

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrINVEGA TRINZA®**

paliperidone palmitate Prolonged-Release Injectable Suspension,  
paliperidone as paliperidone palmitate

Supplied as pre-filled syringes containing

175 mg/0.875 mL,  
263 mg/1.315 mL,  
350 mg/1.75 mL,  
and 525 mg/2.625 mL

paliperidone as paliperidone palmitate,

Intramuscular injection

(3 Months)

Antipsychotic Agent

ATC code: N05AX13

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## RECENT MAJOR LABEL CHANGES

### 7 WARNINGS AND PRECAUTIONS, Immune, Skin

12/2020

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

INVEGA TRINZA<sup>®</sup>, a 3-month injection, is indicated for the treatment of schizophrenia in adult patients. INVEGA TRINZA<sup>®</sup> is to be used only after INVEGA SUSTENNA<sup>®</sup> (1-month paliperidone palmitate prolonged-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<sup>®</sup> be the same dosage strength before starting INVEGA TRINZA<sup>®</sup>.

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of INVEGA TRINZA<sup>®</sup> in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use and its use is not recommended. See **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**.

#### 1.2 Geriatrics

**Geriatrics (> 65 years of age):** Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA TRINZA<sup>®</sup> is not indicated for the treatment of elderly patients with dementia. See **SERIOUS WARNINGS AND PRECAUTIONS BOX** and **WARNINGS AND PRECAUTIONS, Special Populations**.

### 2 CONTRAINDICATIONS

INVEGA TRINZA<sup>®</sup> is contraindicated in patients who are hypersensitive to paliperidone, risperidone, or to any other ingredient in the formulation or component of the container (see **WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity**, and **ADVERSE REACTIONS, Post-Market Adverse Reactions**). For a complete listing of ingredients, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

##### Increased Mortality in Elderly Patients with Dementia

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. 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 (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics, Use in Geriatric Patients with Dementia).

INVEGA TRINZA® is not indicated for the treatment of elderly patients with dementia.

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

Very rare cases of severe hypersensitivity after injection with 1-month injectable paliperidone have been reported during post-marketing experience in patients who have previously tolerated oral paliperidone or oral risperidone. Care should be taken to avoid exposure to those that are suspected to be hypersensitive or have shown hypersensitivity reactions to any of the excipients (see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).

#### 4.2 Recommended Dose and Dosage Adjustment

##### **Adult**

INVEGA TRINZA® is to be used only after INVEGA SUSTENNA® (1-month paliperidone palmitate prolonged-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®.

##### **Dosage**

Initiate INVEGA TRINZA® at the time 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 multiplier as shown in [Table 1.1](#). 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 1.1 Conversion from the last INVEGA SUSTENNA® dose to the INVEGA TRINZA® dose using 3.5 as a multiplier**

<b>If the last dose of INVEGA SUSTENNA® is:</b>	<b>Initiate INVEGA TRINZA® at the following dose:</b>
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

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 **ACTION AND CLINICAL PHARMACOLOGY**).

See **Administration** section following.

### **Dosage Adjustments for Special Populations**

#### ***Patients with Renal Impairment***

INVEGA TRINZA® has not been systematically studied in patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**). For patients with mild renal impairment (creatinine clearance  $\geq 50$  to  $< 80$  mL/min), adjust dosage and stabilize the patients using the 1-month paliperidone palmitate injectable product, then transition to INVEGA TRINZA® in a 3.5 to 1 ratio (see Table 1.1). 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) (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**).

#### ***Patients with 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 **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**).

#### ***Pediatrics***

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

#### ***Elderly***

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 ***Patients with Renal Impairment*** above for dosing recommendations in patients with renal impairment.

### Other Special Populations

No dose adjustment for INVEGA TRINZA® is recommended based on gender, race, or smoking status.

### 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 (INVEGA SUSTENNA®) for at least 4 months (see **Recommended Dose and Dosage Adjustment**).

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 INVEGA SUSTENNA® (1-Month Paliperidone Palmitate Injectable Product)

For switching from INVEGA TRINZA® to INVEGA SUSTENNA® (1-month paliperidone palmitate prolonged-release injectable suspension), 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 (see [Table 1.2](#) below). The 1-month paliperidone palmitate injectable product should then continue to be dosed at monthly intervals.

**Table 1.2. Conversion from INVEGA TRINZA® to INVEGA SUSTENNA® using 3.5 as a conversion factor**

If the last INVEGA TRINZA® dose is:	Initiate INVEGA SUSTENNA® 3 months later at the following dose <sup>a</sup> :
175 mg	50 mg
263 mg	75 mg
350 mg	100 mg
525 mg	150 mg

<sup>a</sup> The initiation dosing as described in the prescribing information for INVEGA SUSTENNA® 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. [Table 1.3](#) provides some guidance for dose conversions. **Doses of oral paliperidone extended-release tablets should however, be individualized taking into consideration the reason for switching, response to previous paliperidone treatment, severity of psychotic symptoms, and/or tolerability.**

**Table 1.3. INVEGA TRINZA® doses and once-daily paliperidone extended-release conversion regimens\***

	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	Daily doses 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**

### 4.3 Administration

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **It is important to shake the syringe vigorously with the tip up and a loose wrist for at least 15 seconds to ensure a homogeneous suspension. The suspension should appear uniform and milky white in colour. Inject INVEGA TRINZA® within 5 minutes of shaking vigorously (see Instructions for Use).**

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 full dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.<sup>1</sup>

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 INVEGA SUSTENNA® pack or other commercially-available needles 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  $\geq 90$  kg ( $\geq 200$  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.

There are no systematically collected safety data to specifically address concomitant use of INVEGA TRINZA® with risperidone, oral paliperidone, or other antipsychotics. Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA TRINZA® is co-administered with risperidone or oral paliperidone.

**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**

<sup>1</sup> Administration in the gluteal muscle may lead to a lower drug exposure than that seen in the deltoid muscle (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

**minutes prior to administration to ensure a homogeneous suspension and ensure that the needle does not get clogged during injection (see Instructions for Use).**

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®.

### Instructions for Use



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

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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.

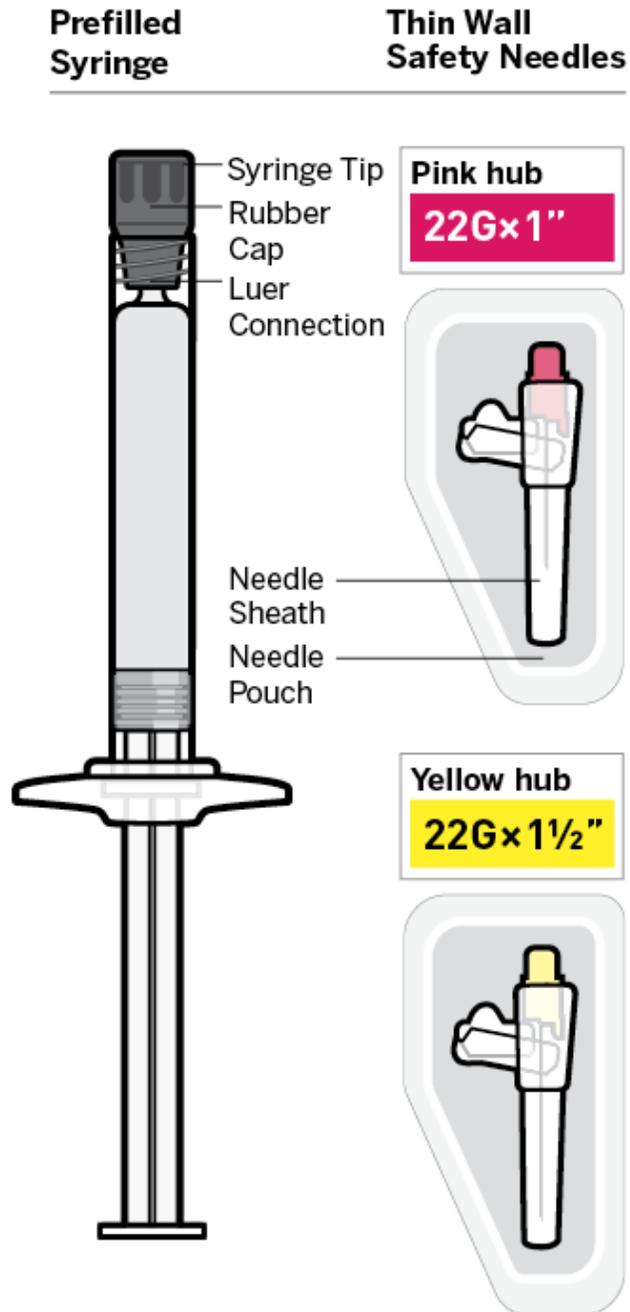
INVEGA TRINZA® requires **longer and more vigorous shaking** than INVEGA SUSTENNA® (1-month paliperidone palmitate prolonged-release injectable suspension). Shake the syringe vigorously, with the syringe tip pointing up, **for at least 15 seconds within 5 minutes prior to administration** (see Step 2).

### 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

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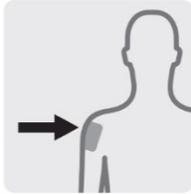
# 1

## Select Needle

Needle selection is determined by injection area and patient weight.

---

### If administering a Deltoid injection



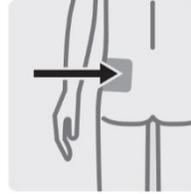
If patient weighs:  
**Less than 200 lbs (90 kg)**  
pink hub

**22G × 1"**

**200 lbs (90 kg) or more**  
yellow hub

**22G × 1½"**

### If administering a Gluteal injection

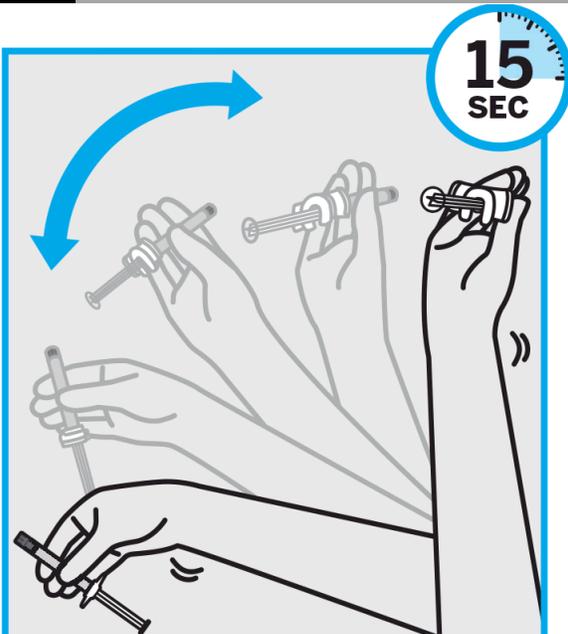


**Regardless of patient weight:**  
yellow hub

**22G × 1½"**



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



**SHAKE VIGOROUSLY**  
for at least 15 seconds

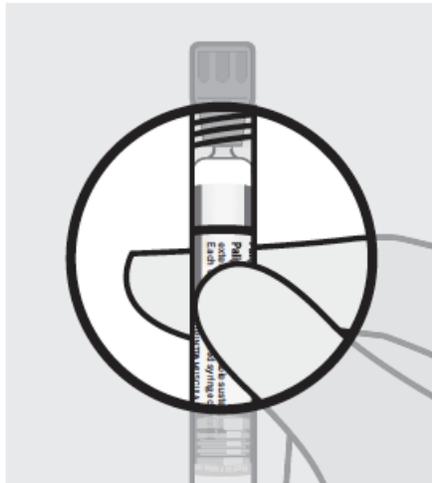
With the syringe tip pointing up, SHAKE VIGOROUSLY with a loose wrist for at least 15 seconds to ensure a homogeneous suspension.

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



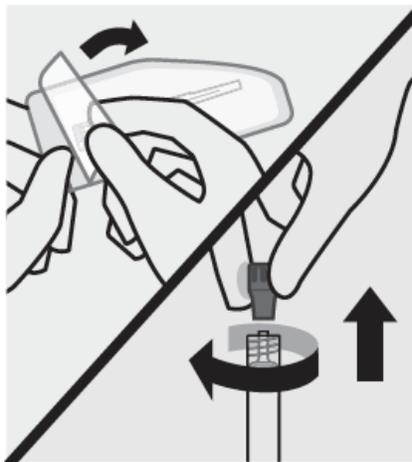
Proceed to the next step immediately after shaking. If **more than 5 minutes pass before injection, shake vigorously, with the syringe tip pointing up, again** for at least 15 seconds to re-suspend the medication.

## Check suspension



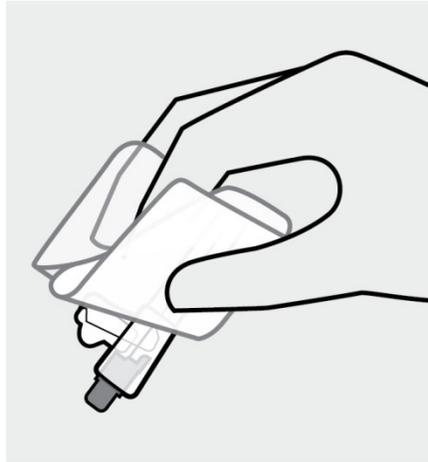
After shaking the syringe for at least 15 seconds, check the liquid in the viewing window. The suspension should appear uniform and milky white in colour. It is also normal to see small air bubbles.

