HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA SUSTENNA safely and effectively. See full prescribing information for INVEGA SUSTENNA.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2006

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.7)	9/2024
Warnings and Precautions (5.10)	1/2025

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

INVEGA SUSTENNA is an atypical antipsychotic indicated for

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

----------DOSAGE AND ADMINISTRATION----------

- For intramuscular injection only. (2.1)
- Each injection must be administered only by a healthcare professional. (2.1)
- For deltoid injection, use 1-inch 23G needle for patients weighing less than 90 kg or 1½-inch 22G needle for patients weighing 90 kg or more. For gluteal injection, use 1½-inch 22G needle regardless of patient weight. (2.1)

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose[a] (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia (2.2)	234 mg	156 mg	39-234 mg[b]	234 mg
Schizoaffective disorder (2.2)	234 mg	156 mg	78-234 mg[c]	234 mg

[a] Administered 5 weeks after the first injection.
[b] The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).
[c] Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

- For patients naïve to oral paliperidone or oral or injectable risperidone, establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA. (2.2)
- Missed Doses: To manage either a missed second initiation dose or a missed monthly maintenance dose, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): INVEGA SUSTENNA is not recommended. (2.5)
- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Administer 156 mg on treatment Day 1 and 117 mg on Day 8, both in the deltoid muscle. Follow with the recommended monthly maintenance dose of 78 mg, administered in the deltoid or gluteal muscle. Adjust monthly maintenance dose based on tolerability and/or efficacy within the strengths of 39 mg, 78 mg, 117 mg, or 156 mg. The maximum monthly dose is 156 mg for patients with mild renal impairment. (2.5)

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

Extended-release injectable suspension: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, or 234 mg/1.5 mL (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack). (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *QT Prolongation:* Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. (5.4)
- *Tardive Dyskinesia:* Discontinue drug if clinically appropriate. (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain. (5.6)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing INVEGA SUSTENNA if clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Hyperprolactinemia:* Prolactin elevations occur and persist during chronic administration. (5.10)

- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.11)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.12)

----------ADVERSE REACTIONS----------

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

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

----------DRUG INTERACTIONS----------

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

----------USE IN SPECIFIC POPULATIONS----------

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

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

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA is not approved for use in patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

INVEGA SUSTENNA (paliperidone palmitate) is indicated for the treatment of:

- Schizophrenia in adults *[see Clinical Studies (14.1)]*.
- Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Each injection must be administered only by a healthcare professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration, whenever product and container permit.

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

INVEGA SUSTENNA must be administered using only the needles that are provided in the INVEGA SUSTENNA kit.

The recommended needle size for administration of INVEGA SUSTENNA into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 23 gauge needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge needle is recommended.

Deltoid injections should be alternated between the two deltoid muscles.

The recommended needle size for administration of INVEGA SUSTENNA into the gluteal muscle is the 1½-inch, 22 gauge needle regardless of patient weight.

Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be

alternated between the two gluteal muscles.

2.2 Schizophrenia and Schizoaffective Disorder

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA.

The recommended dosing of INVEGA SUSTENNA for each approved indication is displayed in Table 1. The recommended initiation of INVEGA SUSTENNA is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

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

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose[a] (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia	234 mg	156 mg	39-234 mg[b]	234 mg
Schizoaffective disorder	234 mg	156 mg	78-234 mg[c]	234 mg

[a] Administered 5 weeks after the first injection.

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

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

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

2.3 Missed Doses

Avoiding Missed Doses

It is recommended that the second initiation dose of INVEGA SUSTENNA be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

Management of a Missed Second Initiation Dose

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

Table 2: Management of a Missed Second Initiation Dose

TIMING OF MISSED SECOND INITIATION DOSE	DOSING
Less than 4 weeks since first injection	**Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible.** 1. It is recommended to administer a third injection of 117 mg in either the deltoid or gluteal muscle 5 weeks after the first injection (regardless of the timing of the second injection). 2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
4 to 7 weeks since first injection	**Resume dosing with two injections of 156 mg in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
More than 7 weeks since first injection	**Restart dosing with recommended initiation** *(see Section 2.2, Table 1)*: 1. Administer a 234 mg deltoid injection on Day 1. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.

Management of a Missed Maintenance Dose

In case of a missed maintenance dose follow the dosing instructions provided in Table 3.

Table 3: Management of a Missed Maintenance Dose

TIMING OF MISSED MAINTENANCE DOSE	DOSING
4 to 6 weeks since last injection	**Resume regular monthly dosing as soon as possible at the patient's previously stabilized dose, followed by injections at monthly intervals.**

More than 6 weeks to 6 months since last injection	**Resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first 2 injections should each be 156 mg) in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later at the same dose. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.
More than 6 months since last injection	**Restart dosing with recommended initiation** (*see Section 2.2, Table 1*)*:* 1. Administer a 234 mg deltoid injection on Day 1. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.

2.4 Use with Risperidone or with Oral Paliperidone

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

2.5 Dosage Adjustments

Patients with Renal Impairment

INVEGA SUSTENNA has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), initiate INVEGA SUSTENNA with a dose of 156 mg on treatment Day 1 and 117 mg on Day 8, both in the deltoid muscle. Follow with the recommended monthly maintenance dose of 78 mg, administered in either the deltoid or gluteal muscle. Adjust monthly maintenance dose based on tolerability and/or efficacy within the strengths of 39 mg, 78 mg, 117 mg, or 156 mg. The maximum monthly dose is 156 mg for patients with mild renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

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

Coadministration with Strong CYP3A4/P-glycoprotein (P-gp) Inducers

Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during the 1-month dosing interval for INVEGA SUSTENNA, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

2.6 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia or schizoaffective disorder from other antipsychotics to INVEGA SUSTENNA, or concerning concomitant administration with other antipsychotics.

Switching from Oral Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA.

Previous oral antipsychotics can be gradually discontinued at the time of initiation of treatment with INVEGA SUSTENNA. Recommended initiation of INVEGA SUSTENNA is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle *[see Dosage and Administration (2.2)]*. Patients previously stabilized on different doses of INVEGA Extended-Release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA SUSTENNA monthly doses as depicted in Table 4.

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

Formulation	**INVEGA Extended-Release Tablet**	**INVEGA SUSTENNA Injection**
Dosing Frequency	**Once Daily**	**Once every 4 weeks**
Dose (mg)	12	234
	9	156
	6	117
	3	39-78

Switching from Long-Acting Injectable Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA.

When switching patients currently at steady-state on a long-acting injectable antipsychotic, initiate INVEGA SUSTENNA therapy in place of the next scheduled injection. INVEGA SUSTENNA

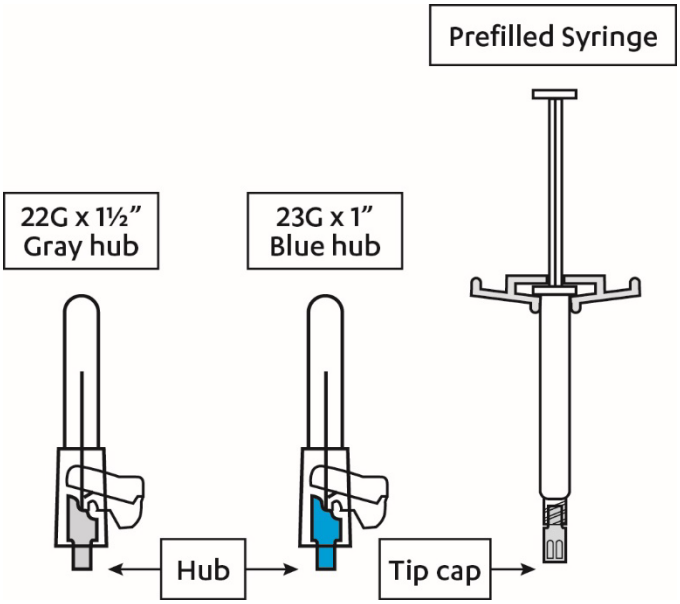
should then be continued at monthly intervals. The one-week initiation dosing regimen as described in Section 2.2 is not required. See Table 1 above for recommended monthly maintenance dosing. Based on previous clinical history of tolerability and/or efficacy, some patients may benefit from lower or higher maintenance doses within the available strengths (39 mg, 78 mg, 117 mg, 156 mg, and 234 mg). The 39 mg strength was not studied in the long-term schizoaffective disorder study. Monthly maintenance doses can be administered in either the deltoid or gluteal muscle *[see Dosage and Administration (2.2)]*.

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

2.7 Instructions for Preparation and Administration

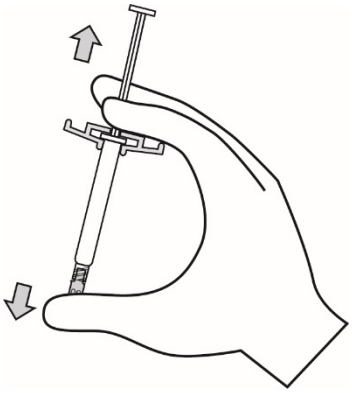
Each injection must be administered only by a healthcare professional.

The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.



INVEGA SUSTENNA is for single use only.

a. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.



b. Select the appropriate needle.

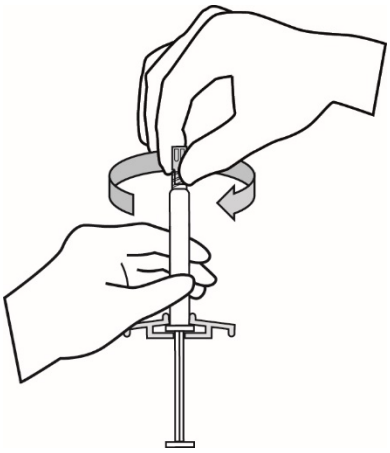
For DELTOID injection:

- If the patient weighs less than 90 kg, use the 1-inch **23** gauge needle (needle with **blue** colored hub).
- If the patient weighs 90 kg or more, use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

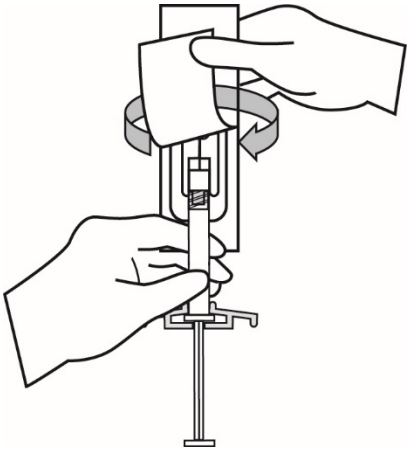
For GLUTEAL injection:

Use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub) regardless of patient's weight.

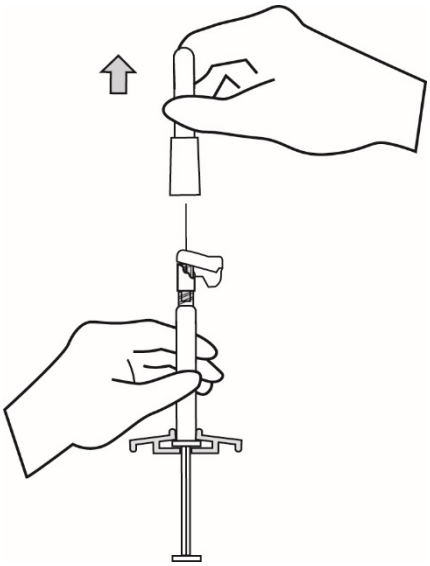
c. Hold the syringe with the tip cap pointing up. Remove the rubber tip cap with a gentle twisting motion.



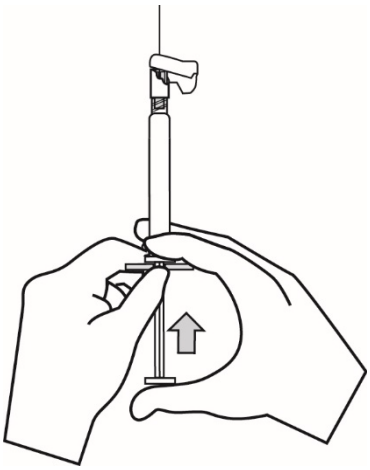
d. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Hold the syringe pointing up. Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage. Always check for signs of damage or leaking prior to administration.



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



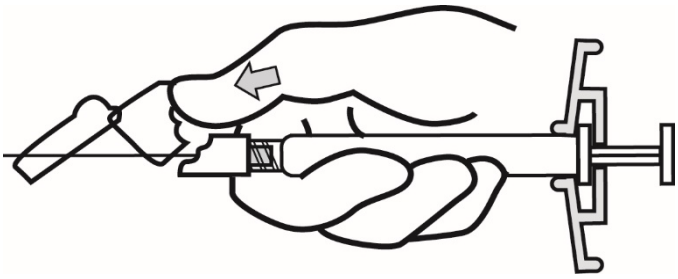
f. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.



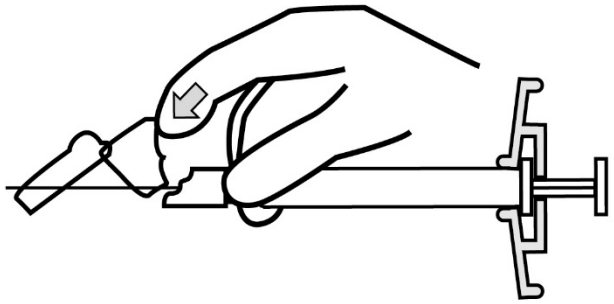
g. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. Do not administer by any other route.

h. After the injection is complete, use either thumb or finger of one hand (h1, h2) or a flat surface (h3) to activate the needle protection system. The needle protection system is fully activated when a ‘click’ is heard. Discard the syringe with needle appropriately.

