Hypothermia, Injection site abscess, Injection site cellulitis, Injection site hematoma
Not known	Injection site cyst, Injection site necrosis, Injection site ulcer

Very rarely, cases of anaphylactic reaction after administration of the 1-month paliperidone palmitate injectable product have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Overdose

Because INVEGA TRINZA® is to be administered by health care professionals, the potential for overdosage by patients is low.

Symptoms and signs

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in the setting of overdose with oral paliperidone. In the case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Consideration should be given to the extended-release *[prolonged-release]* nature of INVEGA TRINZA® and the long apparent half-life of paliperidone when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX13.

Mechanism of action

Paliperidone palmitate, the active ingredient in INVEGA TRINZA®, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives (atypical neuroleptic antipsychotic). INVEGA TRINZA® contains a racemic mixture of (+)- and (-)-paliperidone.

Paliperidone palmitate is hydrolyzed to paliperidone (see *Non-clinical Information*). Paliperidone is a centrally active dopamine D_2 antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β1- and β2-

adrenergic receptors. The pharmacological activity of the (+)– and (-)-paliperidone enantiomers is qualitatively and quantitatively similar.

The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been proposed that the therapeutic activity of paliperidone in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of paliperidone.

Effect on QT/QTc interval and cardiac electrophysiology

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 adults with schizophrenia and schizoaffective disorder, 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 525 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 relapse prevention 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.

Clinical efficacy

The efficacy of INVEGA TRINZA® for the treatment of schizophrenia in subjects who have been adequately treated for at least 4 months with the 1-month paliperidone palmitate injectable product was evaluated in a long-term double-blind, placebo-controlled relapse prevention/randomized withdrawal study and in a long-term double-blind, active-controlled noninferiority study.

Relapse prevention / randomized withdrawal study

Adult subjects who met DSM-IV-TR criteria for schizophrenia 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 subjects 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 subjects switching from LAI medication were treated with the 1-month paliperidone palmitate injectable product in place of the next scheduled injection. Specifically:

- For subjects entering the study who were already being treated with the 1-month paliperidone palmitate injectable product, their dosing remained unchanged. Subjects who were currently receiving the 39 mg dose of 1-month paliperidone palmitate were not eligible to enroll in the study.

- Subjects 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.

- Subjects 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 subjects 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. Subjects 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.

- A 12-week open-label treatment period with INVEGA TRINZA® (second part of a 29-week open-label stabilization phase). A total of 379 subjects received a single-dose of INVEGA TRINZA® which was a 3.5 multiple of the last dose of the 1-month paliperidone palmitate. Subjects 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 PANSS items P1, P2, P3, P6, P7, G8, and G14 at the end of this 12-week period (week 29 of the study).

- A variable length double-blind treatment period. In this period, 305 stabilized subjects were randomized 1:1 to continue treatment with INVEGA TRINZA® or placebo until relapse, early withdrawal, or the end of study. Subjects 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 subjects entering double-blind on each of the dose levels were 6 (4%) for 175 mg, 15 (9%) for 263 mg, 78 (49%) for 350 mg, and 61 (38%) for 525 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 individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness).

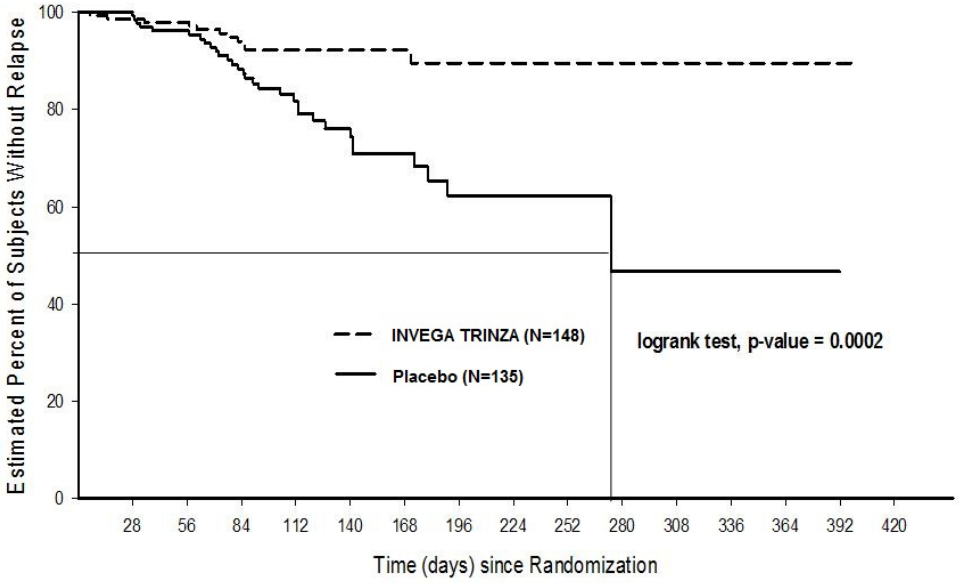
A pre-planned interim analysis showed a statistically significantly longer time to relapse in subjects treated with INVEGA TRINZA® compared to placebo, and the study was stopped early because efficacy was demonstrated. The most common reason for relapse observed across both treatment groups was increase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