## 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.

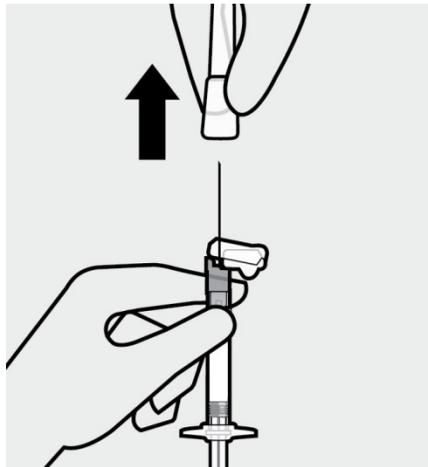
### Attach needle



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.

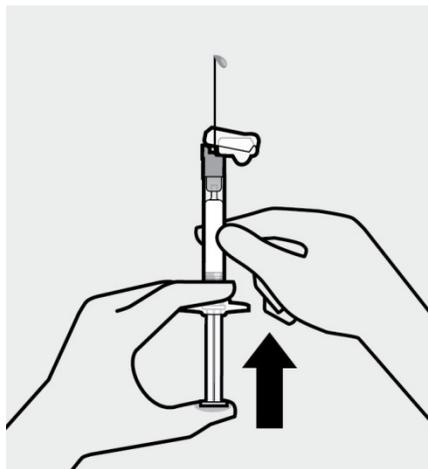
### Remove needle sheath



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



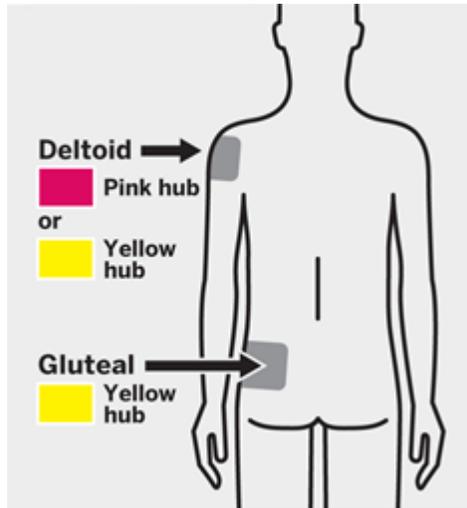
Hold the syringe upright and tap gently to make any air bubbles rise to the top.

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

### 3

## Inject

### Inject dose



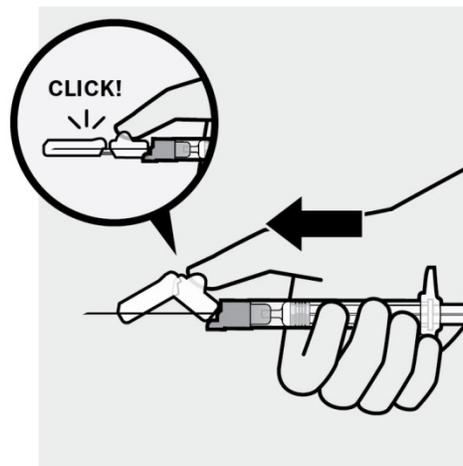
**Slowly inject the entire contents of the syringe** intramuscularly, deep into the selected deltoid or gluteal muscle.

**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<sup>®</sup>. Unused needle should be discarded and not saved for future use.

## 4.4 Missed Dose

**Dosing Window.** Missing doses of INVEGA TRINZA<sup>®</sup> should be avoided. INVEGA TRINZA<sup>®</sup> should be administered every three months. 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 Since Last Injection.** If more than 3½ months (up to 4 months) have elapsed since the last injection of INVEGA TRINZA<sup>®</sup>, the previously administered INVEGA TRINZA<sup>®</sup> 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 Since Last Injection.** If more than 4 months up to 9 months have elapsed since the last injection of INVEGA TRINZA<sup>®</sup>, do NOT administer the next dose of INVEGA TRINZA<sup>®</sup>. Instead, use the re-initiation regimen shown in [Table 1.4](#).

**Table 1.4. Re-initiation regimen after missing > 4 months up to 9 months of INVEGA TRINZA®**

Last INVEGA TRINZA® 3-Month Injectable Product Dose	Administer INVEGA SUSTENNA® 1-Month Injectable Product, two doses one week apart (into deltoid muscle)		Then administer INVEGA TRINZA® 3-Month Injectable Product (into deltoid <sup>a</sup> 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

<sup>a</sup> 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 INVEGA SUSTENNA®, 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.

## 5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

### Symptoms

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. Torsades de pointes and ventricular fibrillation have been reported in the setting of overdose with oral paliperidone. In the case of acute overdose, the possibility of multiple drug involvement should be considered.

### Treatment

Consideration should be given to the 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 fluids 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.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intramuscular injection	Prolonged-Release Injectable Suspension / Supplied as prefilled syringes containing 175 mg/0.875 mL, 263 mg/1.315 mL, 350 mg/1.75 mL, and 525 mg/2.625 mL paliperidone as paliperidone palmitate	Citric acid monohydrate, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection

### Dosage Forms and Packaging

INVEGA TRINZA<sup>®</sup> is available in pre-filled syringes as a white to off-white sterile aqueous prolonged-release suspension for intramuscular injection. The product is supplied as a kit and contains a prefilled syringe and 2 safety needles, a thin walled 22G, 1 ½-inch safety needle and a thin walled 22G, 1-inch safety needle.

The pre-filled syringes are for single use only.

### Composition

The syringes contain 175 mg/0.875 mL, 263 mg/1.315 mL, 350 mg/1.75 mL, and 525 mg/2.625 mL paliperidone (as 273, 410, 546 or 819 mg of paliperidone palmitate respectively).

The inactive ingredients in INVEGA TRINZA<sup>®</sup> are citric acid monohydrate, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

### Incompatibilities

INVEGA TRINZA<sup>®</sup> 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.

## 7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

### General

#### Administration

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

#### 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<sup>®</sup> 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.

### **Concomitant Use of INVEGA TRINZA® with Risperidone or Oral Paliperidone**

There are no systematically collected safety data to specifically address concomitant use of INVEGA TRINZA® with risperidone, oral paliperidone, or other antipsychotics. Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA TRINZA® is co-administered with risperidone or oral paliperidone.

### **Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA TRINZA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

### **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.

### **Carcinogenesis and Mutagenesis**

For animal data, see **NON-CLINICAL TOXICOLOGY**.

### **Cardiovascular**

#### **Orthostatic Hypotension**

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity.

In the long-term relapse prevention trial, syncope was reported in < 1% (1/506) of subjects treated with INVEGA SUSTENNA®, the 1-month paliperidone palmitate injectable product, during the open-label phase; there were no cases reported during the double-blind phase in either treatment group. In the long-term relapse prevention trial, orthostatic hypotension was reported as an adverse event by < 1% (1/506) of subjects treated with the 1-month paliperidone palmitate injectable product 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.

In the INVEGA TRINZA® non-inferiority study, syncope was reported for 2 subjects (0.1%) in the open-label phase with treatment with the 1-month paliperidone palmitate injectable product and 1 subject (0.2%) in the double-blind phase. The incidence of orthostatic hypotension reported as an adverse event was low in the open-label phase (0.1% of subjects) and double-blind phase (0% in the INVEGA TRINZA® group and 1.0% of subjects in the 1-month paliperidone palmitate injectable product 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). Special care should be taken to avoid hypotension in patients with a history of cerebrovascular insufficiency or ischemic heart disease, and in patients taking medications to lower blood pressure.

### **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.

#### QT Prolongation Study R076477-SCH-1009

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicentre QT study in adults with schizophrenia and schizoaffective disorder. Serial ECG assessments were scheduled at multiple days and multiple time points during the day. Least square mean changes from baseline in QTcLD were calculated at each scheduled ECG assessment time point and day.

In study R076477-SCH-1009 (n=141), the 8 mg dose of immediate-release oral paliperidone (n=44) showed a maximal (least square) mean change from baseline in QTcLD of 10.9 msec (90% CI: 8.24; 13.62) and was noted 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 observed for the maximum recommended 525 mg dose of INVEGA TRINZA<sup>®</sup> in the long-term relapse prevention trial and the non-inferiority study.

In study R076477-SCH-1009, a 4 mg dose of the immediate-release oral formulation of paliperidone ( $C_{\max ss} = 35$  ng/mL) showed a maximal (least square) mean change from baseline in QTcLD of 9.3 msec (90% CI: 6.56; 11.98) and was noted on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study. Also, in this study, a 400 mg dose of moxifloxacin (n=58) showed a maximal least square mean change from baseline in QTcLD of 6.1 msec (90% CI: 3.64; 8.53) and was noted on day 8 at 3 hours post-dose. Placebo (n=58) showed a maximal least square mean change from baseline in QTcLD of 3.5 msec (90% CI: 1.05; 5.95) and was noted on day 2 at 30 minutes post-dose.

In the four fixed-dose, double-blind, placebo-controlled studies of INVEGA SUSTENNA<sup>®</sup> in which 1293 subjects with schizophrenia received active drug, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the long-term study, in which 849 subjects received INVEGA SUSTENNA<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> in the double-blind phase, and no subject had a QTcLD value of > 480 msec at any point in the study.

In the non-inferiority study in which subjects received INVEGA SUSTENNA® during the open-label phase, no subject had QTcLD values over 480 msec and no subject experienced a change in QTcLD exceeding 60 msec. During the double-blind phase in which subjects received either INVEGA TRINZA® or INVEGA SUSTENNA®, no subjects treated with INVEGA TRINZA® had QTcLD values over 480 msec. One subject who received INVEGA SUSTENNA® had a QTcLD value of > 500 msec and an increase in QTcLD exceeding 60 msec. One subject had a QTcLD change >60 msec after treatment with INVEGA TRINZA®. No other cardiovascular events were reported for either subject.

## **Endocrine and Metabolism**

### ***Dyslipidemia***

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

### ***Hyperglycemia and Diabetes Mellitus***

Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes, 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, and not in clinical trials.

Diabetic ketoacidosis (DKA) has occurred in patients treated with antipsychotics with no reported history of hyperglycemia. Appropriate clinical monitoring of patients treated with antipsychotics is advisable in accordance with utilized antipsychotic guidelines.

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 treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Any patient treated with atypical antipsychotics, including INVEGA TRINZA® should be monitored for symptoms of hyperglycemia and diabetes mellitus 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. 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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

### ***Hyperprolactinemia***

As with other atypical antipsychotics that antagonize dopamine D<sub>2</sub> receptors, paliperidone

elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone.

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. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects. As is common with dopamine D<sub>2</sub> antagonists, prolonged administration of risperidone in rodent carcinogenicity studies resulted in an increase in the incidence of pituitary gland, mammary gland, and endocrine pancreas hyperplasia and/or tumours (see **WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis**). However, 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; the available evidence is considered too limited to be conclusive at this time. The carcinogenic potential of paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats.

Potentially prolactin-related adverse events in the INVEGA TRINZA<sup>®</sup> development program were reported at a low (<5%) incidence in the open-label and double-blind phases of the controlled studies and were not serious; most were mild or moderate in severity and mostly did not result in discontinuation of study treatment. A higher proportion of females experienced potentially prolactin-related adverse reactions compared to males.

### ***Weight Gain***

Weight gain has been observed with atypical antipsychotic use. Regular clinical monitoring of weight is recommended (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Weight**).

### **Gastrointestinal *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 overdose with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

### **Genitourinary *Priapism***

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during post-marketing surveillance (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**). This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Although no cases of priapism have been reported in clinical trials with INVEGA TRINZA<sup>®</sup>, priapism has been reported with oral paliperidone during post-marketing surveillance.

### **Hematologic *Leukopenia, Neutropenia, and Agranulocytosis***

*Class Effect:* In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia

have been reported temporally related to antipsychotic agents, including INVEGA TRINZA®. Granulocytopenia and agranulocytosis have also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) or history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently 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<sup>9</sup>/L) should discontinue INVEGA TRINZA® and have their WBC counts followed until recovery (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**).

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

### ***Venous Thromboembolism***

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs including paliperidone, in case reports and/or observational studies. When prescribing INVEGA TRINZA® all possible risk factors for VTE should be identified and preventative measures undertaken.

### ***Hepatic/Biliary/Pancreatic***

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.

### ***Immune***

#### ***Hypersensitivity***

There have been very rare spontaneous post-marketing reports of severe hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock) in some patients after injection with 1-month injectable paliperidone. It is unknown how many of these patients previously tolerated oral risperidone or paliperidone. **However, anaphylactic-type reactions have occurred after administration of injectable paliperidone in patients who have previously tolerated oral risperidone or oral paliperidone.** Symptoms of anaphylaxis include skin rash, hives, peripheral edema, swollen eye, tongue and face, hyperhidrosis, dyspnea, and hypotension. Further treatment with INVEGA TRINZA® should be discontinued if such symptoms occur. Patients with hypersensitivity to oral risperidone, paliperidone, or to any other ingredient of the formulation or component of the container, should not be treated with INVEGA TRINZA® (see **CONTRAINDICATIONS**). Caution should also be exercised in patients who have had serious allergic reactions to other medications. For a complete listing of ingredients, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

### ***Neurologic***

#### ***Extrapyramidal Symptoms (EPS) 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 **DRUG INTERACTIONS, Drug-Drug Interactions**).

### ***Neuroleptic Malignant Syndrome (NMS)***

Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including paliperidone.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular blood pressure, tachycardia, cardiac arrhythmias, and diaphoresis). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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. 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 including INVEGA TRINZA<sup>®</sup>, 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<sup>®</sup>. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

### ***Parkinson's Disease and Dementia with Lewy Bodies***

Physicians should weigh the risks versus the benefits when prescribing antipsychotic drugs, including INVEGA TRINZA<sup>®</sup>, 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.