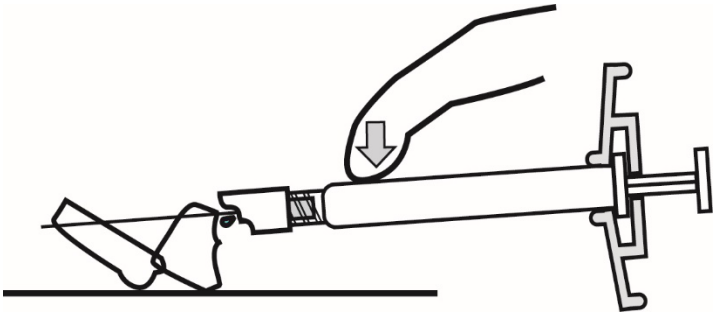
h1



h2



h3



3 DOSAGE FORMS AND STRENGTHS

INVEGA SUSTENNA is available as a white to off-white aqueous extended-release injectable suspension for intramuscular injection in dose strengths of 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, and 234 mg/1.5 mL paliperidone palmitate in single-dose prefilled syringes.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA SUSTENNA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone.

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

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

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA SUSTENNA administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA SUSTENNA in subjects with schizophrenia and in the long-term study in subjects with schizoaffective disorder, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study in subjects with schizophrenia, no subject had a QTcLD

change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, INVEGA SUSTENNA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on INVEGA SUSTENNA, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA despite the presence of the syndrome.

5.6 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

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

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

Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 5.

Table 5: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

		INVEGA SUSTENNA					
	Placebo	39 mg	78 mg	156 mg	234/39 mg[a]	234/156 mg[a]	234/234 mg[a]
	Mean change from baseline (mg/dL)						
	n=367	n=86	n=244	n=238	n=110	n=126	n=115
Serum Glucose Change from baseline	-1.3	1.3	3.5	0.1	3.4	1.8	-0.2
	Proportion of Patients with Shifts						
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	4.6% (11/241)	6.3% (4/64)	6.4% (11/173)	3.9% (6/154)	2.5% (2/79)	7.0% (6/86)	6.6% (5/76)

[a] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*.

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA was associated with a mean change in glucose of -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=100).

During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA was associated with mean change in glucose of +5.3 mg/dL (n=518). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA was associated with a mean change in glucose of +0.3 mg/dL (n=131) compared with a mean change of +4.0 mg/dL in the placebo group (n=120).

Dyslipidemia

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

Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 6.

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

		INVEGA SUSTENNA					
	Placebo	**39 mg**	**78 mg**	**156 mg**	**234/39 mg[a]**	**234/156 mg[a]**	**234/234 mg[a]**
				Mean change from baseline (mg/dL)			
Cholesterol	**n=366**	**n=89**	**n=244**	**n=232**	**n=105**	**n=119**	**n=120**
Change from baseline	-6.6	-6.4	-5.8	-7.1	-0.9	-4.2	9.4
LDL	**n=275**	**n=80**	**n=164**	**n=141**	**n=104**	**n=117**	**n=108**
Change from baseline	-6.0	-4.8	-5.6	-4.8	0.9	-2.4	5.2
HDL	**n=286**	**n=89**	**n=165**	**n=150**	**n=105**	**n=118**	**n=115**
Change from baseline	0.7	2.1	0.6	0.3	1.5	1.1	0.0
Triglycerides	**n=366**	**n=89**	**n=244**	**n=232**	**n=105**	**n=119**	**n=120**
Change from baseline	-16.7	7.6	-9.0	-11.5	-14.1	-20.0	11.9
				Proportion of Patients with Shifts			
Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	3.2% (7/222)	2.0% (1/51)	2.0% (3/147)	2.1% (3/141)	0% (0/69)	3.1% (2/65)	7.1% (6/84)
LDL Normal to High (<100 mg/dL to ≥160 mg/dL)	1.1% (1/95)	0% (0/29)	0% (0/67)	0% (0/46)	0% (0/41)	0% (0/37)	0% (0/44)
HDL Normal to Low (≥40 mg/dL to <40 mg/dL)	13.8% (28/203)	14.8% (9/61)	9.6% (11/115)	14.2% (15/106)	12.7% (9/71)	10.5% (8/76)	16.0% (13/81)
Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	3.6% (8/221)	6.1% (3/49)	9.2% (14/153)	7.2% (10/139)	1.3% (1/79)	3.7% (3/82)	10.7% (9/84)

[a] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*.

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, the mean changes from baseline in lipid values are presented in Table 7.

Table 7: Change in Fasting Lipids from Long-term Open-label Pharmacokinetic and Safety Study in Subjects with Schizophrenia

	INVEGA SUSTENNA 234 mg	
	Week 29	**Week 53**
	Mean change from baseline (mg/dL)	
Cholesterol	**n=112**	**n=100**
Change from baseline	-1.2	0.1
LDL	**n=107**	**n=89**
Change from baseline	-2.7	-2.3
HDL	**n=112**	**n=98**
Change from baseline	-0.8	-2.6
Triglycerides	**n=112**	**n=100**
Change from baseline	16.2	37.4

The mean changes from baseline in lipid values during the initial 25-week open-label period and at the endpoint of the subsequent 15-month double-blind period in a long-term study in subjects with schizoaffective disorder are presented in Table 8.

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

	Open-Label Period	Double-Blind Period	
	INVEGA SUSTENNA	Placebo	INVEGA SUSTENNA
	Mean change from baseline (mg/dL)		
Cholesterol	**n=198**	**n=119**	**n=132**
Change from baseline	-3.9	-4.2	2.3
LDL	**n=198**	**n=117**	**n=130**
Change from baseline	-2.7	-2.8	5.9
HDL	**n=198**	**n=119**	**n=131**
Change from baseline	-2.7	-0.9	-0.7
Triglycerides	**n=198**	**n=119**	**n=132**
Change from baseline	7.0	2.5	-12.3

Weight Gain

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

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of $\geq 7\%$ of body weight from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 9.

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

		INVEGA SUSTENNA					
	Placebo	39 mg	78 mg	156 mg	234/39 mg[a]	234/156 mg[a]	234/234 mg[a]
	n=451	n=116	n=280	n=267	n=137	n=144	n=145
Weight (kg) Change from baseline	-0.4	0.4	0.8	1.4	0.4	0.7	1.4
Weight Gain ≥ 7% increase from baseline	3.3%	6.0%	8.9%	9.0%	5.8%	8.3%	13.1%

[a] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*.

In a long-term open-label pharmacokinetic and safety study in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA was associated with a mean change in weight of +2.4 kg at Week 29 (n=134) and +4.3 kg at Week 53 (n=113).

During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA was associated with a mean change in weight of +2.2 kg and 18.4% of subjects had an increase in body weight of ≥ 7% (n=653). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA was associated with a mean change in weight of -0.2 kg and 13.0% of subjects had an increase in body weight of ≥ 7% (n=161); the placebo group had a mean change in weight of -0.8 kg and 6.0% of subjects had an increase in body weight of ≥ 7% (n=168).

5.7 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with INVEGA SUSTENNA in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA SUSTENNA-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the

long-term studies in subjects with schizophrenia and schizoaffective disorder were similar to those observed in the short-term studies.

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

5.8 Falls

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

5.9 Leukopenia, Neutropenia, and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA SUSTENNA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA in patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) and follow their WBC until recovery.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.

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

Schizophrenia

In a long-term maintenance trial of INVEGA SUSTENNA in schizophrenia patients (Study PSY-3001), see *Clinical Studies (14.1)*, elevations of prolactin to above the reference range (> 18 ng/mL in males and > 30 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in a higher percentage of the patients in the INVEGA SUSTENNA group than those in the placebo group in males (51.9% vs. 29.0%) and in females (50.5% vs. 42.9%). During the double-blind phase, 4 females (4.2%) in the INVEGA SUSTENNA group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.9%) in the INVEGA SUSTENNA group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 33-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.9 (22.3) ng/mL in males (N=490) and 35.2 (39.6) ng/mL in females (N=358). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (22.5) ng/mL in males (N=470) and 59.5 (38.1) ng/mL in females (N=333). During the open-label phases 49.2% of females and 47.7% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of

females experienced potentially prolactin-related adverse reactions compared to males (5.3% vs. 1.8%). Amenorrhea (2.5%) in females and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Schizoaffective Disorder

In a long-term maintenance trial of INVEGA SUSTENNA in patients with schizoaffective disorder (Study SCA-3004) see *Clinical Studies (14.2)*, elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) relative to open-label baseline at any time during the 15-month double-blind phase were noted in a higher percentage of patients in the INVEGA SUSTENNA group than those in the placebo group in males (55.6% vs. 23.2%) and in females (44.3% vs. 25.0%). During the 15-month double-blind phase, 11 females (13.9%) in the INVEGA SUSTENNA group had 14 potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=3; galactorrhea N=3), while 5 females (5.8%) in the placebo group had 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1). Six males (7.1%) in the INVEGA SUSTENNA group experienced 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.2%) in the placebo group experienced adverse reaction of blood prolactin increased.

Prior to the 15-month double-blind phase (during the 25-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.6 (14.0) ng/mL in males (N=352) and 39.1 (44.6) ng/mL in females (N=302). At the end of the open-label phase, mean (SD) prolactin values were 32.8 (17.2) ng/mL in males (N=275) and 72.4 (46.5) ng/mL in females (N=239). During the open-label phase, 48.9% of females and 53.3% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (10.0% vs. 9.0%). Amenorrhea (5.8%) and galactorrhea (2.9%) in females and libido decrease (2.8%) and erectile dysfunction (2.5%) in males were observed with a rate greater than 2%.

5.11 Potential for Cognitive and Motor Impairment

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

5.12 Seizures

In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with INVEGA SUSTENNA in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA SUSTENNA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.13 Dysphagia

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

5.14 Priapism

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

5.15 Disruption of Body Temperature Regulation

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

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*

- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic changes *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.9)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.10)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Priapism *[see Warnings and Precautions (5.14)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

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

Patient Exposure

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

SUSTENNA initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA was similar to that seen in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia.

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

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

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

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

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

Dose-Related Adverse Reactions: Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, among the adverse reactions that occurred with ≥ 2% incidence in the subjects treated with INVEGA SUSTENNA, only akathisia

increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA SUSTENNA-treated subjects from the four fixed-dose studies.

Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA SUSTENNA-Treated Patients: Table 10 lists the adverse reactions reported in 2% or more of INVEGA SUSTENNA-treated subjects and at a greater proportion than in the placebo group with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

Table 10: Incidences of Adverse Reactions 2% or More of INVEGA SUSTENNA-Treated Patients (and Greater than Placebo) with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

		INVEGA SUSTENNA					
System Organ Class Adverse Reactions	**Placebo[a] (N=510)**	**39 mg (N=130)**	**78 mg (N=302)**	**156 mg (N=312)**	**234/39 mg[b] (N=160)**	**234/156 mg[b] (N=165)**	**234/234 mg[b] (N=163)**
Total percentage of subjects with adverse reactions	70	75	68	69	63	60	63
Gastrointestinal disorders							
Abdominal discomfort/abdominal pain upper	2	2	4	4	1	2	4
Diarrhea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reactions	2	0	4	6	9	7	10
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Investigations							
Weight increased	1	4	4	1	1	1	2
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Nightmare	<1	2	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

Percentages are rounded to whole numbers. Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA SUSTENNA dose groups and which occurred at greater incidence than in the placebo group.

[a] Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design.

[b] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[see Clinical Studies (14.1)]*

Adverse reactions for which the INVEGA SUSTENNA incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain upper/stomach discomfort, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse reactions were collapsed and are grouped under "Injection site reactions".

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

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

Ear and labyrinth disorders: vertigo

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

Gastrointestinal disorders: constipation, dyspepsia, flatulence, salivary hypersecretion

Immune system disorders: hypersensitivity

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, hyperinsulinemia, increased appetite

Musculoskeletal and connective tissue disorders: arthralgia, joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, nuchal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, cogwheel rigidity, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restlessness

Reproductive system and breast disorders: amenorrhea, breast discharge, breast enlargement/breast swelling, breast tenderness/breast pain, ejaculation disorder, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: nasal congestion

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

Demographic Differences

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects 65 years of age and older.

Extrapyramidal Symptoms (EPS)

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

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

	Percentage of Subjects			
		INVEGA SUSTENNA		
Scale	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Parkinsonism[a]	9	12	10	6
Akathisia[b]	5	5	6	5
Dyskinesia[c]	3	4	6	4
Use of Anticholinergic Medications[d]	12	10	12	11

[a] For parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)

[b] For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint

[c] For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint

[d] Percent of subjects who received anticholinergic medications to treat EPS

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

	Percentage of Subjects			
		INVEGA SUSTENNA		
EPS Group	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism	5	6	6	4
Hyperkinesia	2	2	2	4
Tremor	3	2	2	3
Dyskinesia	1	2	3	1
Dystonia	0	1	1	2

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

The results across all phases of the maintenance trial in subjects with schizophrenia exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA SUSTENNA 156 mg group (18% and 11%, respectively) than in the INVEGA SUSTENNA 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study in subjects with schizophrenia involving 234 mg initiation dosing, the incidence of any EPS was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA SUSTENNA 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA SUSTENNA 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

In the long-term study in subjects with schizoaffective disorder, EPS reported during the 25-week open-label INVEGA SUSTENNA treatment included hyperkinesia (12.3%), parkinsonism (8.7%), tremor (3.4%), dyskinesia (2.5%), and dystonia (2.1%). During the 15-month double-blind treatment, the incidence of any EPS was similar to that of the placebo group (8.5% and 7.1% respectively). The most commonly reported treatment-emergent EPS-related adverse events (> 2%) in any treatment group in the double-blind phase of the study (INVEGA SUSTENNA versus placebo) were hyperkinesia (3.7% vs. 2.9%), parkinsonism (3.0% vs. 1.8%), and tremor (1.2% vs. 2.4%).

Dystonia

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

Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

In the 13-week study involving 234 mg initiation dosing in subjects with schizophrenia, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA SUSTENNA and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA SUSTENNA groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA SUSTENNA and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA SUSTENNA and placebo groups.

Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

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

Cardiac disorders: bundle branch block left, sinus arrhythmia

Gastrointestinal disorders: abdominal pain, small intestinal obstruction

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

Infections and infestations: rhinitis

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

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

Psychiatric disorders: sleep disorder

Reproductive system and breast disorders: breast engorgement

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

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: hypotension, ischemia

6.2 Postmarketing Experience

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

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the *Adverse Reactions (6)* sections of the package inserts for those products.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with INVEGA SUSTENNA

Because paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Table 13. Clinically Important Drug Interactions with INVEGA SUSTENNA

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Centrally Acting Drugs and Alcohol	Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA SUSTENNA.	INVEGA SUSTENNA should be used with caution in combination with other centrally acting drugs and alcohol *[see Adverse Reactions (6.1, 6.2)]*.
Drugs with Potential for Inducing Orthostatic Hypotension	Because INVEGA SUSTENNA has the potential for inducing orthostatic hypotension, an additive effect may occur when INVEGA SUSTENNA is administered with other therapeutic agents that have this potential *[see Warnings and Precautions (5.7)]*.	Monitor orthostatic vital signs in patients who are vulnerable to hypotension *[see Warnings and Precautions (5.7)]*.
Strong Inducers of CYP3A4 and P-gp (e.g., carbamazepine, rifampin, or St. John's Wort)	The concomitant use of paliperidone and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone *[see Clinical Pharmacology (12.3)]*.	Avoid using CYP3A4 and/or P-gp inducers with INVEGA SUSTENNA during the 1-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets *[see Dosage and Administration (2.5)]*.
Levodopa and Other Dopamine Agonists	Paliperidone may antagonize the effect of levodopa and other dopamine agonists.	Monitor and manage patient as clinically appropriate.

7.2 Drugs Having No Clinically Important Interactions with INVEGA SUSTENNA

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

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA is also unlikely.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely. *[see Clinical Pharmacology (12.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA SUSTENNA, during pregnancy *(see Clinical Considerations).* Paliperidone has been detected in plasma in adult subjects up to 126 days after a single-dose administration of INVEGA SUSTENNA *[see Clinical Pharmacology (12.3)]*, and the clinical significance of INVEGA SUSTENNA administered before pregnancy or anytime during pregnancy is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In animal reproduction studies, there were no treatment related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 10 times the maximum recommended human dose (MRHD) of 234 mg paliperidone based on mg/m^2 body surface area. There were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the

period of organogenesis with up to 8 times the MRHD of 12 mg of paliperidone based on mg/m^2 body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR= 1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 10 times MRHD of 234 mg paliperidone based on mg/m^2 body surface area.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m^2 body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m^2 body surface area; maternal toxicity occurred at 4 times the MHRD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m^2 body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m^2 body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or, to effects on the dams (see RISPERDAL package insert).

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone's parent compound, risperidone *(see Clinical Considerations)*. Paliperidone has been detected in plasma in adult subjects up to 126 days after a single-dose administration of INVEGA SUSTENNA *[see Clinical Pharmacology (12.3)]*, and the clinical significance on the breastfed infant is not known. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA SUSTENNA and any potential adverse effects on the breastfed child from INVEGA SUSTENNA or from the mother's underlying condition.

Clinical Considerations

Infants exposed to INVEGA SUSTENNA through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

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

8.4 Pediatric Use

Safety and effectiveness of INVEGA SUSTENNA in patients < 18 years of age have not been established.

Juvenile Animal Studies

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

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of INVEGA SUSTENNA on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

Clinical studies of INVEGA SUSTENNA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients

with renal impairment *[see Clinical Pharmacology (12.3)]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, adjust dose based on renal function *[see Dosage and Administration (2.5)]*.

8.6 Renal Impairment

Use of INVEGA SUSTENNA is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Dose reduction is recommended for patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

INVEGA SUSTENNA has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to INVEGA SUSTENNA. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA SUSTENNA (paliperidone) is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

10 OVERDOSAGE

10.1 Human Experience

No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA. Because

INVEGA SUSTENNA is to be administered by healthcare professionals, the potential for overdosage by patients is low.

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

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the *OVERDOSAGE* section of the risperidone package insert.

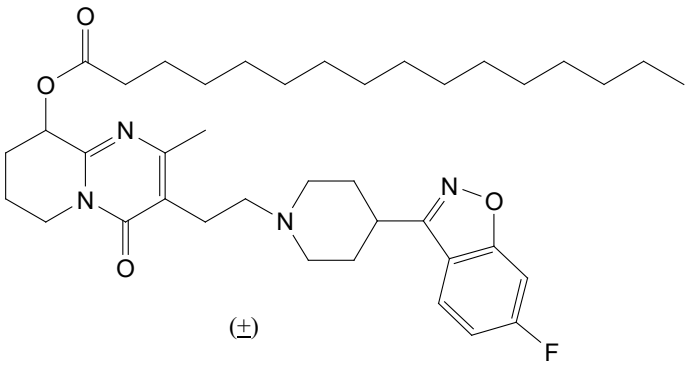
10.2 Management of Overdosage

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

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

11 DESCRIPTION

INVEGA SUSTENNA® contains paliperidone palmitate. The active ingredient, paliperidone, is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. INVEGA SUSTENNA contains a racemic mixture of (+)- and (-)- paliperidone palmitate. The chemical name is (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimadin-9-yl hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



(±)

Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.

INVEGA SUSTENNA is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in the following dose strengths of paliperidone palmitate (and deliverable volumes) of the single-dose prefilled syringes: 39 mg (0.25 mL), 78 mg (0.5 mL), 117 mg (0.75 mL), 156 mg (1.0 mL), and 234 mg (1.5 mL). The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20 (12 mg/mL), polyethylene glycol 4000 (30 mg/mL), citric acid monohydrate (5 mg/mL), disodium hydrogen phosphate anhydrous (5 mg/mL), sodium dihydrogen phosphate monohydrate (2.5 mg/mL), sodium hydroxide (2.84 mg/mL used as an alkalizing agent to set pH at 7), and water for injection.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone is unclear. However, the drug's therapeutic effect in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

In vitro, paliperidone acts as an antagonist at the central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptors with binding affinities (Ki values) of 1.6-2.8 nM for D_2 and 0.8-1.2 nM for $5HT_{2A}$ receptors. Paliperidone is also active as an antagonist at histamine H_1 and α_1 and α_2 adrenergic receptors with binding affinities of 32 nM, 4 nM, 17 nM, respectively. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar.

12.3 Pharmacokinetics

Absorption and Distribution

Due to its extremely low water solubility, the 1-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 13 days. The release of the drug starts as early as day 1 and lasts for as long as 126 days.

Following intramuscular injection of single doses (39 mg - 234 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 234 mg on day 1 and 156 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA SUSTENNA results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA SUSTENNA administration was dose-proportional over a 39 mg-234 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 78 mg. The mean steady-state peak:trough ratio for an INVEGA SUSTENNA dose of 156 mg was 1.8 following gluteal administration and 2.2 following deltoid administration.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6–1.8.

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

Metabolism and Elimination

In a study with oral immediate-release ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 10%

of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

The median apparent half-life of paliperidone following INVEGA SUSTENNA single-dose administration over the dose range of 39 mg - 234 mg ranged from 25 days - 49 days.

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

INVEGA SUSTENNA is designed to deliver paliperidone over a monthly period while extended-release oral paliperidone is administered on a daily basis. The initiation regimen for INVEGA SUSTENNA (234 mg/156 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

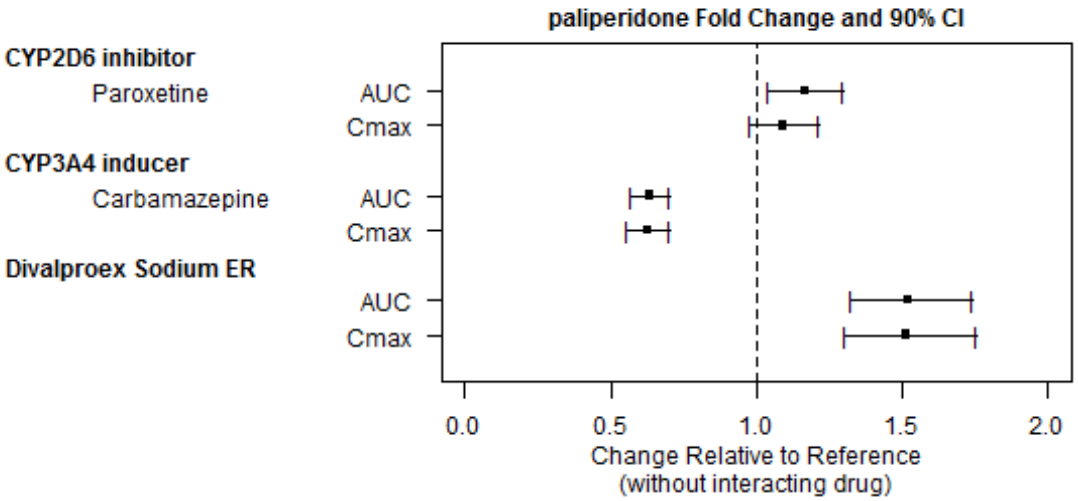
In general, overall initiation plasma levels with INVEGA SUSTENNA were within the exposure range observed with 6-12 mg extended-release oral paliperidone. The use of the INVEGA SUSTENNA initiation regimen allowed patients to stay in this exposure window of 6-12 mg extended-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from INVEGA SUSTENNA was lower relative to the variability determined from extended-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Drug Interaction Studies

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

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

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



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

After oral administration of paliperidone, the steady-state C_{max} and AUC of divalproex sodium extended-release tablets were not affected in 13 patients stabilized on divalproex sodium extended-release tablets. In a clinical study, subjects on stable doses of divalproex sodium extended-release tablets had comparable valproate average plasma concentrations when oral paliperidone extended-release tablets 3-15 mg/day was added to their existing divalproex sodium extended-release tablets treatment *[see Drug Interactions (7.2)]*.

In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism, however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone; they contribute to only a small fraction of total body clearance. *In vitro* studies demonstrated that paliperidone is a substrate of P-glycoprotein (P-gp) *[see Drug Interactions (7.2)]*.

In vitro studies in human liver microsomes demonstrated that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available, and the clinical relevance is unknown.

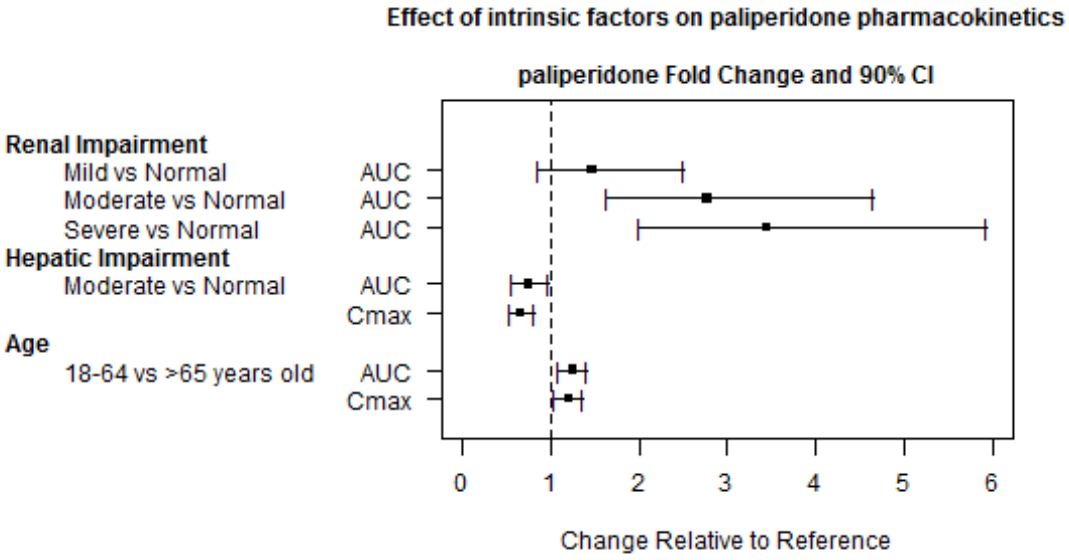
Studies in Specific Populations

No specific pharmacokinetic studies have been performed with INVEGA SUSTENNA in specific populations. All the information is obtained from studies with oral paliperidone or is based on the population pharmacokinetic modelling of oral paliperidone and INVEGA SUSTENNA. Exposures of paliperidone in specific populations (renal impairment, hepatic impairment and elderly) are summarized in Figure 2 *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*.

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

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

Figure 2: Effects of intrinsic factors on paliperidone pharmacokinetics.



Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone.

Slower absorption was observed in females in a population pharmacokinetic analysis. At apparent steady-state with INVEGA SUSTENNA, the trough concentrations were similar between males and females.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Carcinogenicity studies with risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone based on mg/m^2 body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear *[see Warnings and Precautions (5.7)]*.

Mutagenesis

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

Impairment of Fertility

No fertility studies were conducted with paliperidone palmitate.

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

The fertility of male rats was not affected at oral doses of paliperidone of up to 2 times the MRHD of 12 mg/day based on mg/m^2 body surface area, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration (0.6 to 10 times the MRHD of 16 mg/day for risperidone, based on mg/m^2 body surface area). Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

14 CLINICAL STUDIES

14.1 Schizophrenia

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

The efficacy of INVEGA SUSTENNA in the acute treatment of schizophrenia was evaluated in four short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia. The fixed doses of INVEGA SUSTENNA in these studies were given on days 1, 8, and 36 in the 9-week study, and additionally on day 64 of the 13-week studies, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance.

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

In Study 1 (PSY-3007), a 13-week study (n=636) comparing three fixed doses of INVEGA SUSTENNA (initial deltoid injection of 234 mg followed by 3 gluteal or deltoid doses of either 39 mg/4 weeks, 156 mg/4 weeks or 234 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA were superior to placebo in improving the PANSS total score.

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

In Study 3 (PSY-3004), a third 13-week study (n=513) comparing three fixed doses of INVEGA SUSTENNA (39 mg/4 weeks, 78 mg/4 weeks, and 156 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA were superior to placebo in improving the PANSS total score.