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. Twenty-three percent (23%) of subjects in the placebo group and 7.4% of subjects in the INVEGA TRINZA® group experienced a relapse event. The hazard ratio for relapse (placebo/INVEGA TRINZA®) was 3.45 (95% CI: 1.73, 6.88) indicating a 71% decrease in relapse risk with INVEGA TRINZA®. There was a significant difference (p-value <0.001) between the treatment groups in favor of INVEGA TRINZA®. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 1. The median time to relapse (the time at which the cumulative survival function equals 0.5, or 50%) for subjects in the placebo group (274 days) was significantly shorter than for the INVEGA TRINZA®

group (which could not be estimated as less than 15% of the remaining patients at any time during the trial experienced a relapse).

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

Figure 1: Kaplan-Meier Plot of Time to Relapse[a] – Interim Analysis



[a] Also depicted is the median time to relapse of the placebo group (274 days), which is an estimation of the average time it took for 50% of the trial population to relapse after INVEGA TRINZA® was discontinued.

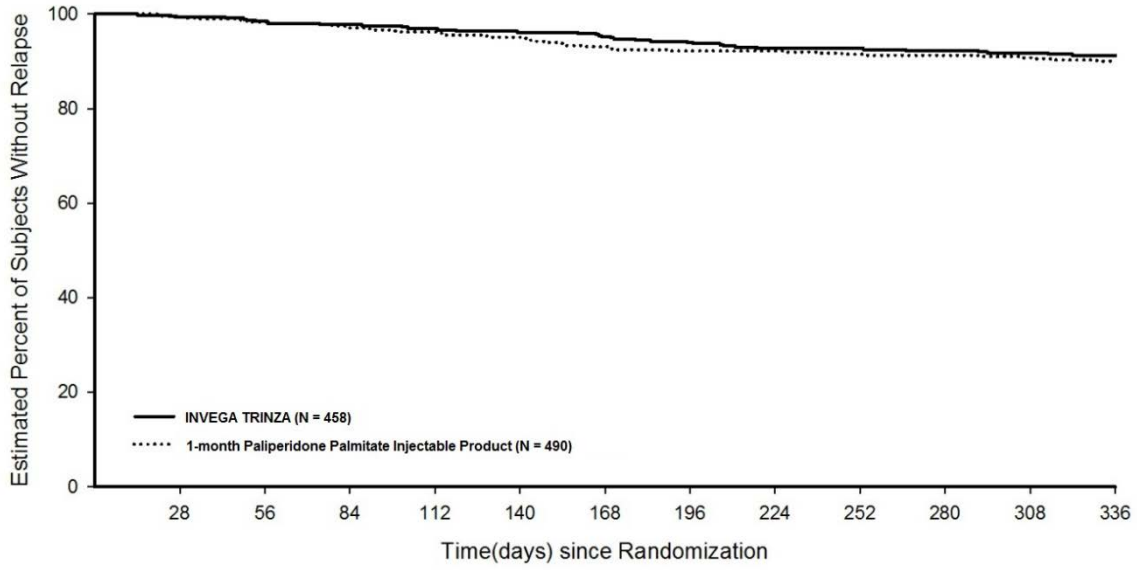
Noninferiority study

In the noninferiority study, 1429 acutely ill subjects (baseline mean PANSS total score: 85.7) were enrolled into the open-label phase and treated with the 1-month paliperidone palmitate injectable product for 17 weeks. The dose could be adjusted (i.e., 50 mg, 75 mg, 100 mg, or 150 mg) at the week 5 and 9 injections and the injection site could be deltoid or gluteal. For subjects that met randomization criteria at weeks 14 and 17, 1016 were randomized in a 1:1 ratio to continue on monthly injections of the 1-month paliperidone palmitate injectable product or to switch to INVEGA TRINZA® with a 3.5 multiple of the week 9 and 13 dose of the 1-month paliperidone palmitate injectable product for 48 weeks. Subjects received INVEGA TRINZA® once every 3 months and received placebo injectable medication for the other months to maintain the blind.