### ***Potential Effect on Cognitive and Motor Performance***

Somnolence and sedation were reported as adverse reactions in subjects treated with INVEGA TRINZA<sup>®</sup> (see **ADVERSE REACTIONS**). Antipsychotics, including INVEGA TRINZA<sup>®</sup>, have the potential to impair judgment, thinking, or motor skills and may have visual effects (e.g., blurred vision). 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.

### ***Seizures***

Antipsychotic drugs are known to lower the seizure threshold. As with other antipsychotic drugs, INVEGA TRINZA<sup>®</sup> should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

### ***Tardive Dyskinesia (TD)***

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD. It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. However, antipsychotic treatment itself may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown.

In view of these considerations, INVEGA TRINZA® should be prescribed in a manner that is most likely to minimize the risk of TD. As with any antipsychotic, INVEGA TRINZA® should generally be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of TD develop during treatment with INVEGA TRINZA®, withdrawal of the drug should be considered. However, some patients may require treatment with INVEGA TRINZA® despite the presence of the syndrome. Consideration should be given to the long-acting nature of INVEGA TRINZA®.

### **Ophthalmologic**

#### ***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, Post-Market Adverse Reactions**).

This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. 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.

### **Psychiatric**

#### ***Suicide***

The possibility of suicide or attempted suicide is inherent in psychosis, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy. INVEGA TRINZA® is to be administered by a health care professional (see **DOSAGE AND ADMINISTRATION**); therefore, suicide due to an overdose is unlikely.

### **Renal**

INVEGA TRINZA® has not been systematically studied in patients with renal impairment.

The disposition of oral paliperidone was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% 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<sub>inf</sub>) of 1.5-fold, 2.6-fold, and 4.8-fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 mL/min).

For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), dose adjustment is done when initiating treatment with INVEGA SUSTENNA®; 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. The maximum recommended dose of INVEGA TRINZA® in patients with mild renal impairment is 350 mg (see **DOSAGE AND ADMINISTRATION**).

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

## **Skin**

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life threatening adverse drug reactions that have been reported with atypical antipsychotic exposure. SCARs commonly present as a combination of the following symptoms: malaise, mucosal ulceration, extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. Discontinue INVEGA TRINZA® if severe cutaneous adverse reactions occur (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**).

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

#### **Teratogenic Effects**

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. Compared to no antipsychotic exposure, the relative risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was statistically significant (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 were not affected at exposures 20- to 22-fold the maximum human dose, or intramuscular exposures 6-fold the maximum human dose of the 1-month paliperidone palmitate injectable product.

### **Non-Teratogenic Effects**

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA TRINZA<sup>®</sup>, consideration should be given to the long-acting nature of INVEGA TRINZA<sup>®</sup> as neonates may be at risk from INVEGA TRINZA<sup>®</sup> administration before pregnancy or during first and second trimesters as well.

INVEGA TRINZA<sup>®</sup> should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus. The effect of INVEGA TRINZA<sup>®</sup> on labour and delivery in humans is unknown.

### **7.1.2 Breast-feeding**

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Patients should be advised not to breast-feed an infant if they are taking INVEGA TRINZA<sup>®</sup>. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA TRINZA<sup>®</sup>, consideration should be given to the long-acting nature of INVEGA TRINZA<sup>®</sup> as nursing infants may be at risk even from INVEGA TRINZA<sup>®</sup> administration long before breast-feeding.

### **7.1.3 Pediatrics**

**Pediatrics (< 18 years of age):** The safety and efficacy of INVEGA TRINZA<sup>®</sup> in children under the age of 18 years has not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

#### 7.1.4 Geriatrics

**Geriatrics (> 65 years of age):** 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 elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment who should be given reduced doses. Because elderly subjects may have diminished renal function, dose adjustments may be required according to their renal function status (see **WARNINGS AND PRECAUTIONS, Renal** above and **DOSAGE AND ADMINISTRATION**).

#### **Use in Geriatric Patients with Dementia**

##### Overall Mortality

In a meta-analysis of 13 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotic drugs had an increased risk of mortality compared to placebo.

##### *Concomitant Use with Furosemide*

INVEGA TRINZA® contains paliperidone, the active metabolite of risperidone. In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone.

INVEGA TRINZA® is not indicated for the treatment of elderly patients with dementia.

##### Cerebrovascular Adverse Events (CVAEs) in Elderly Patients With Dementia

In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo. INVEGA TRINZA® is not indicated for the treatment of elderly patients with dementia.

##### Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA TRINZA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

INVEGA TRINZA® is not indicated for the treatment of elderly patients with dementia.

## **8 ADVERSE REACTIONS**

### **8.1 Clinical Trial Adverse Reactions**

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described in this section are derived from a clinical trial database consisting of a total of 1191 subjects with schizophrenia who received at least one dose of INVEGA TRINZA<sup>®</sup> from three clinical trials in the evaluated dose range of 175 mg to 525 mg.

In a long-term relapse prevention trial, 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<sup>®</sup> during the open-label phase, and 160 subjects were subsequently randomized to receive at least one dose of INVEGA TRINZA<sup>®</sup> 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<sup>®</sup> group.

A second study was a long-term non-inferiority trial, in which 1429 subjects with schizophrenia received INVEGA SUSTENNA<sup>®</sup> (1-month paliperidone palmitate injectable product) during the open-label phase, from which 504 subjects were subsequently randomized to receive at least one dose of INVEGA TRINZA<sup>®</sup> and 512 subjects continued to receive the 1-month paliperidone palmitate injectable product during the double-blind phase. The mean (Standard Deviation [SD]) duration of exposure was 295 (89) days in the INVEGA TRINZA<sup>®</sup> group and 287 (96) days in the INVEGA SUSTENNA<sup>®</sup> group. Over half of the subjects in the INVEGA TRINZA<sup>®</sup> group (291 subjects; 58%) received at least 48 weeks (336 days) of exposure to INVEGA TRINZA<sup>®</sup>.

The third study was a Phase 1 study, in which 308 subjects with schizophrenia or schizoaffective disorder received a single injection of INVEGA TRINZA<sup>®</sup> concomitantly with other oral antipsychotics.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

A causal association with paliperidone palmitate often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse event 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.

The majority of all adverse events were mild to moderate in severity.

The most common adverse events (reported by  $\geq 5\%$  in the long-term relapse prevention study reported during the double-blind phase in any INVEGA TRINZA<sup>®</sup> dose group and at least twice that for placebo) were nasopharyngitis, weight increased, and headache.

The most common adverse events reported by  $\geq 5\%$  in the non-inferiority study in any INVEGA TRINZA<sup>®</sup> dose group during the double-blind phase were weight increased, anxiety, and nasopharyngitis.

The overall safety profile of INVEGA TRINZA<sup>®</sup> was similar to that seen with the 1-month paliperidone palmitate prolonged-release injectable suspension.

#### Discontinuations Due to Adverse Events

During the double-blind phase of the long-term relapse prevention study, no INVEGA TRINZA<sup>®</sup>-treated subject and one placebo-treated subject (0.3%) discontinued due to adverse events.

During the double-blind phase of the non-inferiority trial, 3.0% of INVEGA TRINZA®-treated subjects and 2.5% of subjects treated with the 1-month paliperidone palmitate product discontinued due to adverse events.

Commonly Observed Adverse Drug Events in the Relapse Prevention Study

Table 1.5 enumerates the adverse events reported in  $\geq 2\%$  of patients treated in either treatment group in the long term-relapse prevention study.

**Table 1.5: Treatment Emergent Adverse Events in at least 2% of Subjects in the Long-Term Relapse Prevention Study During the Open-Label and Double-Blind Phases**

Body System Or Organ Class Dictionary-Derived Term	Open-Label Phase	Double-Blind Phase	
	Paliperidone Palmitate <sup>a</sup> (N=506) %	Placebo (N=145) %	INVEGA TRINZA® (N=160) %
<b>Total no. subjects with adverse events</b>	65	58	62
<b>Psychiatric disorders</b>	29	32	19
Anxiety	9	11	8
Insomnia	10	12	7
Agitation	2	2	1
Schizophrenia	3	10	1
Psychotic Disorder	3	0	1
Suicidal ideation	3	2	0
<b>Infections and infestations</b>	10	11	18
Nasopharyngitis	3	1	6
Upper respiratory tract infection	2	2	4
Urinary tract infection	<1	1	3
Influenza	1	2	2
<b>Investigations</b>	14	17	17
Weight increased	10	3	9
Blood glucose increased	0	2	2
Weight decreased	2	8	1
<b>Nervous system disorders</b>	19	7	16
Headache	7	4	9
Akathisia	3	1	4
Somnolence	3	0	1
Tremor	2	0	1
<b>General disorders and administration site conditions</b>	17	4	7
Injection site pain	9	0	1
Fatigue	3	0	1
Injection site swelling	2	0	1
Irritability	1	2	1
<b>Respiratory, thoracic and mediastinal disorders</b>	3	3	4
Cough	1	2	3
<b>Metabolism and nutrition disorders</b>	1	6	3
Decreased appetite	0	2	1
Hyperglycemia	0	3	0

## Gastrointestinal disorders

Nausea 2 0 1

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Adverse events are coded using MedDRA version 16.0

<sup>a</sup> During the open-label phase, subjects received several doses of INVEGA SUSTENNA<sup>®</sup> followed by a single dose of INVEGA TRINZA<sup>®</sup> prior to randomization to either placebo or INVEGA TRINZA<sup>®</sup> in the subsequent double-blind phase.

Table 1.6 shows the incidences of adverse events reported during the non-inferiority study that occurred in at least 2% of subjects in either treatment group. Among treatment-emergent adverse events, there were no events that occurred more frequently in the one group than the other (i.e.,  $\geq 2\%$  difference between groups).

**Table 1.6: Treatment Emergent Adverse Events in at least 2% of Subjects in the Non-inferiority Study**

Body System Or Organ Class Dictionary-Derived Term	Open-Label Phase	Double-Blind Phase	
	INVEGA SUSTENNA <sup>®</sup> (N=1429) %	INVEGA TRINZA <sup>®</sup> (N=504) %	INVEGA SUSTENNA <sup>®</sup> (N=512) %
<b>Total no. subjects with adverse events</b>	59	68	66
<b>Investigations</b>	10	28	30
Weight increased	4	21	21
Weight decreased	1	3	3
<b>Psychiatric disorders</b>	23	18	17
Anxiety	6	5	5
Schizophrenia	3	4	3
Insomnia	7	3	5
Depression	1	2	1
<b>Infections and infestations</b>	12	16	16
Nasopharyngitis	5	7	6
<b>Nervous system disorders</b>	18	13	13
Akathisia	6	4	3
Headache	3	4	5
Somnolence	2	1	1
<b>General disorders and administration site conditions</b>	15	10	7
Injection site induration	3	3	1
Injection site pain	9	2	3
Fatigue	1	2	1
<b>Gastrointestinal disorders</b>	10	10	8
Diarrhea	1	2	1
<b>Metabolism and nutrition disorders</b>	3	4	4
Hyperglycemia	<1	1	2
<b>Vascular disorders</b>	2	4	2
Hypertension	1	2	1

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Adverse events are coded using MedDRA version 17.1

The following additional adverse events were reported in at least 2% of subjects in the Phase 1 study and reported in the INVEGA TRINZA<sup>®</sup> group at least as frequently in the placebo group in

the placebo-controlled Phase 3 study:

Eye disorders: conjunctivitis

Gastrointestinal disorders: abdominal pain, abdominal pain upper

Musculoskeletal and connective tissue disorders: Back pain, pain in extremity, oropharyngeal pain

### Demographics

An examination of population subgroups in the both the long-term relapse prevention and the non-inferiority studies did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects  $\geq 65$  years of age.

### Extrapyramidal Symptoms (EPS)

Data from the long-term relapse-prevention and non-inferiority trials 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 (Tables 1.7 and 1.9), and (5) incidence of spontaneous reports of EPS (Tables 1.8 and 1.10).

**Table 1.7. Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Long-Term Relapse Prevention Study**

Scale	Percentage of Subjects		
	Open-label Phase	Double-blind Phase	
	Paliperidone Palmitate <sup>a</sup>	Placebo	INVEGA TRINZA <sup>®</sup>
	(N=506) %	(N=145) %	(N=160) %
Parkinsonism <sup>b</sup>	6	3	6
Akathisia <sup>c</sup>	3	1	4
Dyskinesia <sup>d</sup>	1	3	3
Use of Anticholinergic Medications <sup>e</sup>	11	9	11

<sup>a</sup> During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate prolonged-release injectable suspension followed by a single dose of INVEGA TRINZA<sup>®</sup>

<sup>b</sup> 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)

<sup>c</sup> For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score  $\geq 2$  at any time

<sup>d</sup> For Dyskinesia, percent of subjects with a score  $\geq 3$  on any of the first 7 items or a score  $\geq 2$  on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at any time

<sup>e</sup> Percent of subjects who received anticholinergic medications to treat EPS

**Table 1.8. Extrapyramidal Symptoms (EPS)-Related Events – Long-Term Relapse Prevention Study**

EPS Group	Percentage of Subjects		
	Open-label Phase	Double-blind Phase	
	Paliperidone Palmitate <sup>a</sup> (N=506) %	Placebo (N=145) %	INVEGA TRINZA <sup>®</sup> (N=160) %
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

<sup>a</sup> During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate prolonged-release injectable suspension followed by a single dose of INVEGA TRINZA<sup>®</sup>. 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.