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

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

Table 14: Schizophrenia Short-term Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	INVEGA SUSTENNA (39 mg/4 weeks)*	86.9 (11.99)	-11.2 (1.69)	-5.1 (-9.01, -1.10)
	INVEGA SUSTENNA (156 mg/4 weeks)*	86.2 (10.77)	-14.8 (1.68)	-8.7 (-12.62, -4.78)
	INVEGA SUSTENNA (234 mg/4 weeks)*	88.4 (11.70)	-15.9 (1.70)	-9.8 (-13.71, -5.85)
	Placebo	86.8 (10.31)	-6.1 (1.69)	--
Study 2[b]	INVEGA SUSTENNA (78 mg/4 weeks)	89.9 (10.78)	-6.9 (2.50)	-3.5 (-8.73, 1.77)
	INVEGA SUSTENNA (156 mg/4 weeks)*	90.1 (11.66)	-10.4 (2.47)	-6.9 (-12.12, -1.68)
	Placebo	92.4 (12.55)	-3.5 (2.15)	--
Study 3	INVEGA SUSTENNA (39 mg/4 weeks)*	90.7 (12.25)	-19.8 (2.19)	-6.6 (-11.40, -1.73)
	INVEGA SUSTENNA (78 mg/4 weeks)*	91.2 (12.02)	-19.2 (2.19)	-5.9 (-10.76, -1.07)
	INVEGA SUSTENNA (156 mg/4 weeks)*	90.8 (11.70)	-22.5 (2.18)	-9.2 (-14.07, -4.43)
	Placebo	90.7 (12.22)	-13.3 (2.21)	--
Study 4	INVEGA SUSTENNA (78 mg/4 weeks)*	88.0 (12.39)	-4.6 (2.43)	-11.2 (-16.85, -5.57)
	INVEGA SUSTENNA (156 mg/4 weeks)*	85.2 (11.09)	-7.4 (2.45)	-14.0 (-19.51, -8.58)
	Placebo	87.8 (13.90)	6.6 (2.45)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

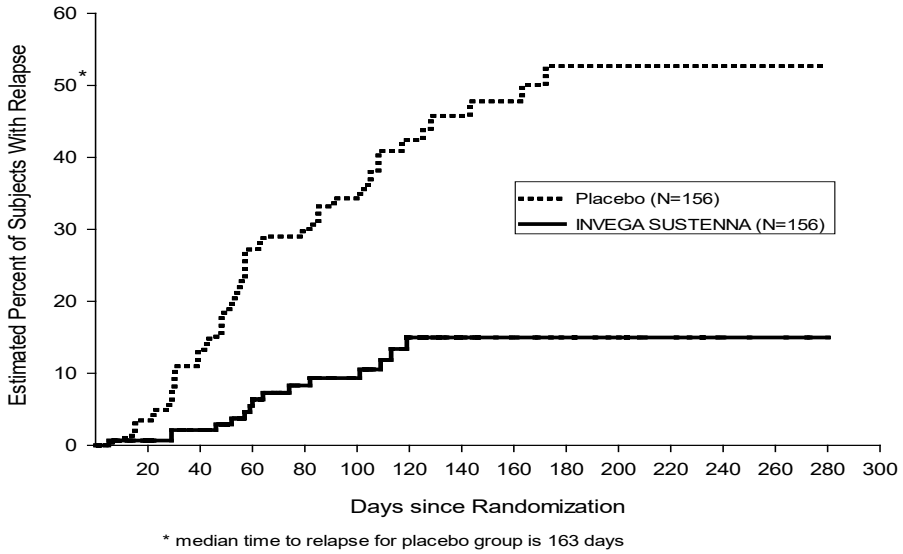
[b] Because an insufficient number of subjects received the 234 mg/4 weeks dose, results from this group are not included.

* $p<0.05$ (Doses statistically significantly superior to placebo).

Maintenance Monotherapy Treatment (Study 5: PSY-3001)

The efficacy of INVEGA SUSTENNA in maintaining symptomatic control in schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia. This study included a minimum 12-week, fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of INVEGA SUSTENNA they received during the stabilization phase, i.e., 39 mg, 78 mg, or 156 mg administered every 4 weeks, or to placebo. A total of 410 stabilized patients were randomized to either INVEGA SUSTENNA or to placebo until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items. The primary efficacy variable was time to relapse. A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA SUSTENNA compared to placebo, and the study was stopped early because maintenance of efficacy was demonstrated. Thirty-four percent (34%) of subjects in the placebo group and 10% of subjects in the INVEGA SUSTENNA group experienced a relapse event. There was a statistically significant difference between the treatment groups in favor of INVEGA SUSTENNA. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 3. The time to relapse for subjects in the placebo group was statistically significantly shorter than for the INVEGA SUSTENNA group. An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

Figure 3: Kaplan-Meier Plot of Cumulative Proportion of Subjects with Relapse Over Time (Schizophrenia Study 5)



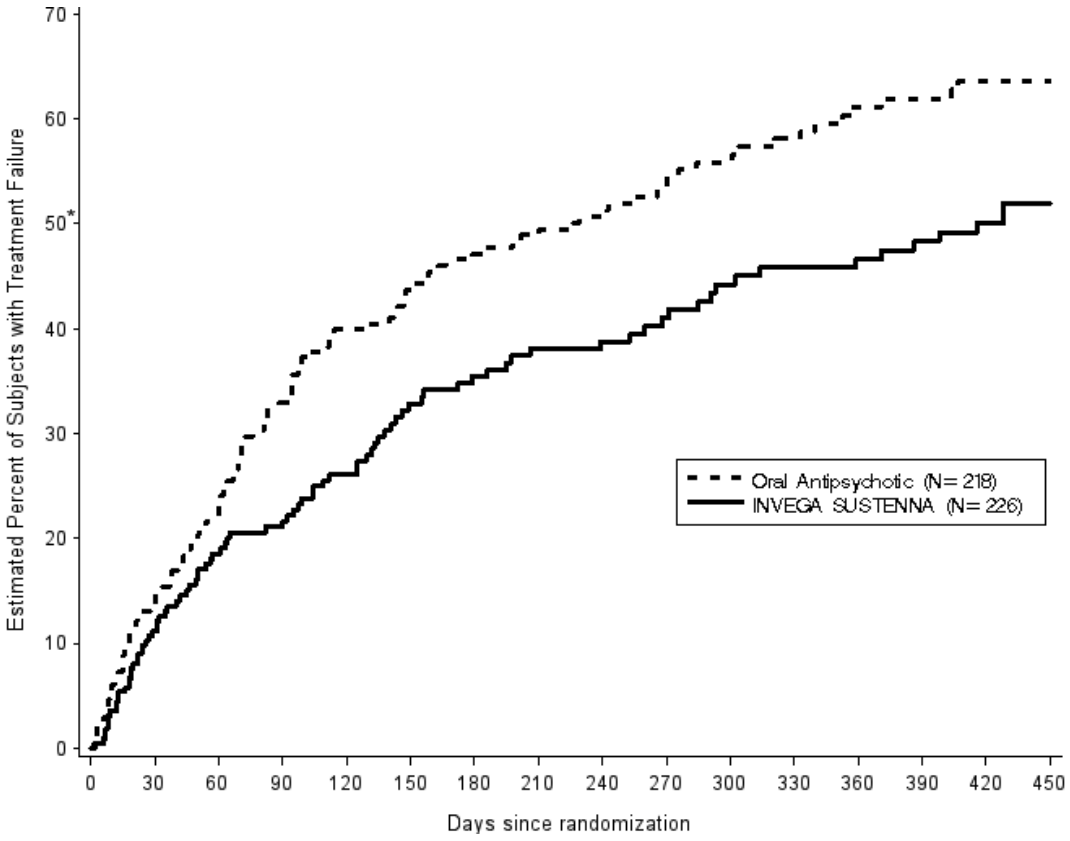
Long-Term Comparative Monotherapy Treatment versus Oral Antipsychotic Therapy (Study 6: SCH-3006)

The efficacy of INVEGA SUSTENNA in delaying time to treatment failure compared with selected oral antipsychotic medications was established in a long-term, randomized, flexible-dose study in subjects with schizophrenia and a history of incarceration. Subjects were screened for up to 14 days followed by a 15-month treatment phase during which they were observed for treatment failure.

The primary endpoint was time to first treatment failure. Treatment failure was defined as one of the following: arrest and/or incarceration; psychiatric hospitalization; discontinuation of antipsychotic treatment because of safety or tolerability; treatment supplementation with another antipsychotic because of inadequate efficacy; need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization; discontinuation of antipsychotic treatment because of inadequate efficacy; or suicide. Treatment failure was determined by an Event Monitoring Board (EMB) that was blinded to treatment assignment. A total of 444 subjects were randomly assigned to either INVEGA SUSTENNA (N = 226; median dose 156 mg) or one of up to seven pre-specified, flexibly-dosed, commonly prescribed oral antipsychotic medications (N = 218; aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone). The selection of the oral antipsychotic medication was determined to be appropriate for the patient by the investigator. A statistically significantly longer time to first treatment failure was seen for INVEGA SUSTENNA compared with oral antipsychotic medications. The median time to treatment failure was 416 days and 226 days for INVEGA SUSTENNA and antipsychotic medications, respectively. A Kaplan-Meier plot of time to first treatment failure is shown in

Figure 4. The frequencies of first treatment failure events by type are shown in Table 15. The time to first arrest and/or incarceration or psychiatric hospitalization was also statistically significantly longer for the INVEGA SUSTENNA group compared to the oral antipsychotic group.

Figure 4: Kaplan-Meier Plot of Time to First Treatment Failure in a Long-Term, Randomized, Flexible-Dose Study in Subjects with Schizophrenia and a History of Incarceration (Schizophrenia Study 6)



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

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

Event Type	INVEGA SUSTENNA N=226 frequency (%)	Oral Antipsychotics N=218 frequency (%)	Hazard Ratio[a] [95% CI]
First Treatment Failures	90 (39.8%)	117 (53.7%)	0.70 [0.53, 0.92]
First Treatment Failure Component Events			
▪ Arrest and/or incarceration	48 (21.2%)	64 (29.4%)	
▪ Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	
▪ Discontinuation of antipsychotic treatment because of safety or tolerability	15 (6.6%)	8 (3.7%)	
▪ Treatment supplementation with another antipsychotic because of inadequate efficacy	5 (2.2%)	6 (2.8%)	
▪ Need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	
▪ Discontinuation of antipsychotic treatment because of inadequate efficacy	1 (0.4%)	9 (4.1%)	
▪ Suicide	0	0	
Arrest and/or Incarceration or Psychiatric Hospitalization Events, regardless of whether they were first events[b]	76 (33.6%)	98 (45.0%)	0.70 [0.52, 0.94]

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

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

14.2 Schizoaffective Disorder

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

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

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

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

A total of 334 subjects who met stabilization criteria for 12 consecutive weeks were randomized (1:1) to continue the same dose of INVEGA SUSTENNA or to placebo in the 15-month, double-blind, maintenance period. For the 164 subjects who were randomized to INVEGA SUSTENNA, dose distribution was 78 mg (4.9%), 117 mg (9.8%), 156 mg (47.0%), and 234 mg (38.4%). The primary efficacy variable was time to relapse. Relapse was defined as the first occurrence of one or more of the following: 1) psychiatric hospitalization; 2) intervention employed to avert hospitalization; 3) clinically significant self-injury, suicidal or homicidal ideation or violent behavior; 4) a score of ≥6 (if the score was ≤4 at randomization) of any of the individual PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, or poor impulse control; 5) on two consecutive assessments within 7 days: ≥25% increase (if the score at randomization was >45) or ≥10-point increase (if the score at randomization was ≤45) in total PANSS score; a score of ≥5 (if the score was ≤3 at randomization) of any of the individual PANSS items: delusions, conceptual disorganization, hallucinatory behavior, excitement, suspiciousness/persecution, hostility, uncooperativeness, or poor impulse control; an increase of ≥2 points (if the score was 1 [not ill] to 3 [mildly ill] at randomization) or increase of ≥1 point (if the score was ≥4 [moderately ill or worse] at randomization) in CGI-S-SCA overall score.

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

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

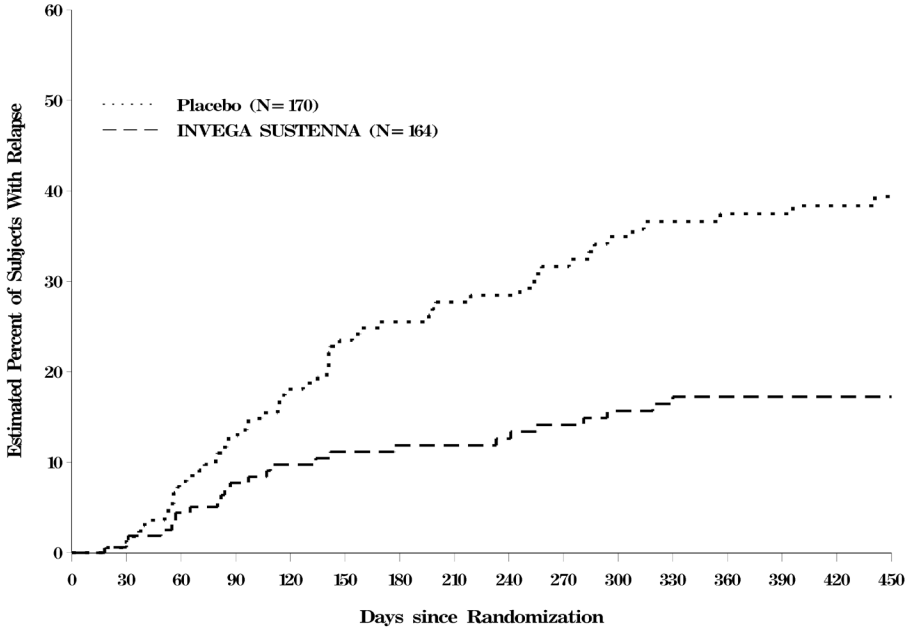


Table 16 summarizes the number of subjects with relapse in the overall population, by subgroup (monotherapy vs. adjunctive therapy), and by symptom type at the first occurrence of relapse.