The primary efficacy endpoint of the study was the percentage of subjects who had not relapsed at the end of the 48-week double-blind phase based on the Kaplan-Meier 48-week estimate (INVEGA TRINZA®: 91.2%, 1-month paliperidone palmitate injectable product: 90.0%). The mean (SD) duration of exposure during the double-blind phase was 295 (88) days in the INVEGA TRINZA® group and 287 (96) days in the 1-month paliperidone palmitate injectable product

group. The median time to relapse in either group could not be estimated due to low percentage of subjects with relapse. The difference (95% CI) between the treatment groups was 1.2% (-2.7%, 5.1%), meeting the pre-specified noninferiority criterion based on a margin of -15%. Thus, the INVEGA TRINZA® treatment group was noninferior to the 1-month paliperidone palmitate injectable product. Improvements in functioning, as measured by the Personal and Social Performance scale (PSP), which was observed during the open-label stabilization phase were maintained during the double-blind phase for both treatment groups.

Figure 2: Kaplan-Meier Plot of time to relapse comparing INVEGA TRINZA® and 1-month paliperidone palmitate injectable product.



The efficacy results were consistent across population subgroups (gender, age, and race) in both studies.

Pharmacokinetic Properties

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.

The data presented in this paragraph are based on a population pharmacokinetic analysis. 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 175-525 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. The total exposure of paliperidone following INVEGA TRINZA® administration was dose-proportional over a 175-525 mg dose range, and approximately dose-proportional for C_{max}. 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 excretion

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. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

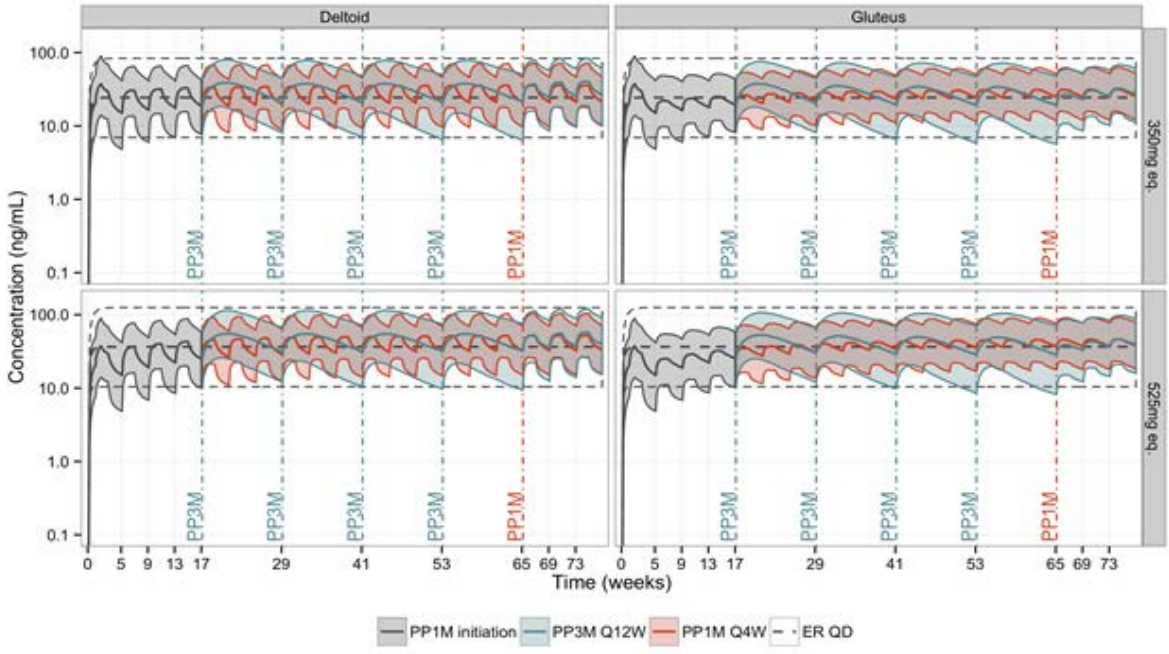
Based on population pharmacokinetic analysis, the median apparent half-life of paliperidone following INVEGA TRINZA® administration over the dose range of 175-525 mg ranged from 84-95 days following deltoid injections and 118-139 days following gluteal injections.