**Table 1.9 Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Non-inferiority Study**

Scale	Percentage of Subjects		
	Open-label Phase	Double-blind Phase	
	INVEGA SUSTENNA <sup>®a</sup> (N=1429) %	INVEGA SUSTENNA <sup>®</sup> (N=512) %	INVEGA TRINZA <sup>®</sup> (N=504) %
Parkinsonism <sup>b</sup>	4	3	3
Akathisia <sup>c</sup>	3	4	4
Dyskinesia <sup>d</sup>	1	1	1
Use of Anticholinergic Medications <sup>e</sup>	18	16	18

<sup>a</sup> During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate prolonged-release injectable suspension.

<sup>b</sup> 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)

<sup>c</sup> For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at any time

<sup>d</sup> 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

<sup>e</sup> Percent of subjects who received anticholinergic medications to treat EPS

**Table 1.10 Extrapyramidal Symptoms (EPS)-Related Events - Non-inferiority Study**

EPS Group	Percentage of Subjects		
	Open-label Phase	Double-blind Phase	
	INVEGA SUSTENNA <sup>®a</sup> (N=1429) %	INVEGA SUSTENNA <sup>®</sup> (N=512) %	INVEGA TRINZA <sup>®</sup> (N=504) %
Overall percentage of subjects with EPS-related adverse events	13	7	8
Parkinsonism	5	3	3
Hyperkinesia	7	3	4
Tremor	2	1	2
Dyskinesia	1	1	1
Dystonia	<1	1	0

<sup>a</sup> During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate prolonged-release injectable suspension.

Parkinsonism group includes: Cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonism, bradykinesia, hypertonia, parkinsonian gait, akinesia, masked facies, nuchal rigidity

Hyperkinesia group includes: Akathisia, restlessness, Restless legs syndrome

Dystonia group includes: Dystonia, muscle spasms, oculogyric crisis, torticollis

Dyskinesia includes dyskinesia, tardive dyskinesia, muscle twitching, myotonia, trismus

### Weight

In the long-term relapse prevention trial, abnormal increases of  $\geq 7\%$  in body weight from double-blind baseline to double-blind end point were reported for 15 subjects (10%) in the INVEGA TRINZA<sup>®</sup> group and 1 subject (1%) in the placebo group. Conversely, abnormal decreases in body weight ( $\geq 7\%$ ) from double-blind baseline to double-blind end point were reported for 2 subjects (1%) in the INVEGA TRINZA<sup>®</sup> 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 (indicating decrease) for the INVEGA TRINZA<sup>®</sup> and placebo groups, respectively.

In the non-inferiority study, 75 subjects (15%) in the INVEGA TRINZA<sup>®</sup> group and 81 subjects (16%) in the INVEGA SUSTENNA<sup>®</sup> group experienced an abnormal increase in body weight ( $\geq 7\%$ ) from double-blind baseline to double-blind end point. Conversely, abnormal decreases in body weight ( $\geq 7\%$ ) from double-blind baseline to double-blind end point were reported for 37 subjects (7%) in the INVEGA TRINZA<sup>®</sup> group and 21 subjects (4%) in the INVEGA SUSTENNA<sup>®</sup> group. The mean increases in body weight from double-blind baseline to double-blind end point were 1.10 kg and 1.46 kg for the INVEGA TRINZA<sup>®</sup> and INVEGA SUSTENNA<sup>®</sup> groups, respectively.

### Pain Assessment and Local Injection Site Reactions

**Investigator ratings of injection site.** Based on investigator ratings of the injection site, redness and swelling were observed in 2% or less of subjects in the INVEGA TRINZA<sup>®</sup> and placebo groups at each timepoint during the double-blind phase of the long-term relapse prevention study, and were mild in nature. There were no reports of induration in either group during the double-blind phase.

In the non-inferiority study, induration, redness, and swelling were observed in  $\leq 5\%$  of subjects in both groups and were mostly mild in nature. The level of induration, redness and swelling was generally similar between INVEGA TRINZA<sup>®</sup> and INVEGA SUSTENNA<sup>®</sup> groups over time.

**Subject ratings of injection site pain.** Subject evaluations of injection pain during the double-blind phase also were similar for placebo and INVEGA TRINZA<sup>®</sup> during the long-term relapse prevention study, and for INVEGA SUSTENNA<sup>®</sup> and INVEGA TRINZA<sup>®</sup> during the non-inferiority study.

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.

**Injection site adverse reactions.** During the double-blind phases of the long-term relapse prevention study and the non-inferiority study, none of the treatment-emergent injection site adverse events suggestive of local injection site reactions were severe in intensity, serious, or resulted in discontinuation.

Following the INVEGA TRINZA<sup>®</sup> injection in the single-dose Phase 1 study, all treatment-emergent injection site adverse events were mild or moderate in intensity and non-serious except for one subject that had a severe intensity related to pain in the deltoid region; no subjects discontinued due to INVEGA TRINZA<sup>®</sup> injection.

#### Constipation

Patients should be advised of the risk of severe constipation during INVEGA TRINZA<sup>®</sup> treatment, and they should tell their doctor if constipation occurs or worsens, since they may need medical intervention.

#### **Adverse Reactions Reported with INVEGA SUSTENNA<sup>®</sup>**

The following additional adverse events were reported in patients with schizophrenia who participated in clinical trials conducted with INVEGA SUSTENNA<sup>®</sup> (1-month paliperidone palmitate prolonged-release injectable suspension).

**Blood and lymphatic system disorders:** Eosinophil count increased, White blood cell decreased

**Cardiac disorders:** Atrioventricular block, Atrioventricular block first degree, Bundle branch block, Conduction disorder, Electrocardiogram abnormal, Palpitations, Tachycardia

**Ear and labyrinth disorders:** Ear pain, Tinnitus, Vertigo

**Endocrine disorders:** Glucose urine present, Hyperprolactinemia

**Eye disorders:** Eye movement disorder, Eye rolling, Eye swelling, Glaucoma, Lacrimation increased, Oculogyric crisis, Ocular hyperemia, Photophobia, Vision blurred

**Gastrointestinal disorders:** Cheilitis, Constipation, Dry mouth, Dysphagia, Fecal incontinence, Fecaloma, Swollen tongue, Toothache

**General disorders and administration site conditions:** Body temperature decreased, Body temperature increased, Chills, Drug withdrawal syndrome, Face edema, Gait abnormal, Induration, Injection site reaction (includes Injection site extravasation, Injection site inflammation, Injection site nodule), Pain, Thirst

**Hepatobiliary disorders:** Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased

**Immune system disorders:** Hypersensitivity

**Infections and infestations:** Acarodermatitis, Cellulitis, Ear infection, Eye infection, Pneumonia, Sinusitis, Subcutaneous abscess, Tonsillitis, Onychomycosis, Respiratory tract infection

**Investigations:** Alanine aminotransferase increased, Blood cholesterol increased

**Injury, poisoning, and procedural complications:** Skin laceration

**Metabolism and nutrition disorders:** Anorexia, Hyperinsulinemia, Polydipsia

**Musculoskeletal and connective tissue disorders:** Back pain, Joint stiffness, Joint swelling, Muscle rigidity, Muscle spasms, Muscle tightness, Muscle twitching, Muscular weakness, Myalgia, Nuchal rigidity, Pain in extremity, Posture abnormal, Rhabdomyolysis

**Nervous system disorders:** Bradykinesia, Balance disorder, Cerebral ischemia, Convulsion, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Disturbance in attention, Dizziness, Dizziness postural, Dysarthria, Head titubation, Hypertonia, Lethargy, Loss of consciousness, Neuroleptic malignant syndrome, Oromandibular dystonia, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia, Unresponsive to stimuli

**Psychiatric disorders:** Anorgasmia, Blunted effect, Confusional state, Hallucination auditory, Libido decreased, Nervousness, Nightmare, Restlessness, Tension

**Renal and urinary disorders:** Dysuria, Pollakiuria, Urinary incontinence

**Reproductive system and breast disorders:** Breast discomfort, Ejaculation disorder, Vaginal discharge

**Respiratory, thoracic and mediastinal disorders:** Dyspnea, Pharyngolaryngeal pain, Pulmonary congestion, Respiratory tract congestion, Wheezing

**Skin and subcutaneous tissue disorders:** Acne, Drug eruption, Dry skin, Erythema, Hyperkeratosis, Pruritus generalized, Rash, Seborrheic dermatitis, Skin discoloration, Urticaria

**Vascular disorders:** Flushing, Orthostatic hypotension

#### **Adverse Reactions Reported with Oral Paliperidone**

The following is a list of additional adverse events that have been reported with oral paliperidone:

**Cardiac disorders:** Bundle branch block left, Sinus arrhythmia

**Eye disorders:** Dry eye

**Gastrointestinal disorders:** Dyspepsia, Flatulence, Intestinal obstruction, Small intestinal obstruction

**General disorders and administration site conditions:** Edema, Pyrexia

**Immune system disorders:** Anaphylactic reaction

**Infections and infestations:** Rhinitis, Viral infection

**Investigations:** Blood creatine phosphokinase increased, Blood pressure increased, Electrocardiogram QT corrected interval prolonged, Electrocardiogram T wave abnormal, Heart rate increased, Insulin C-peptide increased

**Musculoskeletal and connective tissue disorders:** Arthralgia, Neck pain, Shoulder pain, Torticollis, Trismus

**Nervous system disorders:** Cogwheel rigidity, Grand mal convulsion, Parkinsonian gait, Transient ischemic attack

**Psychiatric disorders:** Aggression, Sleep disorder

**Reproductive system and breast disorders:** Breast engorgement, Breast enlargement, Breast tenderness, Retrograde ejaculation

**Respiratory, thoracic and mediastinal disorders:** Dysphonia, Hyperventilation, Pneumonia aspiration

**Skin and subcutaneous tissue disorders:** Rash papular

**Vascular disorders:** Ischemia

### **Adverse Reactions Reported with Risperidone**

Paliperidone is the active metabolite of risperidone. Therefore, the adverse reaction profiles of both the oral and injectable formulations of paliperidone are relevant to one another and, also, to risperidone. In addition to the above adverse reactions, the following adverse reactions have been noted with the use of risperidone products and can be expected to occur with both the oral and injectable formulations of paliperidone:

**Respiratory, thoracic and mediastinal disorders:** Rales

**General disorders and administration site conditions** (observed with the injectable formulation of risperidone): Injection site cyst, Injection site necrosis, Injection site ulcer

See also **ADVERSE REACTIONS, Post-Market Adverse Reactions, Safety Information Reported with Risperidone.**

## **8.2 Less Common Clinical Trial Adverse Reactions**

The following additional adverse events occurred in < 2% of INVEGA TRINZA<sup>®</sup>-treated subjects in the three clinical trials, and occurred in the INVEGA TRINZA<sup>®</sup> group at least as frequently in the placebo group in the placebo-controlled Phase 3 study, and reported in at least 3 subjects

with INVEGA TRINZA® during the three clinical trials. All events assessed as possible drug-related adverse events are included. In addition, medically/clinically meaningful events, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included.

**Blood and lymphatic system disorders:** Anemia

**Cardiac disorders:** Bradycardia, Postural orthostatic tachycardia syndrome, Sinus bradycardia, Sinus tachycardia, Ventricular extrasystoles

**Gastrointestinal disorders:** Abdominal discomfort, Dental caries, Gastritis, Salivary hypersecretion, Vomiting

**General disorders and administration site conditions:** Asthenia, Chest discomfort, Chest pain, Injection site erythema, Injection site mass, Malaise, Edema peripheral

**Hepatobiliary disorders:** Hepatic function abnormal, Hepatic steatosis

**Infections and infestations:** Bronchitis, Cystitis, Gastroenteritis, Gingivitis, Herpes simplex, Pharyngitis, Pneumonia, Tooth abscess, Viral infection

**Injury, poisoning and procedural complications:** Contusion, Excoriation, Fall

**Investigations:** Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood lactate dehydrogenase increased, Blood pressure diastolic increased, Blood pressure systolic increased, Blood triglycerides increased, Electrocardiogram QT prolonged, Neutrophil count increased, White blood cell count increased

**Metabolism and nutrition disorders:** Diabetes mellitus, Gout, Hyperlipidemia, Increased appetite, Type 2 diabetes mellitus

**Musculoskeletal and connective tissue disorders:** Muscle rigidity, Muscle spasms, Muscle tightness, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Osteoarthritis, Tendonitis

**Nervous system disorders:** Cogwheel rigidity, Drooling, Dystonia, Hypoesthesia, Migraine, Parkinsonism, Poor quality sleep, Sciatica, Sedation

**Psychiatric disorders:** Aggression, Delusion, Depressed mood, Irritability, Libido decreased, Paranoia, Psychiatric symptom, Sleep disorder, Suicide attempt

**Reproductive system and breast disorders:** Amenorrhea, Breast pain, Erectile dysfunction, Galactorrhea, Gynecomastia, Menstrual disorder, Menstruation irregular, Sexual dysfunction

**Respiratory, thoracic and mediastinal disorders:** Epistaxis, Nasal congestion, Rhinitis allergic

**Skin and subcutaneous tissue disorders:** Dandruff, Dermatitis contact, Eczema, Pruritus, Rash

**Vascular disorders,** Hematoma, Hypotension, Orthostatic hypotension

### 8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal values in individual subjects and adverse event reports related to abnormal findings, the effects of INVEGA TRINZA® on the results of chemistry and hematology laboratory tests did not show clinically relevant differences from the placebo or INVEGA SUSTENNA® group in either the relapse prevention study or the non-inferiority study.