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

	Number (Percent) of Subjects Who Relapsed	
	Placebo N=170	**INVEGA SUSTENNA N=164**
All Subjects	57 (33.5%)	25 (15.2%)
Monotherapy subset	N=73	N=78
	24 (32.9%)	9 (11.5%)
Adjunct to Antidepressants or	N=97	N=86
Mood Stabilizer subset	33 (34.0%)	16 (18.6%)
Psychotic Symptoms[a]	53 (31.2%)	21 (12.8%)
Mood Symptoms[b]		
Any Mood Symptoms	48 (28.2%)	18 (11.0%)
Manic	16 (9.4%)	5 (3.0%)
Depressive	23 (13.5%)	8 (4.9%)
Mixed	9 (5.3%)	5 (3.0%)

[a] 8 subjects experienced a relapse without psychotic symptoms.
[b] 16 subjects experienced a relapse without any mood symptoms.

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, and 234 mg/1.5 mL paliperidone palmitate in single-dose prefilled syringes. The single-use kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

39 mg paliperidone palmitate kit	(NDC 50458-560-01)
78 mg paliperidone palmitate kit	(NDC 50458-561-01)
117 mg paliperidone palmitate kit	(NDC 50458-562-01)
156 mg paliperidone palmitate kit	(NDC 50458-563-01)
234 mg paliperidone palmitate kit	(NDC 50458-564-01)

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact their healthcare provider or report to the emergency room if they experience signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status including delirium, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

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

Metabolic Changes

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

Orthostatic Hypotension

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

Leukopenia/Neutropenia

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

Hyperprolactinemia

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

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that INVEGA SUSTENNA therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Priapism

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

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.15)]*.

Concomitant Medication

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

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

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

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

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

INVEGA SUSTENNA (paliperidone palmitate) Extended-Release Injectable Suspension

Product of Ireland
Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560, USA
For patent information: www.janssenpatents.com

PATIENT INFORMATION
INVEGA SUSTENNA® (in-VAY-guh suss-TEN-uh)
(paliperidone palmitate)
Extended-Release Injectable Suspension

What is the most important information I should know about INVEGA SUSTENNA?

INVEGA SUSTENNA can cause serious side effects, including:

- **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** INVEGA SUSTENNA is not for treating dementia-related psychosis.

What is INVEGA SUSTENNA?

INVEGA SUSTENNA is a prescription medicine given by injection by a healthcare professional and used to treat:

- schizophrenia in adults
- schizoaffective disorder in adults either alone or with other medicines such as mood stabilizers or antidepressants

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

Who should not receive INVEGA SUSTENNA?
Do not receive INVEGA SUSTENNA if you:

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

What should I tell my healthcare provider before receiving INVEGA SUSTENNA?

Before you receive INVEGA SUSTENNA, tell your healthcare provider about all your medical conditions, including if you:

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

appetite, difficulty breathing, or abnormal movement of arms and legs. Let your healthcare provider know if these symptoms occur.

- are breastfeeding or plan to breastfeed. INVEGA SUSTENNA can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive INVEGA SUSTENNA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show to your healthcare provider or pharmacist when you get a new medicine.

How will I receive INVEGA SUSTENNA?

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

What should I avoid while receiving INVEGA SUSTENNA?

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

What are the possible side effects of INVEGA SUSTENNA?

INVEGA SUSTENNA may cause serious side effects, including:

- See **"What is the most important information I should know about INVEGA SUSTENNA"**
- **stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious problem that can happen in people who receive INVEGA SUSTENNA. NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have any of these symptoms:
  - high fever
  - severe muscle stiffness
  - confusion
  - loss of consciousness
  - changes in your breathing, heartbeat and blood pressure
- **problems with your heartbeat.** These heart problems can cause death. Call your healthcare provider right away if you have any of these symptoms:
  - passing out or feeling like you will pass out
  - dizziness
  - feeling as if your heart is pounding or missing beats
- **uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)**

- **metabolic changes.** Metabolic changes may include high blood sugar (hyperglycemia), diabetes mellitus and changes in the fat levels in your blood (dyslipidemia), and weight gain.
- **low blood pressure and fainting**
- **changes in your blood cell counts**
- **high level of prolactin in your blood (hyperprolactinemia).** INVEGA SUSTENNA may cause a rise in the blood levels of a hormone called prolactin (hyperprolactinemia) that may cause side effects including missed menstrual periods, leakage of milk from the breasts, development of breasts in men, or problems with erection.
- **problems thinking clearly and moving your body**
- **seizures**
- **difficulty swallowing that can cause food or liquid to get into your lungs**
- **prolonged or painful erection lasting more than 4 hours.** Call your healthcare provider or go to your nearest emergency room right away if you have an erection that lasts more than 4 hours.
- **problems with control of your body temperature especially when you exercise a lot or spend time doing things that make you warm. It is important for you to drink water to avoid dehydration.**

The most common side effects of INVEGA SUSTENNA include: injection site reactions, sleepiness or drowsiness, dizziness, feeling restlessness or needing to be constantly moving, abnormal muscle movements including tremor (shaking), shuffling, uncontrolled involuntary movements, and abnormal movements of your eyes.

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

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

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

General information about the safe and effective use of INVEGA SUSTENNA.

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

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

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

What are the ingredients in INVEGA SUSTENNA?

Active ingredient: paliperidone palmitate

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

Manufactured by: Janssen Pharmaceutica NV, Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560, USA
For patent information: www.janssenpatents.com

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: September 2024

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA TRINZA safely and effectively. See full prescribing information for INVEGA TRINZA.

INVEGA TRINZA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2006

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA TRINZA is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.5, 2.8)	9/2024
Warnings and Precautions (5.10)	1/2025

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

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

----------DOSAGE AND ADMINISTRATION----------

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

INVEGA TRINZA Doses for Adult Patients Adequately Treated with INVEGA SUSTENNA

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

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

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

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

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

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). INVEGA TRINZA is not approved for use in patients with dementia-related psychosis (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation of drug and close monitoring (5.3)
- *QT Prolongation:* Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- *Tardive Dyskinesia:* Discontinue drug if clinically appropriate (5.5)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  - *Hyperglycemia and Diabetes Mellitus:* Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  - *Dyslipidemia:* Undesirable alterations have been observed. (5.6)
  - *Weight Gain:* Significant weight gain has been reported. Monitor weight gain. (5.6)
- *Orthostatic Hypotension and Syncope:* Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.9)
- *Hyperprolactinemia:* Prolactin elevations occur and persist during chronic administration (5.10)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.11)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. (6)

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

----------DRUG INTERACTIONS----------

Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for INVEGA TRINZA. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

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

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

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA TRINZA is not approved for use in patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

INVEGA TRINZA should be administered once every 3 months.

Each injection must be administered only by a healthcare professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **It is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension. Inject INVEGA TRINZA within 5 minutes of shaking vigorously** *[see Dosage and Administration (2.8)]***.**

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

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

Deltoid Injection

The recommended needle size for administration of INVEGA TRINZA into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

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

Gluteal Injection

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

Incomplete Administration

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

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

2.2 Schizophrenia

Adults

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

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

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

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

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

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

2.3 Missed Doses

Dosing Window

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

Missed Dose 3½ Months to 4 Months Since Last Injection

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

Missed Dose 4 Months to 9 Months Since Last Injection

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

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

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

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

Missed Dose Longer than 9 Months Since Last Injection

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

after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

2.4 Use with Risperidone or with Oral Paliperidone

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

2.5 Dosage Recommendations in Patients with Renal Impairment

INVEGA TRINZA has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), adjust dosage and stabilize the patient using the 1-month paliperidone palmitate extended-release injectable suspension, then transition to INVEGA TRINZA *(see Table 1) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].* Refer to the Prescribing Information of the 1-month paliperidone palmitate extended-release injectable suspension product for the recommended dosage in patients with mild renal impairment.

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

2.6 Switching from INVEGA TRINZA to the 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension

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

Table 3. Conversion from INVEGA TRINZA to INVEGA SUSTENNA

If the Last Dose of INVEGA TRINZA is:	Initiate[a] INVEGA SUSTENNA 3 Months Later at the Following Dose:
273 mg	78 mg
410 mg	117 mg
546 mg	156 mg
819 mg	234 mg

[a] The initiation dosing as described in the prescribing information for INVEGA SUSTENNA is not required.

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

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

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

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

2.8 Instructions for Preparation and Administration

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

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

Important

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

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

Read complete instructions prior to use.

Dosing

This medication should be administered **once every 3 months**.

Preparation

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

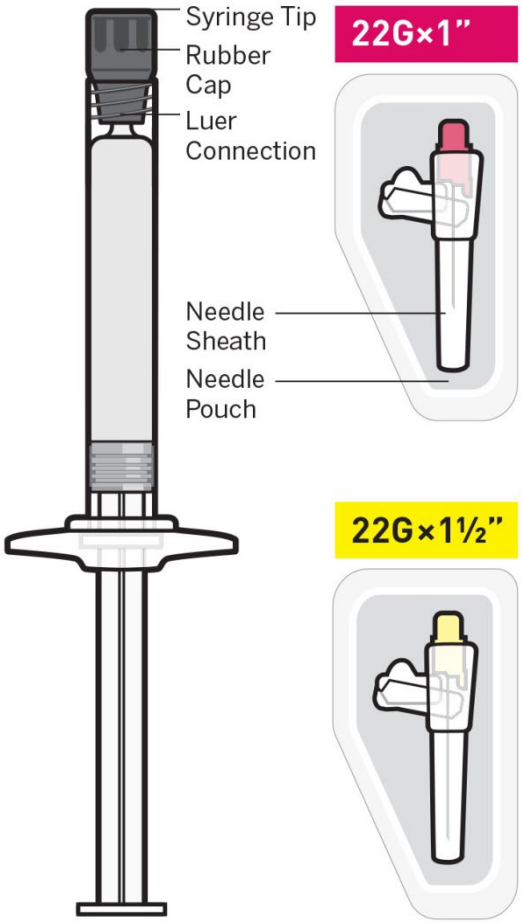
INVEGA TRINZA requires longer and more vigorous shaking than INVEGA SUSTENNA (1-month paliperidone palmitate extended-release injectable suspension). Shake the syringe vigorously, with the syringe tip pointing up, for **at least 15 seconds within 5 minutes prior to administration** (see Step 2).

Thin Wall Safety Needle Selection

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

Dose pack contents

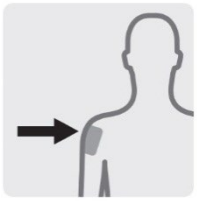
Prefilled Syringe	Thin Wall Safety Needles



1 Select needle

Needle selection is determined by injection area and patient weight.

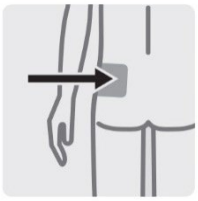
If administering a **Deltoid** injection



If patient weighs:
Less than 90 kg
pink hub
22G × 1”

90 kg or more
yellow hub
22G × 1½”

If administering a **Gluteal** injection

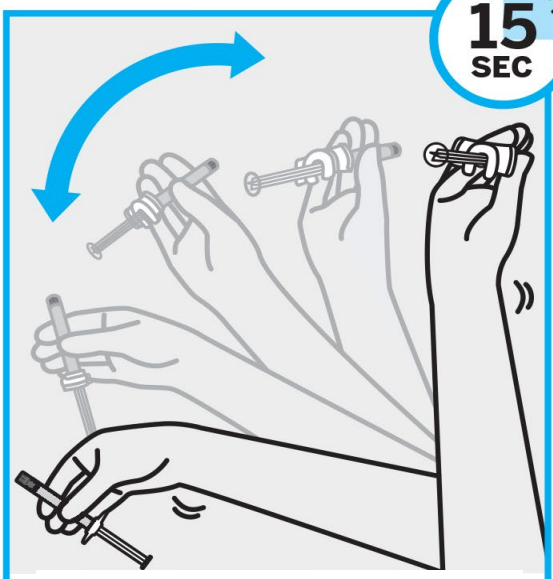


If patient weighs:
Less than 90 kg
yellow hub
22G × 1½”

90 kg or more
yellow hub
22G × 1½”

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

2 Prepare for injection



SHAKE VIGOROUSLY for at least 15 seconds

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

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

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

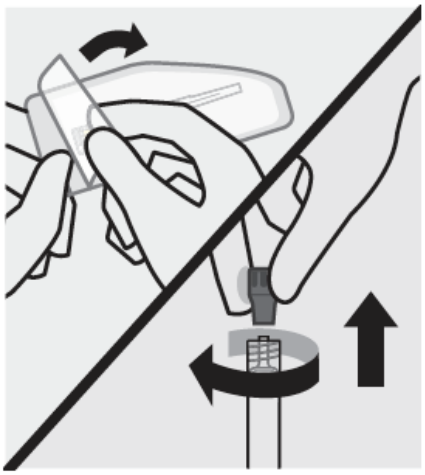
Check suspension

After shaking the syringe for at least 15 seconds, check the liquid in the viewing window.

The suspension should appear uniform and milky white in color.

It is also normal to see small air bubbles.

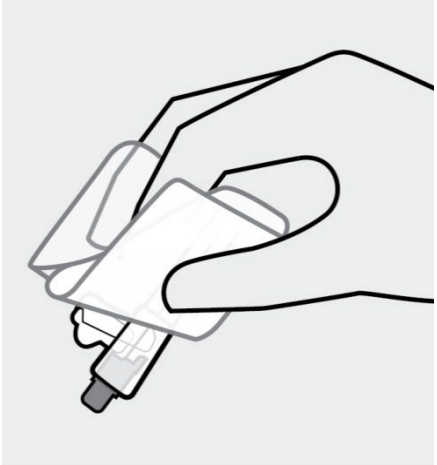
Open needle pouch and remove cap



First, open needle pouch by peeling the cover back half way. Place on a clean surface.

Then, holding the syringe upright, twist and pull the rubber cap to remove.

Grasp needle pouch

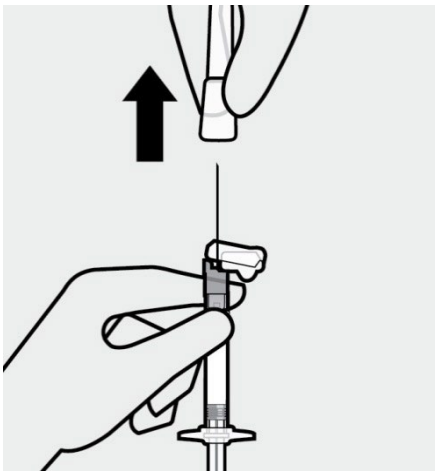


Fold back needle cover and plastic tray. Then, firmly grasp the needle sheath through the pouch, as shown.