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.

Figure 3 presents the population predicted median pharmacokinetic profiles for paliperidone following INVEGA TRINZA® administration using the 350 mg and 525 mg doses compared to the administration of monthly injections of 100 mg and 150 mg 1-month paliperidone palmitate injection and to oral extended-release tablet administration (8 mg or 12 mg). Treatment with 1-month paliperidone palmitate injection for at least 4 months prior to initiating treatment with INVEGA TRINZA® resulted in maintenance of steady-state paliperidone plasma exposures.

Figure 3. Predicted paliperidone plasma concentrations versus time for INVEGA TRINZA® (PP3M) 350 mg and 525 mg dose groups compared to the monthly dosing of 1-month paliperidone palmitate injection (PP1M) 100 mg and 150 mg. The dashed lines represent the predicted paliperidone concentrations following treatment with 8 mg and 12 mg oral paliperidone extended-release tablets.



Special populations

Elderly (65 years of age and older)

No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see *Renal impairment* below and *Dosage and Administration*).

Renal impairment

INVEGA TRINZA® has not been systematically studied in patients with renal impairment. The disposition of a single oral dose of a paliperidone 3 mg extended-release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA TRINZA® in subjects with mild renal impairment and pharmacokinetic simulations, the initiation and maintenance dose of 1-month paliperidone palmitate injection should be reduced in patients with mild renal impairment. Subjects can be transitioned over to INVEGA TRINZA® using the corresponding 3.5-multiple dose for mild renal impaired subjects. No additional dose reduction upon starting INVEGA TRINZA® is necessary (see *Dosage and Administration*).

Hepatic impairment

Paliperidone is not extensively metabolized in the liver. Although INVEGA TRINZA® was not studied in patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. In a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. Paliperidone has not been studied in patients with severe hepatic impairment.

Race

Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA TRINZA® administration.

Gender

No clinically significant differences were observed between men and women.

Smoking status

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. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

Body Mass Index (BMI)/Body Weight

No dose adjustment is needed based on BMI. 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.

NON-CLINICAL INFORMATION

Toxicology

As with other drugs that antagonize dopamine D_2 receptors, intramuscularly-injected paliperidone palmitate, as well as orally-dosed paliperidone, elevated serum prolactin levels in repeat-dose toxicity studies.

In a 7-week juvenile toxicity study in rats with oral doses of paliperidone of 0.16, 0.63, and 2.5 mg/kg/day, which are 0.12, 0.5, and 1.8 times the maximum recommended human oral dose of 12 mg/day for adolescents on a mg/m^2 basis, no effects on growth, sexual maturation, and reproductive performance were observed. Oral doses up to 2.5 mg/kg/day did not impair neurobehavioral development in males and females, except for an effect on learning and memory in female rats treated at 2.5 mg/kg/day. This effect was not observed after discontinuation of treatment.

In a 40-week study in juvenile dogs treated with oral risperidone (which is extensively converted to paliperidone) at doses of 0.31, 1.25, and 5 mg/kg/day, sexual maturation was not adversely affected at 0.31 and 1.25 mg/kg/day. Long bone growth was not affected at 0.31 mg/kg/day; effects were observed at 1.25 and 5 mg/kg/day.

Carcinogenicity

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30, and 60 mg/kg/month, which are 0.2, 0.6, and 1.1 times the maximum recommended INVEGA TRINZA® human dose of 525 mg on a mg/m^2 body surface area basis. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 1.3 and 2.5 times the maximum recommended human 525 mg dose of INVEGA TRINZA® on a mg/m^2 basis.

The carcinogenic potential of oral paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats. Risperidone was administered at doses up to 10 mg/kg/day for 18 months to mice and for 25 months to rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. An increase in mammary, pituitary, and endocrine pancreas tumors has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism. The relevance of these tumor findings in rodents in terms of human risk is unknown.

Mutagenicity

No evidence of mutagenic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the rat micronucleus test. Paliperidone palmitate showed no genotoxic properties in the Ames reverse mutation test or the mouse lymphoma assay.

Fertility

Although oral paliperidone treatment resulted in prolactin- and CNS-mediated effects, the fertility of male and female rats was not affected. At a maternally toxic dose, female rats showed a slightly lower number of live embryos.