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. See **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**.

### 8.4 Post-Market Adverse Reactions

Adverse events first identified as adverse drug reactions (ADR) during post-marketing experience with paliperidone are included in [Table 1.11](#). In [Table 1.11](#), ADRs are presented by frequency category based on spontaneous reporting rates 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 1.11. Adverse Reactions Identified During Post-Marketing Experience with Paliperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Paliperidone**

<b>Blood and lymphatic system disorders</b> <i>Very rare</i>	Thrombocytopenia
<b>Cardiac disorders</b> <i>Very rare</i>	Atrial fibrillation
<b>Endocrine disorders</b> <i>Not known</i>	Inappropriate antidiuretic hormone secretion
<b>Eye disorders</b> <i>Not known</i>	Floppy iris syndrome (intraoperative)
<b>Gastrointestinal disorders</b> <i>Very rare</i> <i>Very rare</i>	Pancreatitis Ileus
<b>General disorders and administration site conditions</b> <i>Very rare</i>  <i>Not known</i>	Hypothermia, Injection site abscess, Injection site cellulitis, Injection site hematoma Injection site cyst, Injection site necrosis, Injection site ulcer
<b>Hepatobiliary disorders</b> <i>Not known</i>	Jaundice
<b>Immune System Disorders</b> <i>Rare</i>	Hypersensitivity (including very rare events of angioedema, anaphylaxis, and anaphylactic shock)
<b>Metabolism and nutrition disorders</b> <i>Very rare</i> <i>Not known</i>	Diabetic ketoacidosis, Hypoglycemia Water intoxication
<b>Nervous system disorders</b> <i>Very rare</i>	Dysgeusia
<b>Pregnancy, puerperium and perinatal conditions</b> <i>Very rare</i>	Drug withdrawal syndrome neonatal
<b>Psychiatric disorders</b> <i>Very rare</i>	Catatonia, Mania
<b>Renal and urinary disorders</b> <i>Very rare</i>	Urinary retention
<b>Reproductive system and breast disorders</b> <i>Very rare</i>	Priapism
<b>Respiratory, thoracic and mediastinal disorders</b> <i>Very rare</i>	Sleep apnea syndrome

<b>Skin and subcutaneous tissue disorders</b>	
<i>Rare</i>	Angioedema
<i>Very rare</i>	Alopecia
<i>Not known</i>	Stevens-Johnson syndrome/Toxic epidermal necrolysis
<b>Vascular disorder</b>	
<i>Very rare</i>	Pulmonary embolism, Venous thrombosis

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including paliperidone. Granulocytopenia and agranulocytosis have also been reported (see **WARNINGS AND PRECAUTIONS, Hematologic**). Agranulocytosis has been reported very rarely during post-marketing surveillance.

Atypical antipsychotic drugs, such as paliperidone, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of, or that are at risk of, sleep apnea, INVEGA TRINZA<sup>®</sup> should be prescribed with caution.

Risks of somnambulism (sleep walking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics including INVEGA TRINZA<sup>®</sup>.

### Hypersensitivity

There have been very rare spontaneous reports of severe hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock) in some patients after injection with 1-month injectable paliperidone. Symptoms of anaphylaxis include skin rash, hives, peripheral edema, swollen eye, tongue and face, hyperhidrosis, dyspnea, and hypotension. It is unknown as to how many of these patients previously tolerated oral risperidone or paliperidone. However, anaphylactic-type reactions have occurred after injection with injectable paliperidone in patients who have previously tolerated oral risperidone or oral paliperidone (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity** and **DOSAGE AND ADMINISTRATION**).

### Safety Information Reported with Risperidone

Paliperidone is the major active metabolite of risperidone. The release profile and pharmacokinetic characteristics of INVEGA TRINZA<sup>®</sup> are considerably different from those observed with oral immediate-release risperidone formulations, as well as those from risperidone long-acting injection (see **ACTION AND CLINICAL PHARMACOLOGY**); however, the receptor binding profile of paliperidone is very similar to that of the parent compound. Safety information reported with oral risperidone and risperidone long-acting injection in clinical trials and post-marketing experience that may be relevant to INVEGA TRINZA<sup>®</sup> can be found in local labelling for risperidone, as well as **ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Adverse Reactions Reported with Risperidone**.

## 9 DRUG INTERACTIONS

### 9.1 Drug-Drug Interactions

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

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

Paliperidone at relevant clinical concentrations had no or only marginal inhibitory effect on the major CYP450s including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Paliperidone was shown to be a P-glycoprotein substrate but the influence of any drug-drug interaction with P-glycoprotein at the level of the blood-brain barrier is likely to be modest.

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

#### Potential for INVEGA TRINZA<sup>®</sup> 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 of this with respect to P-gp mediated transport of other drugs is unknown.

Given the primary CNS effects of paliperidone (see **ADVERSE REACTIONS**), INVEGA TRINZA<sup>®</sup> 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, Cardiovascular**), an additive effect may be observed when INVEGA TRINZA<sup>®</sup> 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<sup>®</sup> and lithium is unlikely.

#### Potential for Other Drugs to Affect INVEGA TRINZA<sup>®</sup>

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 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

A population pharmacokinetic analysis from a study using oral paliperidone extended-release tablets to evaluate the influence of predicted CYP2D6 phenotype on exposure indicated that no adjustment in the paliperidone dose on the basis of predicted phenotype is warranted.

In an interaction study in healthy subjects in which oral paliperidone extended-release tablets once daily was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

#### *Carbamazepine and other potent CYP3A4 inducers*

Co-administration of oral paliperidone extended-release tablets 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. As is typical of CYP3A4 inducers, carbamazepine is also a P-glycoprotein (P-gp) inducer. Although *in vitro* studies have shown that paliperidone is a substrate of both P-gp and CYP3A4, the relative contributions of P-gp and CYP3A4 to changes in the pharmacokinetic parameters are unclear.

On initiation of carbamazepine, the dose of INVEGA TRINZA<sup>®</sup> should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA TRINZA<sup>®</sup> should be re-evaluated and decreased if necessary. Consideration should be given to the long-acting nature of INVEGA TRINZA<sup>®</sup>. Until more data are available, these recommendations should be extended to other potent CYP3A4 inducers and/or P-glycoprotein up-regulators.

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 oral paliperidone extended-release tablets 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<sup>®</sup> prolonged-release injectable suspension. This interaction has not been studied with INVEGA TRINZA<sup>®</sup>.

Pharmacokinetic interaction between lithium and INVEGA TRINZA<sup>®</sup> is unlikely.

#### Concomitant Use with Furosemide

See **WARNINGS AND PRECAUTIONS, Special Populations** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide plus risperidone.

#### Concomitant Use of INVEGA TRINZA<sup>®</sup> with Risperidone or Oral Paliperidone

There are no systematically collected safety data to specifically address concomitant use of INVEGA TRINZA<sup>®</sup> with risperidone, oral paliperidone, or other antipsychotics. Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA TRINZA<sup>®</sup> is co-administered with risperidone or oral paliperidone.

#### Concomitant use of INVEGA TRINZA<sup>®</sup> 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, Neurologic).

### 9.2 Drug-Food Interactions

Interactions with food have not been established.

### 9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

### 9.5 Drug-Lifestyle Interactions

#### Smoking

No dosage adjustment is recommended based on smoking status. Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking, a CYP1A2 inducer, should, therefore, not have an effect on the pharmacokinetics of paliperidone.

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

## 10 ACTION AND CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone (see **Pharmacokinetics**). The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D<sub>2</sub>) and serotonin Type 2 (5HT<sub>2A</sub>) receptor antagonism. Antagonism at receptors other than D<sub>2</sub> and 5HT<sub>2A</sub> may explain some of the other effects of paliperidone.

### 10.2 Pharmacodynamics

Paliperidone is a centrally active dopamine D<sub>2</sub> antagonist with predominant serotonergic 5-HT<sub>2A</sub> antagonistic activity. Paliperidone is also active as an antagonist at  $\alpha_1$  and  $\alpha_2$  adrenergic receptors and H<sub>1</sub> histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar.

## Preclinical Pharmacodynamics

I.m. injected paliperidone palmitate is converted to paliperidone, with minimal systemic exposure to paliperidone palmitate in animals as well as in humans. Systemic effects following i.m. administration of paliperidone palmitate are mediated through paliperidone.

Paliperidone is the major active metabolite of risperidone and is pharmacologically very similar to the parent compound. In a series of standard *in vivo* pharmacology tests, paliperidone, its enantiomers and risperidone showed similar effects at closely related doses. *In vitro*, paliperidone and risperidone (1) shared nearly the same binding affinity for 5-HT<sub>2A</sub>, D<sub>2</sub>, α<sub>1</sub>, and α<sub>2</sub> receptors, (2) reversed dopamine-induced suppression of PRL release from anterior pituitary cells, and (3) reduced 5-HT-induced human platelet aggregation.

Paliperidone displays approximately 15 times higher affinity towards 5-HT<sub>2A</sub> receptors when compared with clozapine and approximately 120 times higher affinity compared with haloperidol. The affinity to D<sub>2</sub> receptors was about 20 times higher compared to clozapine and only 2 to 3 times lower compared with haloperidol. Paliperidone differed from clozapine and haloperidol by the remarkably shallow slope of its D<sub>2</sub> receptor dose occupancy curve.

Similar to risperidone, paliperidone does not interact with cholinergic muscarinic receptors.

## Cardiovascular Pharmacology

Paliperidone was devoid of major effects on several electrophysiological parameters in isolated cells and cardiac tissues *in vitro*, at concentrations matching and slightly exceeding therapeutically achieved plasma levels in man. Paliperidone and risperidone produced similar effects on cardio-hemodynamic parameters. Following administration of paliperidone in awake rats (i.v., s.c.) and dogs (p.o.), and in anesthetized dogs, guinea pigs and rabbits (i.v.) at higher tested dose levels, paliperidone produced cardiovascular effects consisting mainly of increased heart rate, decreased blood pressure, and changes in QT- and PQ-intervals. However, the results from these *in vivo* studies indicated an absence of cardiac electrophysiological effects, including QTc changes, with paliperidone at doses yielding plasma concentrations slightly in excess of the therapeutic ones in humans.

## 10.3 Pharmacokinetics

After i.m. administration of paliperidone palmitate, the exposure to the unhydrolyzed prodrug is very low, whereas a prolonged release of paliperidone, with a duration of at least one month, is observed both in humans and all animal species tested. Nonclinical animal models were also used to simulate the consequences of accidental partial intravenous administration or intralipomatous injection. Following i.v. administration, there was no instantaneous release of the entire dose, but a prolonged release of paliperidone. An injection in the subcutaneous fat layer produced a similar profile, but with lower paliperidone plasma concentrations to that observed after i.m. dosing.

After i.m. injection, paliperidone palmitate forms an agglomerate of nanoparticles. There is a dissociation of the product, most likely by hydrolysis, in the muscle cells surrounding this depot. After hydrolysis paliperidone enters the systemic circulation, whereas the palmitate moiety is probably oxidized in the muscle cells.

Paliperidone exhibited species-dependent stereoselectivity in disposition and plasma protein binding. (-)-Paliperidone was more abundant than (+)-paliperidone in plasma of laboratory animals but not in humans. In mice and rats, (+)-paliperidone showed a higher free fraction, while in dogs and humans, the free fraction of (-)-paliperidone was higher than that of (+)-paliperidone.

Paliperidone was shown to distribute to specific brain regions with high density of 5-HT<sub>2A</sub>- and D<sub>2</sub>-receptors and to achieve exposure that was in excess of that in plasma. There was no undue tissue retention of paliperidone except in melanin-containing tissues of pigmented rats. The melanin binding of paliperidone was shown to be reversible.

The major biotransformation routes of paliperidone were similar in laboratory animals and in humans. All metabolites identified in the human mass balance study were also observed in at least one laboratory animal species. All the metabolites that were identified following paliperidone administration in humans were also observed following risperidone administration in humans.

### **Absorption and Distribution**

Due to its extremely low water solubility, the three-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<sup>®</sup>, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T<sub>max</sub> of 24-34 days. After single-dose 450 mg administration of INVEGA TRINZA<sup>®</sup> in the deltoid muscle, the median C<sub>max</sub> in adult patients was 40 ng/mL and the median concentration at Day 84 (3 months) was approximately 15 ng/mL. The median terminal half-life appeared to be approximately 72 days. After 36 weeks of INVEGA TRINZA<sup>®</sup> dosing, the geometric mean peak:trough ratio appeared to be approximately 1.9.

The total exposure of paliperidone following INVEGA TRINZA<sup>®</sup> administration was dose-proportional over a 175-525 mg dose range. The plasma protein binding of racemic paliperidone is 74%.

Following administration of INVEGA TRINZA<sup>®</sup>, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.7-1.8.