Attach needle

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

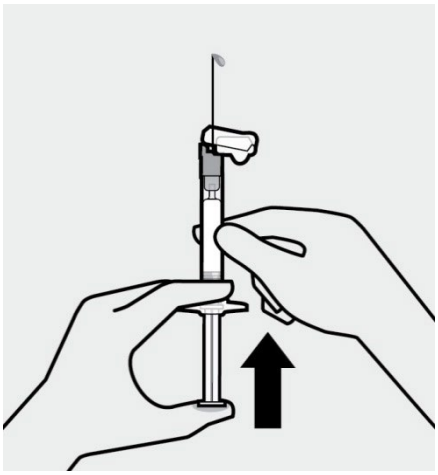
Remove needle sheath



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

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

Remove air bubbles

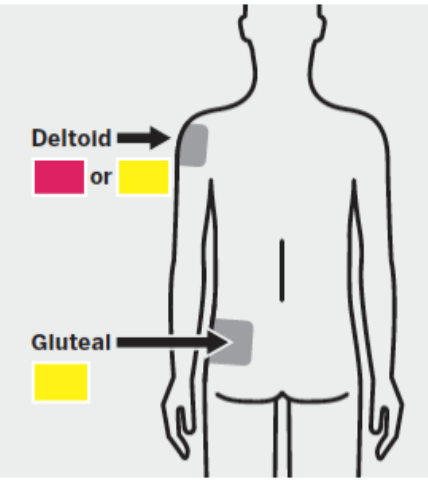


Hold the syringe upright and tap gently to make any air bubbles rise to the top.

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

3 Inject

Inject dose

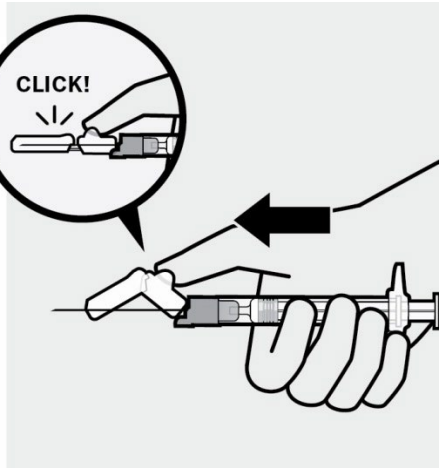


Slowly inject the entire contents of the syringe intramuscularly, deep into the selected deltoid or gluteal muscle.

Do not administer by any other route.

4 After injection

Secure needle



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

Dispose properly

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA TRINZA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, the 1-month paliperidone palmitate extended-release injectable suspension, or INVEGA TRINZA in elderly patients with dementia. These medications are not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone.

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

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

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter Thorough QT study with oral paliperidone in adult patients, and in four fixed-dose efficacy studies and one maintenance study of the 1-month paliperidone palmitate injectable product.

In the Thorough QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD (QT interval corrected for heart rate using the population specified linear derived method) of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$=113 ng/mL) was approximately 2-fold the exposure with the maximum recommended 819 mg dose of INVEGA TRINZA administered in the deltoid muscle (predicted median $C_{max\ ss}$=56 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$=35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the four fixed-dose efficacy studies of the 1-month paliperidone palmitate injectable product, no subject had a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

In the long-term maintenance trial of INVEGA TRINZA in subjects with schizophrenia, an increase in QTcLD exceeding 60 msec was observed in 1 subject (< 1%) in the open-label phase, no subject had an increase in QTcLD exceeding 60 msec after treatment with INVEGA TRINZA

in the double-blind phase, and no subject had a QTcLD value of > 480 msec at any point in the study.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, INVEGA TRINZA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

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

5.6 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

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

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

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

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

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

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

Dyslipidemia

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

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

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

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

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

Weight Gain

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

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

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

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

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

5.7 Orthostatic Hypotension and Syncope

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

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

5.8 Falls

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

5.9 Leukopenia, Neutropenia, and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA TRINZA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue INVEGA TRINZA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.

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

Prior to the double-blind phase (during the 29-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline in males (N=368) were 17.1 (13.55) ng/mL and 51.6 (40.85) ng/mL in females (N=122). Twelve weeks after a single injection of INVEGA TRINZA at the end of the open-label phase, mean (SD) prolactin values were 25.8 (13.49) ng/mL in males (N=322) and 70.6 (40.23) ng/mL in females (N=107). During the open-label phases 27% of females and 42% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (7.9% vs. 3.7%). Amenorrhea (4.7%) and galactorrhea (3.1%) were the most commonly observed (≥3%) potentially prolactin-related adverse reactions in females. Among males in the open-label phase, no potentially prolactin-related adverse reaction was observed with a rate greater than 3%.

5.11 Potential for Cognitive and Motor Impairment

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

5.12 Seizures

In the long-term maintenance trial there were no reports of seizures or convulsions. In the pivotal clinical studies with the 1-month paliperidone palmitate extended-release injectable suspension which included four fixed-dose, double-blind, placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with the 1-month injection experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA TRINZA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.13 Dysphagia

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

5.14 Priapism

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

5.15 Disruption of Body Temperature Regulation

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

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic changes *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*

- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.9)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.10)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Priapism *[see Warnings and Precautions (5.14)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

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

Patient Exposure

The data described in this section include data from two clinical trials. One is a long-term maintenance trial, in which 506 subjects with schizophrenia received several doses of the 1-month paliperidone palmitate extended-release injectable suspension during the open-label phase, of which 379 subjects continued to receive a single injection of INVEGA TRINZA during the open-label phase, and 160 subjects were subsequently randomized to receive at least one dose of INVEGA TRINZA and 145 subjects received placebo during the double-blind placebo-controlled phase. The mean (SD) duration of exposure during the double-blind phase was 150 (79) days in the placebo group and 175 (90) days in the INVEGA TRINZA group. The other is a Phase 1 study (N=308), which included patients with schizophrenia who received a single injection of INVEGA TRINZA concomitantly with other oral antipsychotics.

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

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

Discontinuation of Treatment Due to Adverse Events: The percentages of subjects who discontinued due to adverse events in the long-term maintenance trial were 5.1% during the open-

label phase. During the double-blind phase, no INVEGA TRINZA-treated subject and one placebo-treated subject discontinued due to adverse events.

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

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

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

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

[a] During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA prior to randomization to either placebo or INVEGA TRINZA in the subsequent double-blind phase *[see Clinical Studies (14)]*.

[b] The following terms were combined:

Injection site reaction includes Injection site reaction, Injection site erythema, Injection site extravasation, Injection site induration, Injection site inflammation, Injection site mass, Injection site nodule, Injection site pain, Injection site swelling.

Weight increased includes Weight increased, Waist circumference increased.

Upper respiratory tract infection includes Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Rhinitis.

Akathisia includes Akathisia, Restlessness.

Parkinsonism includes Parkinsonism, Cogwheel rigidity, Drooling, Extrapyramidal disorder, Hypokinesia, Muscle rigidity, Muscle tightness, Musculoskeletal stiffness, Salivary hypersecretion.

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

Demographic Differences

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

Extrapyramidal Symptoms (EPS)

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

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

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

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

[b] 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)

[c] For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at any time

[d] 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

[e] Percent of subjects who received anticholinergic medications to treat EPS

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

	Percentage of Subjects		
	Open-label Phase	Double-blind Phase	
EPS Group	Paliperidone Palmitate[a] (N=506) %	Placebo (N=145) %	INVEGA TRINZA (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

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

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

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

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

Dystonia

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

Pain Assessment and Local Injection Site Reactions

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

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

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

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

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

Cardiac disorders: tachycardia

Gastrointestinal disorders: nausea, vomiting

Metabolism and nutrition disorders: hyperinsulinemia

Psychiatric disorders: anxiety

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

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

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

Ear and labyrinth disorders: vertigo

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

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

General disorders and administration site conditions: asthenia, fatigue

Immune system disorders: hypersensitivity

Investigations: electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, increased appetite

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

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

Psychiatric disorders: agitation, nightmare

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

Respiratory, thoracic and mediastinal disorders: cough

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

Vascular disorders: hypertension

Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

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

Cardiac disorders: bundle branch block left, sinus arrhythmia

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

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

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

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

Psychiatric disorders: sleep disorder

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

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

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: hypotension, ischemia

6.2 Postmarketing Experience

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

Cases of anaphylactic reaction after injection with the 1-month paliperidone palmitate extended-release suspension have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the *Adverse Reactions (6)* sections of the package inserts for those products.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with INVEGA TRINZA

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

Table 11. Clinically Important Drug Interactions with INVEGA TRINZA

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

7.2 Drugs Having No Clinically Important Interactions with INVEGA TRINZA

Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA TRINZA is required when administered concomitantly with valproate *[see Clinical Pharmacology (12.3)].* Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA TRINZA *[see Clinical Pharmacology (12.3)]*.

Pharmacokinetic interaction between lithium and INVEGA TRINZA is unlikely.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely. *[See Clinical Pharmacology (12.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA TRINZA during pregnancy *(see Clinical Considerations)*. Paliperidone has been detected in plasma in adult subjects up to 18 months after a single-dose administration of INVEGA TRINZA *[see Clinical Pharmacology (12.3)]*, and the clinical significance of INVEGA TRINZA administered before pregnancy or anytime during pregnancy is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse

outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In animal reproduction studies, there were no treatment related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 10 times the maximum recommended human dose (MRHD) of 234 mg paliperidone based on mg/m^2 body surface area. There were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg of paliperidone based on mg/m^2 body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

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

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with 1-month paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 3 times the MRHD of 819 mg of the 3-month paliperidone palmitate extended-release injectable suspension based on mg/m^2 body surface area.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m^2 body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m^2 body surface area; maternal toxicity occurred at 4 times the MHRD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m^2 body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m^2 body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or, to effects on the dams (see RISPERDAL package insert).

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant, or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone's parent compound, risperidone *(see Clinical Considerations)*. Paliperidone has been detected in plasma in adult subjects up to 18 months after a single-dose administration of INVEGA TRINZA, and the clinical significance on the breastfed infant is not known *[see Clinical Pharmacology (12.3)].* The

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

Clinical Considerations

Infants exposed to INVEGA TRINZA through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of paliperidone (D_2 receptor antagonism), treatment with INVEGA TRINZA may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.10)]*.

8.4 Pediatric Use

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

Juvenile Animal Studies

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

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

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen

at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of INVEGA TRINZA on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

Clinical studies of INVEGA TRINZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment *[see Clinical Pharmacology (12.3)]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, monitor renal function and adjust dosage *[see Dosage and Administration (2.5)]*.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

INVEGA TRINZA has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to INVEGA TRINZA. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA TRINZA (paliperidone) is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

10 OVERDOSAGE

10.1 Human Experience

No cases of overdose were reported in premarketing studies with paliperidone palmitate injection. Because INVEGA TRINZA is to be administered by healthcare professionals, the potential for overdosage by patients is low.

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

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the *OVERDOSAGE* section of the risperidone package insert.

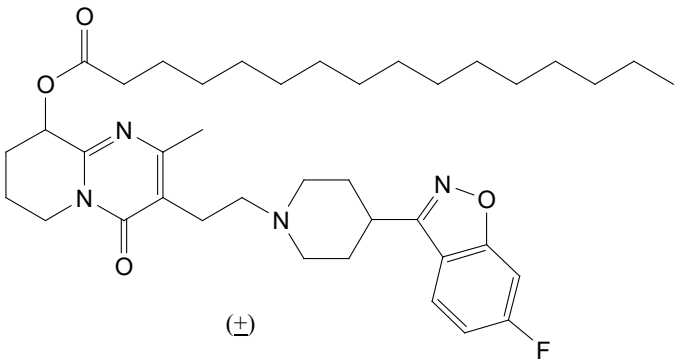
10.2 Management of Overdosage

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

Consider the prolonged-release characteristics of INVEGA TRINZA and the long apparent half-life of paliperidone when assessing treatment needs and recovery.

11 DESCRIPTION

INVEGA TRINZA® contains paliperidone palmitate. The active ingredient, paliperidone, is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. INVEGA TRINZA contains a racemic mixture of (+)- and (-)- paliperidone palmitate. The chemical name is (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimadin-9-yl hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



(±)

Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.

INVEGA TRINZA is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate in single-dose prefilled syringes. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 175 mg, 263 mg, 350 mg, and 525 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20 (10 mg/mL), polyethylene glycol 4000 (75 mg/mL), citric acid monohydrate (7.5 mg/mL), sodium dihydrogen phosphate monohydrate (6 mg/mL), sodium hydroxide (5.4 mg/mL used as an alkalizing agent to set the pH at 7), and water for injection.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone is unclear. However, the drug's therapeutic effect in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

In vitro, paliperidone acts as an antagonist at the central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptors with binding affinities (Ki values) of 1.6-2.8 nM for D_2 and 0.8-1.2 nM for $5HT_{2A}$ receptors. Paliperidone is also active as an antagonist at histamine H_1 and α_1 and α_2 adrenergic receptors with binding affinities of 32 nM, 4 nM, 17 nM, respectively. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar.

12.3 Pharmacokinetics

Absorption and Distribution

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

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

The plasma protein binding of racemic paliperidone is 74%.

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

Metabolism and Elimination

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

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

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

INVEGA TRINZA is designed to deliver paliperidone over a 3-month period, while 1-month paliperidone palmitate injection is administered on a monthly basis. INVEGA TRINZA, when administered at doses that are 3.5-fold higher than the corresponding dose of 1-month paliperidone palmitate injection, results in paliperidone exposures similar to those obtained with corresponding monthly doses of 1-month paliperidone palmitate injection and corresponding once daily doses of paliperidone extended-release tablets. The exposure range for INVEGA TRINZA is encompassed within the exposure range for the approved dose strengths of paliperidone extended-release tablets.