PHARMACEUTICAL INFORMATION

List of Excipients

Inactive ingredients in INVEGA TRINZA® are citric acid monohydrate, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

Incompatibilities

INVEGA TRINZA® should not be mixed with any other product or diluent and is intended for intramuscular administration directly from the syringe in which it is packaged.

Shelf Life

See expiry date on the outer carton.

Storage Conditions

Do not store above 30°C. Keep out of the sight and reach of children.

Nature and Contents of Container

Kit containing a 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 wall 22G, 1½-inch safety needle and a thin wall 22G, 1-inch safety needle.

Instructions for Use and Handling and Disposal

INVEGA TRINZA®

Paliperidone palmitate
Extended-release
Injectable suspension

Administer once 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 health care 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**.

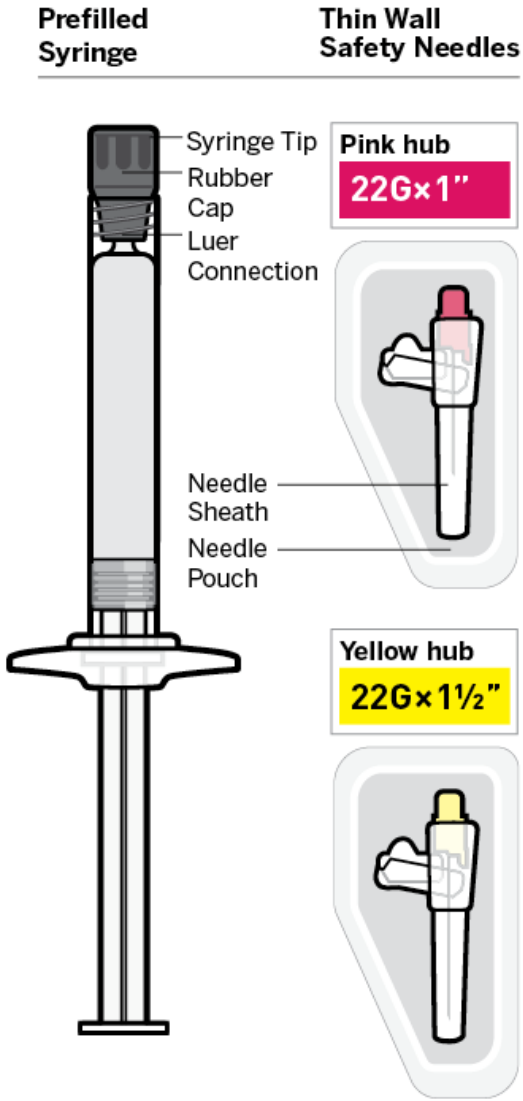
Preparation

Peel off tab label from the syringe and place in patient record.
INVEGA TRINZA® requires **longer and more vigorous shaking** than the 1-month paliperidone palmitate injectable product. 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**.

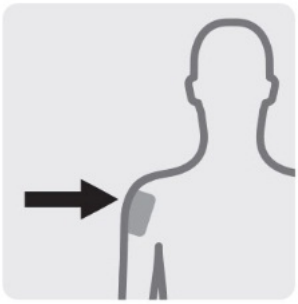
Dose pack contents



1 Select Needle

Needle selection is determined by injection area and patient weight

If administering a Deltoid injection



If patient weighs:

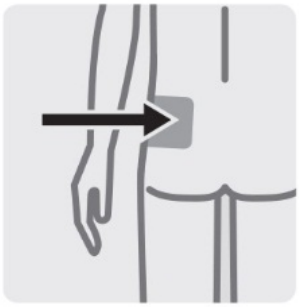
Less than 90 kg
Pink hub

22G×1”

90 kg or more
Yellow hub

22G×1½”

If administering a Gluteal injection



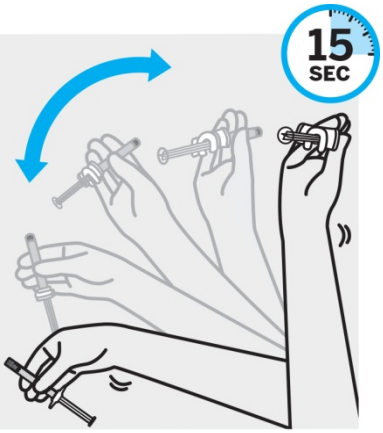
Regardless of patient weight:

Yellow hub

22G×1½”