### ***Long-acting 3-month paliperidone palmitate injection versus other paliperidone formulations***

INVEGA TRINZA<sup>®</sup> is designed to deliver sustained therapeutic paliperidone concentrations over a 3-month period, while 1-month paliperidone palmitate injection INVEGA SUSTENNA<sup>®</sup> is designed to deliver paliperidone over a one month period. INVEGA TRINZA<sup>®</sup>, when administered in the deltoid muscle at doses that are 3.5-fold higher than the corresponding dose of INVEGA SUSTENNA<sup>®</sup>, results in paliperidone total systemic exposures similar to those obtained with corresponding three monthly doses of INVEGA SUSTENNA<sup>®</sup> and corresponding once daily doses of paliperidone extended-release tablets. However, administration of INVEGA TRINZA<sup>®</sup> in the gluteal muscle may result in lower exposure than INVEGA TRINZA<sup>®</sup> administered in the deltoid muscle, and lower exposure than the corresponding three monthly doses of INVEGA SUSTENNA<sup>®</sup>, especially in the third month.

## Metabolism and Excretion

In a study with oral immediate-release <sup>14</sup>C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release <sup>14</sup>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.

The median apparent half-life of paliperidone following INVEGA TRINZA<sup>®</sup> administration over the dose range of 175-525 mg ranged from 52-74 days following deltoid injections and 69-82 days following gluteal injections.

## Special Populations and Conditions

**Pediatrics:** No data available.

**Geriatrics:** 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 Insufficiency** below and **DOSAGE AND ADMINISTRATION**).

**Sex:** No clinically significant differences were observed between men and women.

**Race:** Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone.

**Hepatic Insufficiency:** Paliperidone is not extensively metabolized in the liver. Although INVEGA TRINZA<sup>®</sup> 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 unbound paliperidone were similar to those of healthy subjects. No dose adjustment is required in patients with mild to moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment.

**Renal Insufficiency:** INVEGA TRINZA<sup>®</sup> has not been systematically studied in patients with renal impairment.

The disposition of a single oral dose 3 mg of paliperidone 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<sub>inf</sub>) of 1.5-, 2.6-, and 4.8-fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 mL/min). Paliperidone has not been studied in subjects with creatinine clearance < 10 mL/min.

Based on a limited number of observations with INVEGA TRINZA<sup>®</sup> in subjects with mild renal impairment, 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<sup>®</sup> using the corresponding 3.5-multiple dose for mild renal impaired subjects. No additional dose reduction upon starting INVEGA TRINZA<sup>®</sup> is necessary (see **DOSAGE AND ADMINISTRATION**).

**Smoking Status:** No dosage adjustment is recommended based on 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 statistically significant differences between smokers and non-smokers in an analysis performed with oral paliperidone extended-release tablets.

**Body Mass Index (BMI) / Body Weight:** No dose adjustment is needed based on BMI or body weight.

## 11 STORAGE, STABILITY AND DISPOSAL

INVEGA TRINZA<sup>®</sup> should be stored at room temperature (15–30°C).

Keep out of the sight and reach of children.

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

## 12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

INVEGA TRINZA® is an atypical antipsychotic medication containing a racemic mixture of the active ingredient, paliperidone palmitate. After injection, paliperidone palmitate is hydrolyzed to paliperidone (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Paliperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives.

Proper name	Paliperidone palmitate (prodrug)	Paliperidone (active moiety)
Chemical name	(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate	(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
Molecular formula	C <sub>39</sub> H <sub>57</sub> FN <sub>4</sub> O <sub>4</sub>	C <sub>23</sub> H <sub>27</sub> FN <sub>4</sub> O <sub>3</sub>
Molecular mass	664.8	426.49
Structural formula		
Physical Appearance	Paliperidone palmitate is a white to almost white powder.	Paliperidone is a white to yellow powder.
Dissociation Constants	pKa <sub>1</sub> = 8.3 (piperidone moiety) pKa <sub>2</sub> < 3 (pyrimidine moiety)	pKa <sub>1</sub> = 8.2 (piperidone moiety) pKa <sub>2</sub> = 2.6 (pyrimidine moiety)
Partition Coefficients	log p > 5	log p = 2.39
Solubility	Paliperidone palmitate is insoluble in 0.1N HCl, 0.1N NaOH, and water; very slightly soluble in ethanol, methanol, and 2-propanol; freely soluble in dichloromethane.	Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; practically insoluble in water, 0.1N NaOH, and hexane; and slightly soluble in N,N-dimethylformamide.

## 14 CLINICAL TRIALS

The efficacy of INVEGA TRINZA® in achieving and maintaining symptomatic control and preventing relapse in adult subjects who met the DSM-IV-TR criteria for schizophrenia and who had been adequately treated for at least 4 months with the 1-month paliperidone palmitate injectable product was established in two randomized, double-blind trials.

The first trial was a long-term double-blind, placebo-controlled, randomized withdrawal study to evaluate the efficacy of INVEGA TRINZA® on time to relapse in patients who had first been adequately treated with INVEGA SUSTENNA® for at least 4 months. Subjects 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 INVEGA SUSTENNA®, the paliperidone palmitate 1-month initiation regimen (deltoid injections of 150 mg and 100 mg one week apart), while those subjects switching from LAI medication were treated with INVEGA SUSTENNA® in place of the next scheduled injection. Specifically:

- For subjects entering the study who were already being treated with INVEGA SUSTENNA®, their dosing remained unchanged. Subjects who were currently receiving the 25 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 50 mg, 75 mg, or 100 mg, respectively, of INVEGA SUSTENNA® administered in the deltoid muscle.
- Subjects entering the study who were being treated with any other LAI product were switched to 150 mg of INVEGA SUSTENNA® administered in the deltoid muscle.

This study consisted of the following three treatment periods:

- A 17-week flexible-dose open-label period with INVEGA SUSTENNA® (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). At the end of the open-label treatment, the majority (90%) of subjects were receiving INVEGA SUSTENNA® 100 mg or 150 mg.

- A variable length double-blind treatment period. In this period, 305 stabilized subjects were randomized 1:1 to continue treatment with INVEGA TRINZA<sup>®</sup> or placebo until relapse, early withdrawal, or the end of study. Subjects were randomized to the same dose of INVEGA TRINZA<sup>®</sup> they received during the open-label phase (i.e., 175 mg, 263 mg, 350 mg, or 525 mg) or to placebo administered every 12 weeks. Thus, for subjects randomized to INVEGA TRINZA<sup>®</sup> in the double-blind phase, the majority of patients were given either the 350 mg or 525 mg doses.

The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization,  $\geq 25\%$  increase (if the baseline score was  $> 40$ ) or a 10-point increase (if the baseline score was  $\leq 40$ ) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of  $\geq 5$  (if the maximum baseline score was  $\leq 3$ ) or  $\geq 6$  (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). Secondary efficacy end points included the change from baseline to end point during the double-blind phase in PANSS (total, subscales scores, and Marder Factor scores) and CGI-S.

A group sequential design was utilized in this study with one interim analysis for efficacy to be performed by an independent data monitoring committee. This design allowed for recommendation of early termination of the study if significant evidence of efficacy was obtained based on the interim efficacy analysis results.

The pre-planned interim analysis showed a statistically significantly longer time to relapse in subjects treated with INVEGA TRINZA<sup>®</sup> 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<sup>®</sup> group.

Based on the interim analysis, twenty-three percent 23% (n=31) of the 135 subjects in the placebo group and 7.4% (n=11) of 148 subjects in the INVEGA TRINZA<sup>®</sup> group experienced a relapse event. There was a significant difference (p-value  $<0.001$ ) between the treatment groups in favour of INVEGA TRINZA<sup>®</sup>. The risk (hazard) of relapse was higher in the placebo group compared to INVEGA TRINZA<sup>®</sup>, (HR= 3.45, 95% CI: 1.73, 6.88) indicating a 71% decrease in relapse risk with INVEGA TRINZA<sup>®</sup>. A Kaplan-Meier plot of time to relapse by treatment group is shown in

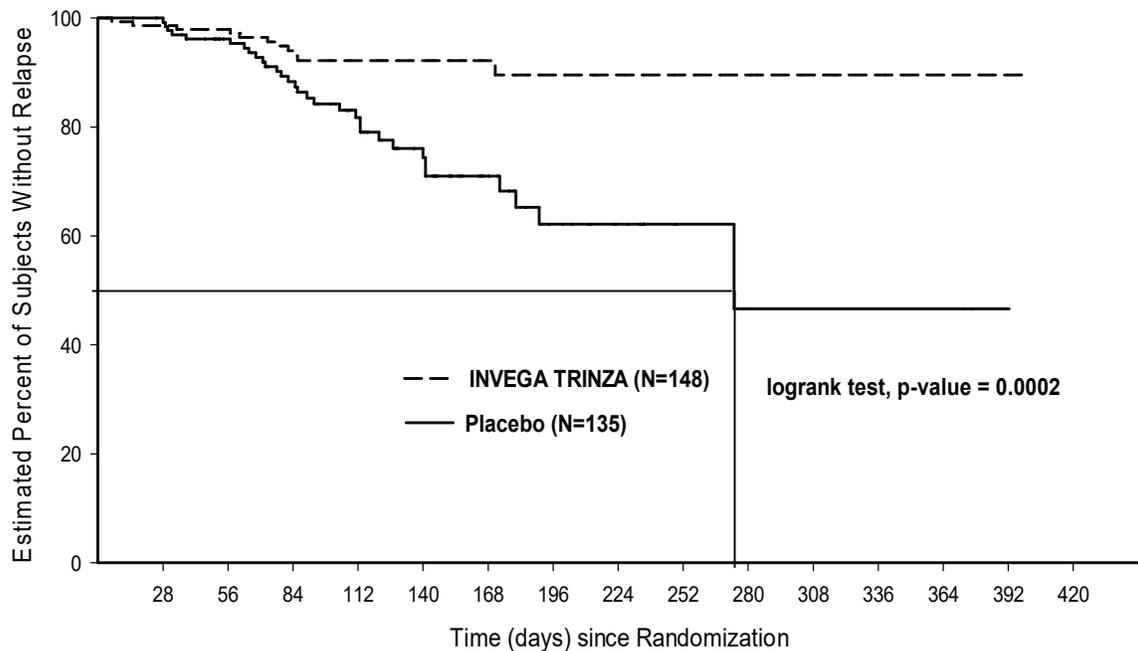
[Figure 2.1](#). The time to relapse of the placebo group (median 274 days) was significantly shorter than for the INVEGA TRINZA<sup>®</sup> group (the median could not be estimated due to the low percentage of subjects with relapse [7.4%]).

The final analysis of the relapse data confirmed the findings of the interim analysis. For the final analysis, 29.0% (n=42) of the 145 subjects in the placebo group, compared with 8.8% (n=14) of the 160 subjects in the INVEGA TRINZA<sup>®</sup> group, experienced a relapse event, and there was a significant difference in the time to relapse favoring INVEGA TRINZA<sup>®</sup> (p $<0.001$  based on log rank test). The median time to the first relapse event, based on Kaplan-Meier estimation, was 395 days for the placebo group and was not estimable in the INVEGA TRINZA<sup>®</sup> group.

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

Secondary endpoints evaluating psychiatric symptoms severity during double-blind treatment, were consistent with the maintained treatment response that was observed with INVEGA TRINZA<sup>®</sup> compared to placebo.

**Figure 2.1. Kaplan-Meier Plot of Time to Relapse<sup>a</sup> – Interim Analysis**



<sup>a</sup> 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<sup>®</sup> was discontinued. The median time to relapse in the INVEGA TRINZA<sup>®</sup> group could not be estimated due to low percentage (7.4%) of subjects with relapse.

The second study was a double-blind, randomized, multicenter, non-inferiority trial comparing INVEGA TRINZA<sup>®</sup> and INVEGA SUSTENNA<sup>®</sup>, the one month formulation of paliperidone palmitate (PP1M). In this study, 1429 acutely ill patients (baseline mean PANSS total score 85.7) were enrolled into the open-label phase and treated with INVEGA SUSTENNA<sup>®</sup> 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 patients that met randomization criteria at weeks 14 and 17 (PANSS total score of < 70, scores of ≤4 for PANSS items P1, P2, P3, P6, P7, G8, and G14, and an improvement in CGI-S of ≥ 1), 1016 patients were randomized in a 1:1 ratio to continue on monthly injections of INVEGA SUSTENNA<sup>®</sup> or to switch to INVEGA TRINZA<sup>®</sup> with a 3.5 multiplier of the week 9 and 13 dose of the INVEGA SUSTENNA<sup>®</sup> dose. Patients received INVEGA TRINZA<sup>®</sup> every 3 months and received placebo injectable medication for the other months to maintain the blind.

During the open-label treatment, after the first two loading doses, most patients were stabilized on 100 mg (40%) or 150 mg (49%) at the end of the open-label phase, with only 3% stabilized on a 50 mg dose. During the double blind, dosing continued in the same manner. For subjects

randomized to INVEGA TRINZA<sup>®</sup> during the double-blind phase, the majority of patients were thus given either the 350 mg, or 525 mg dosages.

The primary efficacy endpoint of the study was the percentage of patients who had not relapsed at the end of the 48-week double-blind phase based on the Kaplan-Meier 48-week estimate. The objective of this study was to demonstrate, in patients first stabilized on INVEGA SUSTENNA<sup>®</sup>, that INVEGA TRINZA<sup>®</sup> was not less effective than INVEGA SUSTENNA<sup>®</sup> as measured by the percentage of patients who had not relapsed after 48 weeks based on the Kaplan-Meier cumulative estimate of survival. The pre-defined relapse criteria were the same as that described above for the long-term relapse prevention study.