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

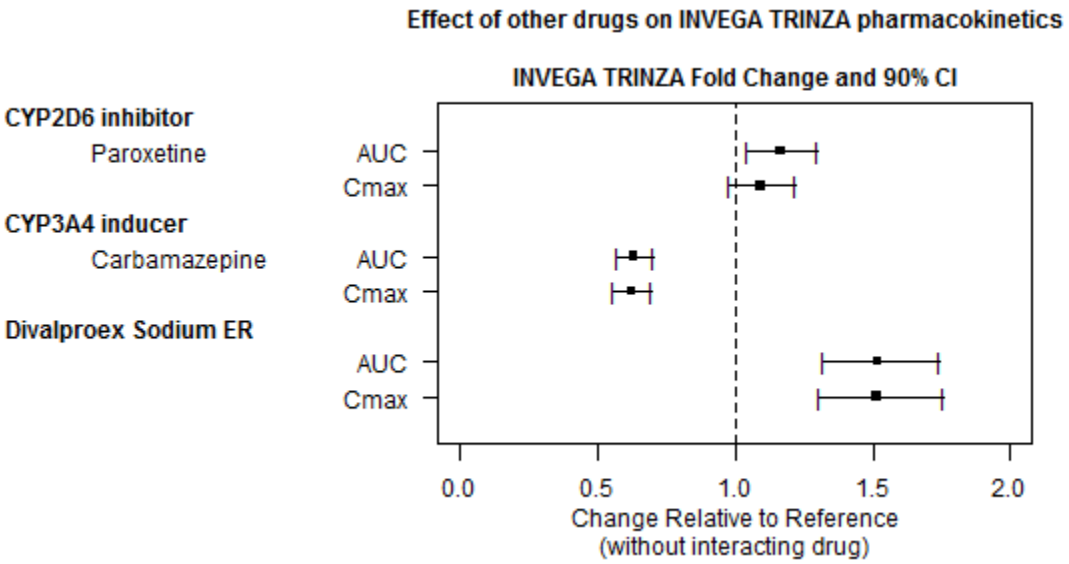
Drug Interaction Studies

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

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

C_{max} and AUC values at steady-state was observed (see Figure 1). Higher doses of paroxetine have not been studied. The clinical relevance is unknown. After oral administration, a decrease in mean C_{max} and AUC values at steady state is expected when patients are treated with carbamazepine, a strong inducer of both CYP3A4 and P-gp *[see Drug Interactions (7.1)]*. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone.

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



In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism, however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone; they contribute to only a small fraction of total body clearance. *In vitro* studies demonstrated that paliperidone is a substrate of P-glycoprotein (P-gp) *[see Drug Interactions (7.2)]*.

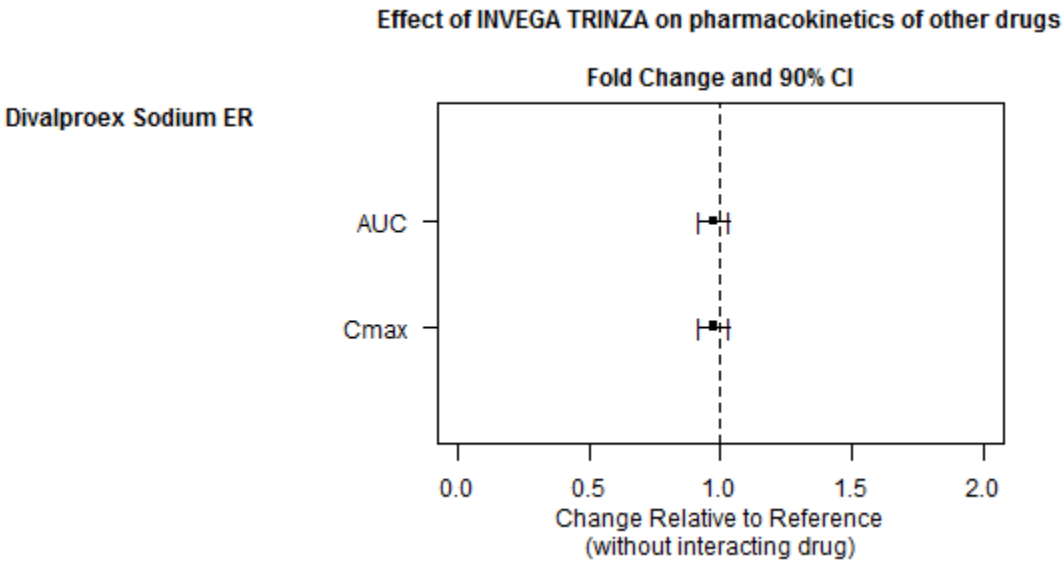
In vitro studies in human liver microsomes demonstrated that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available, and the clinical relevance is unknown.

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

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

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



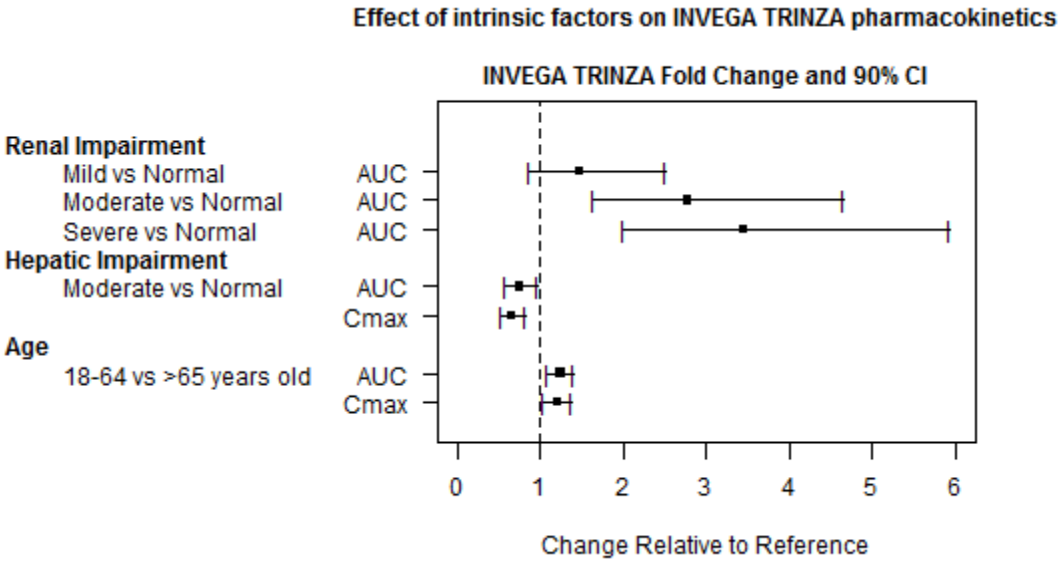
Studies in Specific Populations

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

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

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

Figure 3: Effects of intrinsic factors on paliperidone pharmacokinetics.



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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

The carcinogenic potential of intramuscularly injected 1-month paliperidone palmitate extended-release injectable suspension was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg/kg/month, which is 0.2, 0.6, and 1 times, respectively, the MRHD of 819 mg of INVEGA TRINZA based on mg/m^2 body surface area. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 0.6 and 1 times the MRHD based on mg/m^2 body surface area. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies with risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone based on mg/m^2 body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear *[see Warnings and Precautions (5.7)]*.

Mutagenesis

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

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

Impairment of Fertility

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

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

The fertility of male rats was not affected at oral doses of paliperidone of up to 2 times the MRHD of 12 mg/day based on mg/m^2 body surface area, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration (0.6 to 10 times the MRHD of 16 mg/day for risperidone, based on mg/m^2 body surface area).

Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

13.2 Animal Toxicology and/or Pharmacology

Injection site toxicity was assessed in minipigs injected intramuscularly with the 3-month paliperidone palmitate extended-release injectable suspension at doses up to 819 mg, which is equal to the MRHD. Injection site inflammatory reactions were greater and more advanced than reactions to the 1-month paliperidone palmitate extended-release injectable suspension. Reversibility of these findings was not examined.

14 CLINICAL STUDIES

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

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

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

This study consisted of the following three treatment periods:

- A 17-week flexible-dose open-label period with the 1-month paliperidone palmitate (first part of a 29-week open-label stabilization phase). A total of 506 patients entered this phase of the study. Dosing of the 1-month paliperidone palmitate was individualized based on symptom response, tolerability, and previous medication history. Specifically, the dose could be adjusted at the week 5 and 9 injections and the injection site could be deltoid or gluteal. The week 13 dose had to be the same as the week 9 dose. Patients had to be clinically stable at the end of this period before receiving INVEGA TRINZA at the week 17 visit. Clinical stability was defined as achieving a PANSS total score <70 at week 17. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210.

- A 12-week open-label treatment period with INVEGA TRINZA (second part of a 29-week open-label stabilization phase). A total of 379 patients received a single-dose of INVEGA TRINZA which was a 3.5 multiple of the last dose of the 1-month paliperidone palmitate. Patients had to remain clinically stable before entry into the next period (double-blind). Clinical stability was defined as achieving a PANSS total score <70 and scores of ≤ 4 for seven specific PANSS items.

- A variable length double-blind treatment period. In this period, 305 stabilized patients were randomized 1:1 to continue treatment with INVEGA TRINZA or placebo until relapse, early withdrawal, or the end of study. Patients were randomized to the same dose of INVEGA TRINZA they received during the open-label phase (i.e., 273 mg, 410 mg, 546 mg, or 819 mg) or to placebo administered every 12 weeks. The numbers (%) of patients entering double-blind on each of the dose levels were 6 (4%) for 273 mg, 15 (9%) for 410 mg, 78 (49%) for 546 mg, and 61 (38%) for 819 mg.

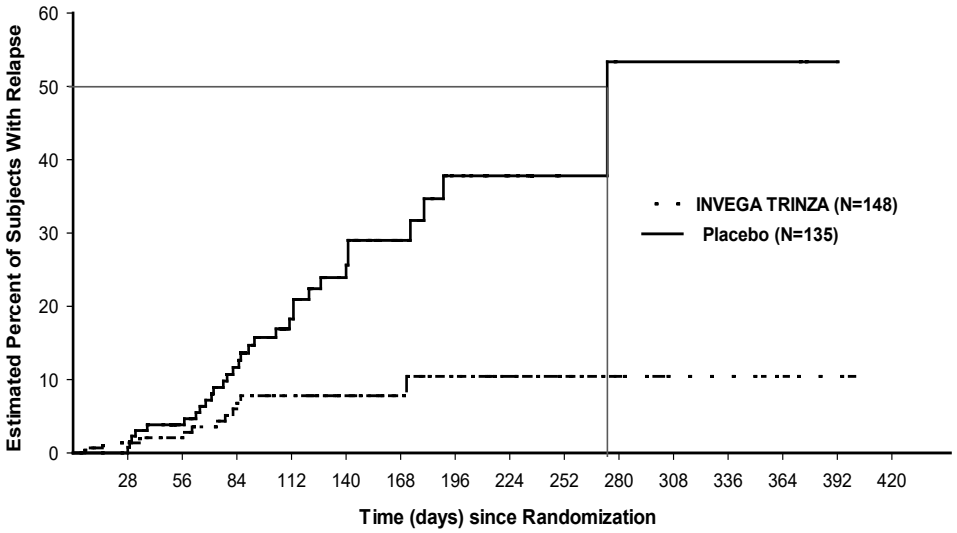
The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items.

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

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

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

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



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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

273 mg paliperidone palmitate kit (NDC 50458-606-01)

410 mg paliperidone palmitate kit (NDC 50458-607-01)

546 mg paliperidone palmitate kit (NDC 50458-608-01)

819 mg paliperidone palmitate kit (NDC 50458-609-01)

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact their healthcare provider or report to the emergency room if they experience signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status including delirium, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

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

Metabolic Changes

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

Orthostatic Hypotension

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

Leukopenia/Neutropenia

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

Hyperprolactinemia

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

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery, or operating a motor vehicle until they are reasonably certain that INVEGA TRINZA therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Priapism

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

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.15)]*.

Concomitant Medication

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

Alcohol

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

Pregnancy

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

Lactation

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

Infertility

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

INVEGA TRINZA (paliperidone palmitate) Extended-Release Injectable Suspension

Product of Ireland

Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

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

For patent information: www.janssenpatents.com

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

What is the most important information I should know about INVEGA TRINZA?

INVEGA TRINZA can cause serious side effects, including:

- **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** INVEGA TRINZA is not for treating dementia-related psychosis.

What is INVEGA TRINZA?

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

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

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

Who should not receive INVEGA TRINZA?

Do not receive INVEGA TRINZA if you:

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

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

Before you receive INVEGA TRINZA, tell your healthcare provider about all your medical conditions, including if you:

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

- are breastfeeding or plan to breastfeed. INVEGA TRINZA can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive INVEGA TRINZA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show to your healthcare provider or pharmacist when you get a new medicine.

How will I receive INVEGA TRINZA?

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

What should I avoid while receiving INVEGA TRINZA?

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

What are the possible side effects of INVEGA TRINZA?

INVEGA TRINZA may cause serious side effects, including:

- See **"What is the most important information I should know about INVEGA TRINZA?"**
- **stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious problem that can happen in people who receive INVEGA TRINZA. NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have any of these symptoms:
  - high fever
  - severe muscle stiffness
  - confusion
  - loss of consciousness
  - changes in your breathing, heartbeat and blood pressure
- **problems with your heartbeat.** These heart problems can cause death. Call your healthcare provider right away if you have any of these symptoms:
  - passing out or feeling like you will pass out
  - dizziness
  - feeling as if your heart is pounding or missing beats
- **uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)**
- **metabolic changes.** Metabolic changes may include high blood sugar (hyperglycemia), diabetes mellitus and changes in the fat levels in your blood (dyslipidemia), and weight gain.
- **low blood pressure and fainting**
- **changes in your blood cell counts**
- **high level of prolactin in your blood (hyperprolactinemia).** INVEGA TRINZA may cause a rise in the blood levels of a hormone called prolactin (hyperprolactinemia) that may cause side effects

including missed menstrual periods, leakage of milk from the breasts, development of breasts in men, or problems with erection.