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

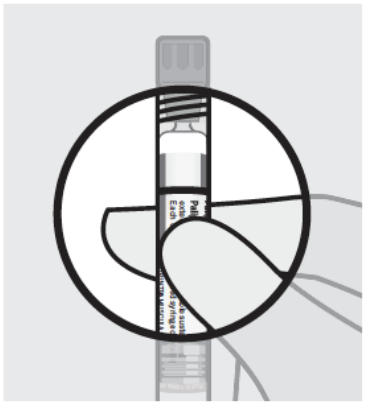
2 Prepare for injection



(i) SHAKE VIGOROUSLY for at least 15 seconds

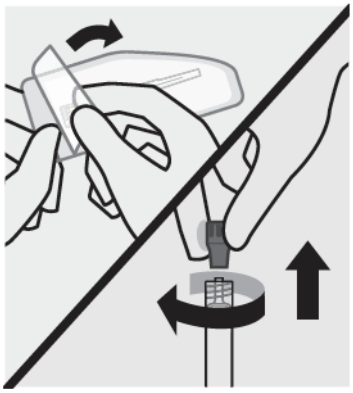
With the syringe tip pointing up, SHAKE VIGOROUSLY with a **loose wrist** for at least 15 seconds to ensure a homogeneous suspension.
NOTE: This medication requires longer and more vigorous shaking than the 1 month paliperidone palmitate injectable product.

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



(ii) Check suspension

After shaking the syringe for 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.

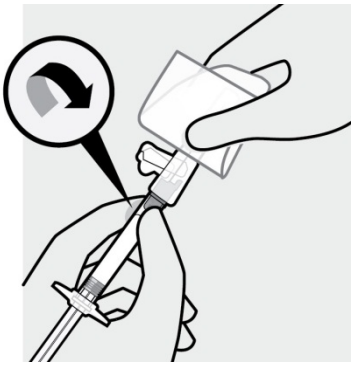


(iii) Open needle pouch and remove cap

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.

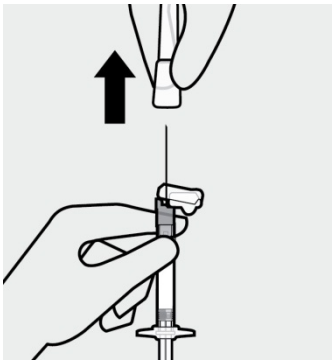
(iv) Grasp needle pouch

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



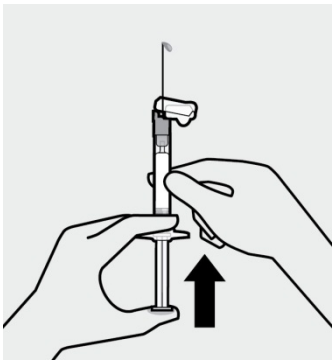
(v) Attach needle

Hold the syringe pointing up. Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage. Always check for signs of damage or leakage prior to administration.



(vi) Remove needle sheath

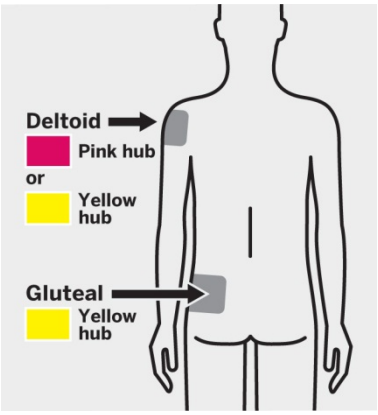
Pull the needle sheath away from the needle in a straight motion. **Do not** twist the sheath, as this may loosen the needle from the syringe.



(vii) 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

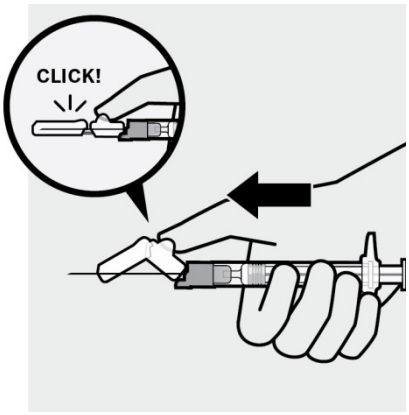
3 Inject



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



(i) 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.

(ii) 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.

BATCH RELEASER

Janssen Pharmaceutica NV
30 Turnhoutseweg
B-2340 Beerse, Belgium

PRODUCT REGISTRANT

Johnson & Johnson International (Singapore) Pte Ltd
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

DATE OF REVISION OF THE TEXT

13 February 2023 (CCDS 05 December 2022)