The primary analysis for efficacy was performed on the per protocol analysis set. Thirty seven (8.1%) subjects in the INVEGA TRINZA<sup>®</sup> group and 45 (9.2%) subjects in the INVEGA SUSTENNA<sup>®</sup> group experienced a relapse event during the double-blind phase. The mean (SD) duration of exposure during the double-blind phase was 295 (88) days in the INVEGA TRINZA<sup>®</sup> group and 287 (96) days in the INVEGA SUSTENNA<sup>®</sup> group. The estimated difference (95% CI) between the treatment groups (INVEGA TRINZA<sup>®</sup> - INVEGA SUSTENNA<sup>®</sup>) in percentages of subjects who remained relapse free (INVEGA TRINZA<sup>®</sup>: 91.2%; INVEGA SUSTENNA<sup>®</sup>: 90.0%) was 1.2% (-2.7%, 5.1%). The lower bound of the 95% confidence interval was larger than the pre-specified non-inferiority margin of -15%, demonstrating that INVEGA TRINZA<sup>®</sup> was non-inferior to INVEGA SUSTENNA<sup>®</sup> (Figure 2.2). Based upon a Cox Proportional Hazards Model, the ratio (95% CI) of the instantaneous risk (hazard) of relapse for a subject switching from INVEGA SUSTENNA<sup>®</sup> to INVEGA TRINZA<sup>®</sup> during the double-blind phase versus the risk for a subject remaining on INVEGA SUSTENNA<sup>®</sup> in the double-blind phase was 0.87 (95% CI: 0.56, 1.34). The summary of analysis of time to relapse event is provided in Table 2.1 and the Kaplan-Meier plot is provided in Figure 2.2.

Neither the 25% quantile of time to relapse (the estimated time point at which 25% of subjects have experienced a relapse event) nor the median time to relapse (median survival time refers to the time at which the cumulative survival function equals 0.5 [or 50%]) was estimable for either the INVEGA TRINZA<sup>®</sup> or INVEGA SUSTENNA<sup>®</sup> groups.

**Table 2.1: Time to Relapse During the Double-blind Phase and Number (%) of Subjects that Remained Relapse Free in the Non-inferiority Study: Per-protocol Analysis Set**

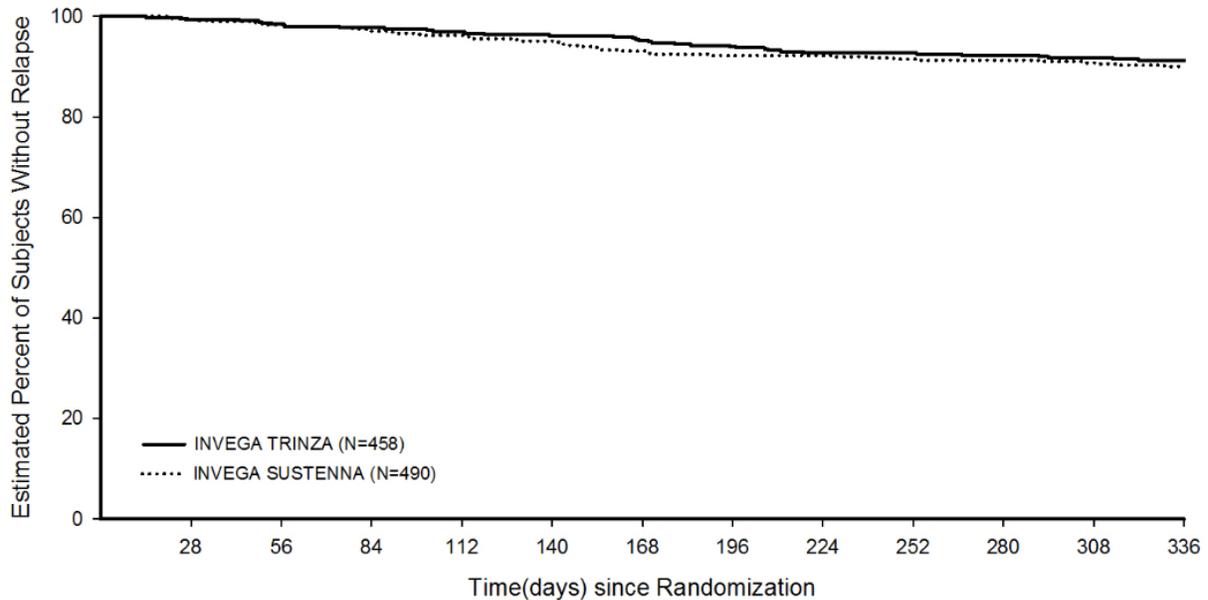
	INVEGA TRINZA <sup>®</sup>	INVEGA SUSTENNA <sup>®</sup>	Total
Number of Assessed	458	490	948
Number of Censored* (%)	421 (91.9)	445 (90.8)	866 (91.4)
Number of Relapsed (%)	37 (8.1)	45 (9.2)	82 (8.6)
<b>Relapse Free (a)</b>			
Week 48 (DB) (day 337 (DB))			
Percentage Relapse Free	91.2	90.0	
Difference (INVEGA TRINZA <sup>®</sup> – INVEGA SUSTENNA <sup>®</sup> )		1.2	
95% CI		(-2.7; 5.1)	

(a) Based on Kaplan-Meier product limit estimates.

Note: 25%, 50%, and 75% quantiles of time to relapse are not estimable.

\*: Censored include subjects who completed the double-blind phase without relapse and subjects who withdrew early during the double-blind phase.

**Figure 2.2. Kaplan-Meier Plot of Time to Relapse During the Double-blind Phase Comparing INVEGA TRINZA® and INVEGA SUSTENNA®: Per-protocol Analysis Set**



The secondary efficacy results assessing PANSS, CGI-S and PSP scores using the mITT (DB) analysis set, supported the demonstration of primary efficacy for non-inferiority of INVEGA TRINZA® to INVEGA SUSTENNA®.

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

## 15 MICROBIOLOGY

Not applicable.

## 16 NON-CLINICAL TOXICOLOGY

Paliperidone palmitate and paliperidone were tested in an extensive series of toxicity studies. At equal dose levels, the toxicity profile of oral paliperidone was similar to oral risperidone in comparative repeat-dose toxicity studies in mice, rats and dogs. The systemic toxicity profile of paliperidone palmitate and paliperidone mainly consisted of findings related to exaggerated pharmacodynamic effects of CNS- and PRL-mediated actions.

In the repeat-dose toxicity studies with intramuscularly injected paliperidone palmitate, NOAELs could not be established due to injection site tolerability issues which in the animal studies occurred at all dose levels. This poor injection site tolerability does not translate to humans.

In the repeat-dose toxicity studies with oral paliperidone, NOELs could not be established because signs of exaggerated pharmacology were evident at the lowest dose tested; however, NOAELs were established. Exposure-based safety margins generally were low compared to the systemic exposure at the maximum recommended oral human dose. However, the main toxicity findings are either species-specific or can be easily assessed in the clinic.

Genotoxicity studies were negative.

Slight pre-implantation loss was noted at the highest dose level (2.5 mg/kg/day for 21 days) in the female fertility study conducted with oral paliperidone. The estimated exposure at the embryo-fetal NOEL in this study is similar to that attained in humans at the maximum recommended human oral dose. Since the increase in pre-implantation loss only occurred in the presence of maternal toxicity, this effect is of little relevance in terms of human risk.

The embryo-fetal developmental toxicity study with oral paliperidone in rabbits showed slight post-implantation loss at the highest dose level (5 mg/kg/day). The embryo-fetal NOAEL in this study yielded systemic exposure 22- to 34-fold higher than in humans at the maximum recommended human oral dose. These findings are considered to be of little relevance in terms of human risk.

The carcinogenic potential of paliperidone, an active metabolite of risperidone, was assessed based on studies with oral risperidone conducted in mice and rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be of little predictive value to humans.

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 10, 30, and 60 mg/kg/month, which is 0.2, 0.6, and 1.1 times, respectively, the maximum recommended human 525 mg dose of INVEGA TRINZA<sup>®</sup> on a mg/m<sup>2</sup> basis. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 30 and 60 mg/kg/month. These findings are considered to be of little relevance in terms of human risk.

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 maximum human oral exposure of 12 mg/day in adolescents on a mg/m<sup>2</sup> basis, CNS clinical signs and increased serum prolactin levels in both sexes and pseudopregnancy in females were evident at all dose levels, however no effects on growth, sexual maturation, and reproductive performance were observed after cessation of treatment. Oral doses up to 2.5 mg/kg/day did not generally affect neurobehavioral development in males and females, except for an impairment of learning and memory in female rats treated at 2.5 mg/kg/day and thus there was no safety margin. This effect was not observed on repeated daily testing 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, 0.31, 1.25, and 5 mg/kg/day, sexual maturation was arrested/delayed at all dose levels, but showed evidence of recovery after discontinuation of treatment in both sexes at 0.31 and 1.25 mg/kg/day and males at 5 mg/kg/day. Effects seen include increased serum prolactin levels in both sexes presumably due to dopamine receptor antagonist activity of risperidone; decreased plasma testosterone levels and sperm counts in males; plasma progesterone undetectable, absence of estrus cycling, low ovary and

uterus/cervix weights, absence of active mammary gland development, prominent luteal cells in the ovaries, and endometrial gland hyperplasia in the uterus in females. Reduced body weight gain at all dose levels correlated with reduced long bone growth at 1.25 and 5 mg/kg; however all effects were reversible and 0.31 mg/kg was a NOAEL. Mainly CNS-related clinical signs and increased heart rate at all dose levels were transient and/or reversible.

Local tolerability studies with the 3-month injectable formulation (F015) in the minipig were conducted to investigate the effect of the injection of the higher volume of formulation and the higher amount of paliperidone palmitate as compared to the 1-month injectable formulation (F013). Minipigs received 1.9 or 7.6-fold the highest clinical dose of the 3-month injectable formulation, 525 mg eq./person, and was compared with the 1-month injectable formulation (F013) given at 1.9 or 7.6-fold the MRHD of 150 mg eq./person. The dose volume to be injected for the high dose level in the study was approximately the same as the clinical dose volume at the MRHD of 2.625 mL/injection. White/yellow discoloration/deposits were noted at the injection site at necropsy. Histopathology found an increase in macrophages/giant cells/cholesterol clefts, and crystalline material (larger than nucleus) at the skeletal muscle injection sites of the animals receiving the F015 (3-month) formulation while an increase in histiocytosis and crystalline material (smaller than nucleus) was noted in animals receiving F013 (1-month) formulation.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

Not applicable.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**  
**PATIENT MEDICATION INFORMATION**

**INVEGA TRINZA®**

**paliperidone palmitate Prolonged-Release Injectable Suspension**

Read this carefully before you start taking **INVEGA TRINZA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **INVEGA TRINZA®**.

**Serious Warnings and Precautions**

**Increased Risk of Death in Elderly People with Dementia**

Medicines like **INVEGA TRINZA®** can raise the risk of death in elderly people who have dementia. **INVEGA TRINZA®** is not approved for use in patients with dementia.

**What is INVEGA TRINZA® used for?**

**INVEGA TRINZA®** is given by your healthcare professional and is used in adults to treat symptoms of schizophrenia.

Not all people with schizophrenia have the same symptoms.

Some of the most common symptoms of schizophrenia may include:

- hallucinations (seeing, feeling, hearing or smelling things that are not there)
- delusions (believing things that are not true)
- paranoia (not trusting others and feeling very suspicious)
- avoiding family and friends and wanting to be alone

**INVEGA TRINZA®** is an injection that is given to you once **every 3 months**. Before you start taking this drug, you will **first** be given **INVEGA SUSTENNA®**. **INVEGA SUSTENNA®** contains the same medication as **INVEGA TRINZA®** and is given once a month. You will get this injection for at least 4 months. Once your symptoms are under control with **INVEGA SUSTENNA®**, your doctor will switch you to **INVEGA TRINZA®**. You will be given one injection **every 3 months**

**How does INVEGA TRINZA® work?**

**INVEGA TRINZA®** belongs to a group of medicines called antipsychotic drugs. Antipsychotic medications affect dopamine and serotonin (chemicals found in the brain) that allow for the communication between your nerve cells. Exactly how this medication works is not known. However, it seems that **INVEGA TRINZA®** corrects the balance of dopamine and serotonin in your body.

**What are the ingredients in INVEGA TRINZA®?**

Medicinal ingredients: Paliperidone (as paliperidone palmitate)

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

**INVEGA TRINZA® comes in the following dosage forms:**

Prolonged-Release Injectable Suspension in pre-filled syringes: 175 mg / 0.875 mL, 263 mg / 1.315 mL, 350 mg / 1.75 mL, and 525 mg / 2.625 mL.

**Do not use INVEGA TRINZA® if:**

- you or the person you are caring for has had an allergic reaction to:
  - paliperidone,
  - risperidone (paliperidone is a compound resulting from the breakdown of risperidone in the body) or
  - any of the other ingredients in INVEGA TRINZA®

Signs of an allergic reaction include:

- itching
- skin rash
- swelling of the face, lips or tongue
- shortness of breath

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take INVEGA TRINZA®. Talk about any health conditions or problems you may have, including if you:**

- are taking or planning to take any other medication (prescription, over-the-counter and natural health products)
  - are taking risperidone
- have had serious allergic reactions to other medications, including oral risperidone or oral paliperidone. Even if you have not had a reaction to oral paliperidone or risperidone before, it can occur very rarely after receiving injections of INVEGA TRINZA®.
- have a history of having:
  - stroke
  - mini-stroke
  - high cholesterol or
  - high blood pressure

**Medicines like INVEGA TRINZA® can raise the risk of stroke/mini-stroke in elderly people with dementia.**

- have or are at risk for diabetes or high blood sugar or have a family history of diabetes
- are pregnant, think you may be pregnant, or are planning to become pregnant
- are breast-feeding or are planning to breast-feed. INVEGA TRINZA® can pass into your breast milk. You should not breast-feed while taking this medication.
- have had or have prolonged and/or painful erection
- are prone to hypotension (low blood pressure), have or have had heart disease treatment that makes you more likely to have low blood pressure or feeling dizzy or faint when you stand up from lying or sitting positions
- have a history of:
  - heart problems
  - any problems with the way your heart beats
  - congenital long QT syndrome
- are being treated for high blood pressure
- are taking any medications that affect how your heart beats
- have or have ever had blackouts or seizures

- have or have had low white blood cell count in your blood. Let your doctor know right away if you develop a fever or infection while being treated with INVEGA TRINZA®
- have high levels of cholesterol or fats (triglycerides) in your blood
- have a history of or are at risk of:
  - sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
  - sleep walking
  - sleep-related eating disorder
- have Parkinson's disease or dementia with Lewy bodies (DLB)
- have or have had breast cancer
- have pituitary gland tumours
- drink alcoholic beverages or use drugs
- have a history of kidney problems
- have liver problems
- suffer from Alzheimer's disease
- are feeling thirsty and unwell
- exercise strenuously. This kind of medication may interfere with your body's ability to adjust to heat. You should avoid becoming overheated or dehydrated (for example with vigorous exercise or exposure to extreme heat) while taking INVEGA TRINZA®.
- have a fever or infection
- are at risk for developing blood clots. Risk factors include:
  - a family history of blood clots
  - being over the age over 65
  - smoking
  - being overweight
  - having a recent major surgery (such as hip or knee replacement)
  - not being able to move due to air travel or other reasons
  - taking oral birth control ("The Pill")
- are planning to have surgery on your eye(s). During surgery to treat the cloudiness of the lens in your eye(s) (known as cataract surgery):
  - the pupil (the black circle in the middle of your eye) may not increase in size as needed
  - the iris (the coloured part of the eye) may become floppy during surgery. This may lead to eye damage.

Tell your eye doctor you are taking this medicine

### **Other warnings you should know about:**

**Elderly Patients with Dementia:** Drugs that contain risperidone are similar to drugs that contain paliperidone (such as INVEGA TRINZA®). Studies have shown that when risperidone and furosemide (a "water pill") are taken together by elderly patients who have dementia, it is linked to a higher rate of death.

- Tell your doctor if you are taking furosemide. This drug can be used to treat:
  - swelling of parts of the body caused by the build-up of too much fluid
  - some heart problems
  - high blood pressure

In elderly patients who have dementia, other drugs that belong to the same group of drugs as INVEGA TRINZA® have also been linked to side effects that include:

- a sudden change in mental state

- sudden weakness or numbness of the face, arms or legs, especially on one side of the body
- slurred speech
- vision problems

If you have any of these symptoms, **get medical help right away.**

**Dysphagia:** Tell your doctor if you have difficulty swallowing food or have esophageal dysmotility (problems with your food pipe) as there is a risk of pneumonia caused by inhaling food or liquid that gets into your lungs.

**Effects on newborns:** You should not take INVEGA TRINZA® while you are pregnant or if you are planning on becoming pregnant unless you have talked to your doctor about it.

If you took INVEGA TRINZA® at any time while you were pregnant or if you took it before you became pregnant, the following symptoms may happen in your newborn baby:

- shaking
- stiffness in their muscles and/or weakness
- sleepiness
- agitation
- breathing problems
- difficulty feeding

**Get medical help right away** if your newborn baby has any of these symptoms.

In some cases, babies born to a mother who took paliperidone while she was pregnant have had to be hospitalized after experiencing symptoms that were severe.

**Driving and using machines:** Do not drive or operate machinery until you know how you respond to INVEGA TRINZA®. Some people experience drowsiness or blurred vision while taking INVEGA TRINZA®.

**Falls:** Feeling sleepy, a fall in blood pressure when you stand up from sitting or lying down, vision and speech problems have been reported with the use of antipsychotic drugs. This can lead to falls that may cause fractures or other fall related-injuries. Certain medications, diseases or conditions can make this worse.

**Weight gain:** Weight gain has been seen in patients who are taking antipsychotic drugs. Your doctor may monitor your body weight when you are taking INVEGA TRINZA®.

**Blood tests:** Your doctor should do blood tests before you start taking INVEGA TRINZA®. They will check your blood sugar levels, and for those with certain risk factors, the level of white blood cells in your blood. Your doctor should continue to do blood test for as long as you are being treated with INVEGA TRINZA®.

The following serious or life-threatening side effects have been reported with similar atypical antipsychotics drugs such as INVEGA TRINZA®:

- **Neuroleptic Malignant Syndrome (NMS):**
  - mental changes such as agitation, hallucinations, confusion, or other changes in

- mental status
  - coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes)
  - restlessness
  - racing or fast heartbeat, high or low blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - stiff muscles
- **Severe Skin Reactions:** In very rare cases, skin reactions that can be serious or life-threatening have been reported. This includes skin conditions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). The following symptoms may be related to these skin reactions:
    - Early warnings for patients:
      - fever
      - severe rash
      - swollen lymph glands
      - flu-like feeling
      - blisters and peeling skin that may start in and around the mouth, nose, eyes, and genitals and spread to other areas of the body
    - Later developments:
      - yellow skin or eyes
      - shortness of breath
      - dry cough
      - chest pain or discomfort
      - feeling thirsty
      - urinating less often, less urine

Call your doctor **right away** if you start to have any of the following symptoms while taking INVEGA TRINZA®.

**Tardive Dyskinesia (TD):** INVEGA TRINZA®, like other antipsychotic medications, can cause potentially irreversible muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body.

**Increased levels of prolactin:** INVEGA TRINZA® can raise your levels of a hormone called “prolactin”. This is measured with a blood test. Symptoms may include:

- In men:
  - swelling in the breast
  - difficulty in getting or maintaining an erection or other sexual dysfunction
- In women:
  - discomfort in the breasts
  - leaking of milk from the breasts (even if not pregnant)
  - missing your menstrual period or other problems with your cycle

If you have high levels of prolactin and a condition called hypogonadism, you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

**Tell your healthcare professional about all the medicines you take, including any drugs,**

**vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with INVEGA TRINZA®:**

- **DO NOT** drink alcohol and only take medications prescribed by your doctor. Since INVEGA TRINZA® works primarily in the brain, interference with other drugs that also work in the brain could occur.
- Risperidone or oral paliperidone. Taking either of these drugs together with INVEGA TRINZA® can increase the amount of paliperidone in your body.
- INVEGA TRINZA® can make you feel sleepy or drowsy. You should be careful when you take this drug with other drugs that can also cause you to become sleepy or drowsy.
- Dopamine agonists, such as levodopa (used to treat Parkinson's disease) may decrease the effects of INVEGA TRINZA®. Also, INVEGA TRINZA® can affect how drugs used to treat Parkinson's disease work.
- Carbamazepine (used to treat seizures) has been shown to decrease the levels of INVEGA TRINZA® in your blood.
- INVEGA TRINZA® can lower your blood pressure; care should be taken when this medicine is taken with other drugs that lower your blood pressure.
- INVEGA TRINZA® should be used with caution with medicines that increase the activity of the central nervous system (psychostimulants such as methylphenidate).

This list is not complete and there may be other drugs that can interact with INVEGA TRINZA®.

**How INVEGA TRINZA® is given:**

INVEGA TRINZA® is a long-acting medicine. It will be given to you:

- by your healthcare professional
- as an injection into your muscle (intramuscularly) located on the uppermost part of your arm or in the upper outer side of your buttocks **every 3 months**.

INVEGA TRINZA® is designed to release medication slowly over time and provide a steady level of medication **over the 3 months**.

It is important for you to be treated **first** with INVEGA SUSTENNA® (a once a month injection) for at least 4 months before you start taking INVEGA TRINZA®. This is so that your doctor can decide if you can safely switch to INVEGA TRINZA® and what dose will work best for you.

It is important not to miss your scheduled dose. If you cannot keep your appointment with the doctor, make sure you call him/her right away so another appointment can be made as soon as possible.

**Usual adult dose:**

Your doctor has decided on the best dose for you. Your dose may be increased or decreased depending on:

- other health conditions you may have

- how you respond to the medication

Maintenance dose: (given either into your upper arm or buttocks)  
Once every 3 months: 175 mg / 0.875 mL – 525 mg / 2.625 mL

**Overdose:**

If you think you have been given too much INVEGA TRINZA<sup>®</sup>, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Patients who have been given too much paliperidone may experience the following symptoms:

- feeling drowsy or sleepy
- a fast heart rate
- low blood pressure
- irregular heart beat or other symptoms of an irregular heartbeat, such as lightheadedness or fainting
- unusual movements of the face, body, arms or legs (such as excessive trembling or muscle stiffness)

**Missed Dose:**

It is important not to miss your scheduled dose.

If you cannot keep your appointment with the doctor, make sure you call him/her right away so another appointment can be made as soon as possible. Your doctor or treatment team will decide what you should do next.

If you stop going for your injections, your symptoms may return. You should not stop this medicine unless told to do so by your doctor.

**What are possible side effects from using INVEGA TRINZA<sup>®</sup>?**

These are not all the possible side effects you may feel when taking INVEGA TRINZA<sup>®</sup>. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:

- headache
- trouble falling asleep or waking up during the night or too early in the morning
- faster heart rate
- slow heart rate
- irregular heartbeat
- stomach ache
- constipation
- diarrhea
- nausea and vomiting
- lack of energy
- fatigue
- injection site pain
- increased weight
- feeling restless

- dizziness
- uncontrollable movements of the face or body, rigid muscles
- slowness of movement and muscle stiffness or spasms
- feeling sleepy
- rash
- high blood pressure
- urinary tract infection
- high blood triglycerides (a fat)
- feeling like you have the flu
- fever (let your doctor know right away if you develop a fever or infection while on this medication)
- weight loss
- depression
- anxiety
- tremors (shaking)
- low blood sugar, diabetes or worsening of diabetes
  - high blood sugar has been reported; see your doctor if you experience symptoms such as excessive thirst or urination
- blurred vision
- dry mouth
- increased saliva
- decreased or increased appetite
- seizures
- feeling dizzy when you stand up
- drooling
- itching
- feeling pain when you move your eye and problems with moving your eyes
- glaucoma (increased pressure within the eyeball)
- lack of bowel muscle movement that causes blockage (may occur very rarely)
- low blood sugar (hypoglycemia).
- glaucoma (increased pressure within the eyeball), and problems with the movement of your eyes

Since paliperidone (the ingredient in INVEGA TRINZA<sup>®</sup>) is a compound resulting from the breakdown of risperidone in the human body, any side effects that may occur after taking risperidone may also occur with INVEGA TRINZA<sup>®</sup>.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b> Skin rash on its own		✓	
Swelling or itching at the injection site, injection site pain		✓	
New or worsening constipation		✓	

<b>Dystonia:</b> twisting movements that you cannot control, and can affect posture or the face, including eyes, mouth, tongue or jaw		✓	
<b>UNCOMMON</b> <b>Severe allergic reactions:</b> fever, difficulty swallowing or breathing, shortness of breath; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
<b>Tardive Dyskinesia:</b> Muscle twitching or unusual / abnormal movements of the face, tongue or other parts of your body		✓	
<b>Leukopenia / Neutropenia (decreased white blood cells):</b> infections, fatigue, fever, aches, pains, and flu-like symptoms			✓
Bruise easily, excessive bleeding		✓	
<b>RARE</b> A state of confusion, reduced consciousness, high fever, or pronounced muscle stiffness, pain and swelling			✓
Marked changes in body temperature (generally as a result of several factors together including extreme heat or cold)			✓
Seizure (fits) (i.e., loss of consciousness with uncontrollable shaking)			✓
<b>Stroke:</b> sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause.			✓
Life-threatening complications of uncontrolled diabetes such as shortness of breath, confusion and loss of consciousness			✓
<b>Pancreatitis (inflammation of the pancreas):</b> severe upper abdominal pain, fever, rapid pulse, nausea, vomiting, tenderness when touching the abdomen			✓

<b>Blood clots:</b> swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.			✓
<b>Dysphagia:</b> difficulty swallowing that can cause food or liquid to get into your lungs		✓	
<b>Catatonia:</b> unable to move or respond while awake		✓	
<b>UNKNOWN</b> Serious allergic reactions even if you have previously tolerated oral risperidone or oral paliperidone; symptoms include rash, swelling of your throat, itching or problems breathing. These may be signs of a serious allergic reaction			✓
<b>Rhabdomyolysis:</b> very dark (“tea coloured”) urine, muscle tenderness and/or aching			✓
<b>Priapism:</b> long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
<b>Jaundice:</b> yellowing of the skin and eyes, dark urine			✓
<b>Neuroleptic Malignant Syndrome (NMS):</b> pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			✓
<b>Severe skin reactions:</b> fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

## Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## Storage:

Store INVEGA TRINZA®:

- between 15–30°C in its original package

Keep out of reach and sight of children.

The expiry date for INVEGA TRINZA® is printed on the package. Do not use the medicine after this date.

## If you want more information about INVEGA TRINZA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website Janssen Inc., [www.janssen.com/canada](http://www.janssen.com/canada), or by calling 1-800-567-3331 or 1-800-387-8781.

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