- **problems thinking clearly and moving your body**
- **seizures**
- **difficulty swallowing that can cause food or liquid to get into your lungs**
- **prolonged or painful erection lasting more than 4 hours.** Call your healthcare provider or go to your nearest emergency room right away if you have an erection that lasts more than 4 hours.
- **problems with control of your body temperature especially when you exercise a lot or spend time doing things that make you warm. It is important for you to drink water to avoid dehydration.**

The most common side effects of INVEGA TRINZA include: injection site reactions, weight gain, headache, upper respiratory tract infections, feeling restlessness or difficulty sitting still, slow movements, tremors, stiffness and shuffling walk.

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

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

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

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

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

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

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

What are the ingredients in INVEGA TRINZA?

Active ingredient: paliperidone palmitate

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

Manufactured by: Janssen Pharmaceutica NV Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560, USA
For patent information: www.janssenpatents.com

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: September 2024

USA - MU_12349210

Instructions for Use
INVEGA TRINZA®

paliperidone palmitate
extended-release injectable
suspension

Administer every 3 months

Shake syringe vigorously for at least 15 seconds

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

Instructions for Use
INVEGA TRINZA®

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USA - MU_12349210

Important

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

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

Read complete instructions prior to use.

Dosing

This medication should be administered **once every 3 months**.

Preparation

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

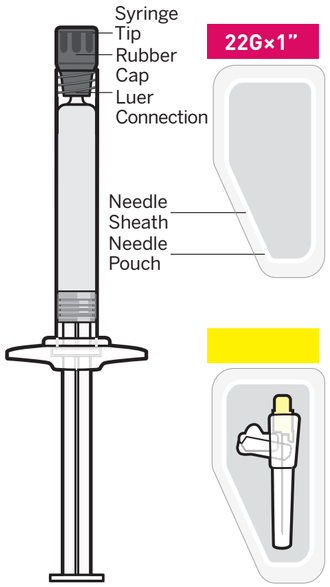
INVEGA TRINZA requires longer and more vigorous shaking than INVEGA SUSTENNA (1-month paliperidone palmitate extended-release injectable suspension). Shake the syringe vigorously, with the syringe tip pointing up, for **at least 15 seconds within 5 minutes prior to administration** (see Step 2).

Thin Wall Safety Needle Selection

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

Dose pack contents

Prefilled Syringe | **Thin Wall Safety Needles**

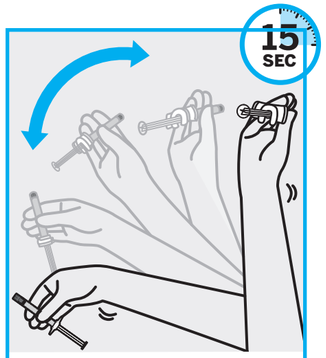


Needle selection is determined by injection area and patient weight.

If administering a **Deltoid** injection	If administering a **Gluteal** injection
	
If patient weighs:	If patient weighs:
Less than 90 kg pink hub	**Less than 90 kg** yellow hub
22G×1”	
90 kg or more yellow hub	**90 kg or more** yellow hub

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

Prepare for injection



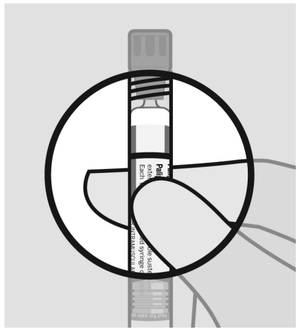
SHAKE VIGOROUSLY for at least 15 seconds

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

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

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

Check suspension

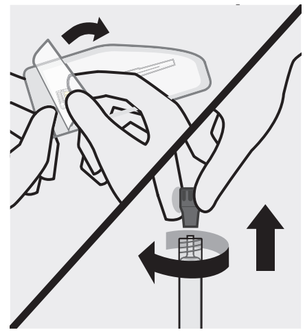


After shaking the syringe for at least 15 seconds, check the liquid in the viewing window.

The suspension should appear uniform and milky white in color.

It is also normal to see small air bubbles.

Open needle pouch and remove cap

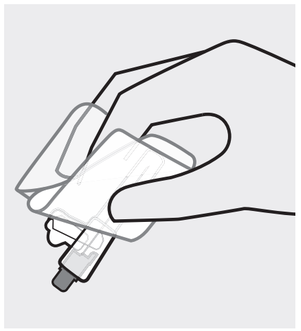


First, open needle pouch by peeling the cover back half way. Place on a clean surface.

Then, holding the syringe upright, twist and pull the rubber cap to remove.

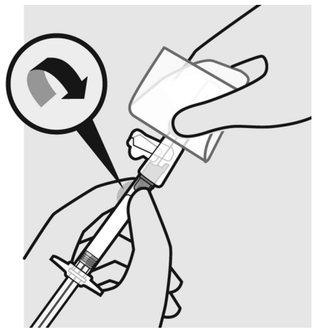
2 Prepare for injection

Grasp needle pouch



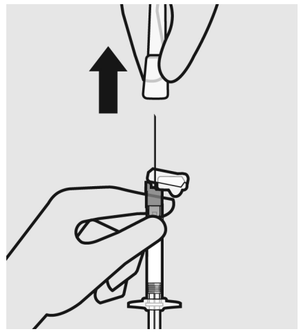
Fold back needle cover and plastic tray. Then, firmly grasp the needle sheath through the pouch, as shown.

Attach needle



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

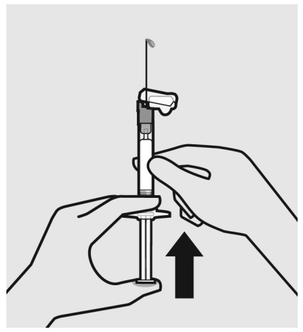
Remove needle sheath



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

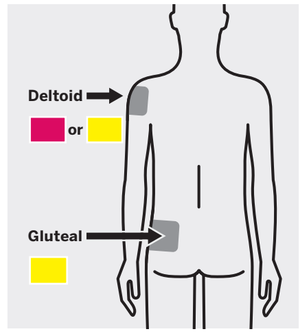


Hold the syringe upright and tap gently to make any air bubbles rise to the top.

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

3 Inject

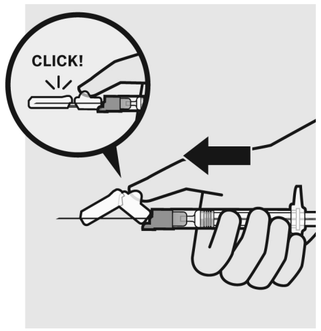
Inject dose



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

Do not administer by any other route.

Secure needle



After the injection is complete, use your thumb or a flat surface to secure the needle in the safety device.

The needle is secure when a “click” sound is heard.

Dispose properly

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

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

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
For patent information:
www.janssenpatents.com

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 9/2024

Reference ID: 5517951

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA HAFYERA safely and effectively. See full prescribing information for INVEGA HAFYERA.

INVEGA HAFYERA® (paliperidone palmitate) extended-release injectable suspension, for gluteal intramuscular use
Initial U.S. Approval: 2006

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

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA HAFYERA is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.4, 2.5)	9/2024
Warnings and Precautions (5.10)	1/2025

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

INVEGA HAFYERA, an every-six-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in adults after they have been adequately treated with:

- A once-a-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA SUSTENNA) for at least four months or
- An every-three-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA TRINZA) for at least one three-month cycle. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer INVEGA HAFYERA by gluteal injection once every 6 months by a healthcare professional. Do not administer by any other route. (2.1)
- See Full Prescribing Information for complete dosing information. (2.2)
- Initiate INVEGA HAFYERA when the next once-a-month or every three-month paliperidone palmitate extended-release injectable suspension dose is scheduled. Dose is based on the previous once-a-month or every-three-month product. (2.2):

INVEGA HAFYERA Doses for Adults Adequately Treated with Once-a-month paliperidone palmitate extended-release injectable suspension (PP1M)*

If the Last Dose of PP1M is:	Initiate INVEGA HAFYERA at the Following Dose:
156 mg	1,092 mg
234 mg	1,560 mg

*Switching from the PP1M 39 mg, 78 mg and 117 mg doses was not studied.

INVEGA HAFYERA Doses for Adults Adequately Treated with Every-three-month paliperidone palmitate injectable suspension (PP3M)*

If the Last Dose of PP3M is:	Initiate INVEGA HAFYERA at the Following Dose:
546 mg	1,092 mg
819 mg	1,560 mg

*Switching from the PP3M 273 mg and 410 mg doses was not studied.

- Missed Doses: Refer to the Full Prescribing Information. (2.3)
- See Full Prescribing Information for important preparation and administration information. (2.5)
- Moderate to severe renal impairment (creatinine clearance <50 mL/min): INVEGA HAFYERA is not recommended. (2.4)
- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Adjust dosage and stabilize the patient using PP1M before transitioning to INVEGA HAFYERA, or from PP1M to PP3M before transitioning to INVEGA HAFYERA. See appropriate table above. (2.4)

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

Extended-release injectable suspension: 1,092 mg/3.5 mL or 1,560 mg/5 mL single-dose prefilled syringes. (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis*: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities). (5.2)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *QT Prolongation*: Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. (5.4)
- *Tardive Dyskinesia*: Discontinue treatment if clinically appropriate (5.5)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- *Orthostatic Hypotension and Syncope*: Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing INVEGA HAFYERA if a clinically significant decline in WBC occurs in the absence of other causative factors. (5.9)
- *Hyperprolactinemia*: Prolactin elevations occur and persist during chronic administration. (5.10)
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery. (5.11)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.12)

----------ADVERSE REACTIONS----------

The most common adverse reactions were upper respiratory tract infection, injection site reaction, weight increased, headache, and parkinsonism. (6.1)

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

----------DRUG INTERACTIONS----------

Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using strong CYP3A4 and/or P-gp inducers during a dosing interval for INVEGA HAFYERA. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets. (7.1, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

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

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

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA HAFYERA is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

INVEGA HAFYERA, an every-six-month injection, is indicated for the treatment of schizophrenia in adults after they have been adequately treated with:

- A once-a-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA SUSTENNA) for at least four months, or
- An every-three-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA TRINZA) for at least one three-month cycle.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- INVEGA HAFYERA must be administered as a gluteal intramuscular injection by a healthcare professional once every 6 months. Do not administer by any other route *[see Dosage and Administration (2.5)]*.
- Initiate INVEGA HAFYERA only after adequate treatment has been established with either:
    - A once-a-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA SUSTENNA), referred to as PP1M, once monthly for at least four months; or
    - An every-three-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA TRINZA), referred to as PP3M, once every three months for at least one three-month injection cycle.
- See Prescribing Information of the PP1M and PP3M products for the recommended dosage of these products.

2.2 Recommended Dosage for INVEGA HAFYERA

Switching to INVEGA HAFYERA from a PP1M Product

The recommended initial INVEGA HAFYERA dose is based on the previous PP1M dose (see Table 1). Initiate INVEGA HAFYERA when the next PP1M dose is scheduled. INVEGA HAFYERA may be administered up to 1 week before or 1 week after the next scheduled PP1M

dose. When switching from PP1M to INVEGA HAFYERA, the two injection cycles immediately preceding the switch should be the same dosage strength before starting INVEGA HAFYERA.

Table 1. Initial INVEGA HAFYERA Dose for Adult Patients Switching from a PP1M* Product

Last Dose of PP1M**	Initial Dose of INVEGA HAFYERA
156 mg	1,092 mg
234 mg	1,560 mg

* PP1M: Once-a-month paliperidone palmitate extended-release injectable suspension

** There are no equivalent doses of INVEGA HAFYERA for 39 mg, 78 mg, or 117 mg doses of a PP1M product, which were not studied *[see Clinical Studies (14)]*.

Switching to INVEGA HAFYERA from a PP3M Product

The recommended initial INVEGA HAFYERA dose is based on the previous PP3M dose (see Table 2). Initiate INVEGA HAFYERA when the next PP3M dose is scheduled. INVEGA HAFYERA may be administered up to 2 weeks before or 2 weeks after the next scheduled PP3M dose.

Table 2. Initial INVEGA HAFYERA Dose for Adult Patients Switching from a PP3M* Product

Last Dose of PP3M**	Initial Dose of INVEGA HAFYERA
546 mg	1,092 mg
819 mg	1,560 mg

* PP3M: Every-three-month paliperidone palmitate extended-release injectable suspension

** There are no equivalent doses of INVEGA HAFYERA for the 273 mg or 410 mg doses of a PP3M product, which were not studied *[see Clinical Studies (14)]*.

Dosing Interval and Dosage Adjustments of INVEGA HAFYERA

Following the initial dose, administer INVEGA HAFYERA once every 6 months.

If needed, dosage adjustment can be made every 6 months between the dose of 1,092 mg to 1,560 mg based on individual response and tolerability. Because of the potential longer duration of INVEGA HAFYERA, the patient's response to an adjusted dose may not be apparent for several months *[see Clinical Pharmacology (12.3)]*.

2.3 Missed Doses

Dosing Window

To avoid a missed dose, patients may be given the injection up to 2 weeks before or 3 weeks after the scheduled 6-month dose.

Missed Dose

If a dose of INVEGA HAFYERA is missed, re-initiate with a PP1M product using the re-initiation regimens described in Tables 3 and 4.

More than 6 Months and 3 Weeks, up to but Less than 8 Months Since Last Dose

If more than 6 months and 3 weeks but less than 8 months have elapsed since the last dose of INVEGA HAFYERA, do not administer the next dose of INVEGA HAFYERA. Instead, use the re-initiation regimen shown in Table 3:

Table 3. Re-initiation Regimen for Missed Dose (more than 6 months and 3 weeks, but less than 8 months since last dose)

Last Dose of INVEGA HAFYERA	Administer PP1M Product* into deltoid muscle	Administer INVEGA HAFYERA into gluteal muscle
	Day 1	1 month after Day 1
1,092 mg	156 mg	1,092 mg
1,560 mg	234 mg	1,560 mg

* PP1M: Once-a-month paliperidone palmitate extended-release injectable suspension

8 Months Up to and including 11 Months Since Last Dose

If 8 months but up to and including 11 months have elapsed since the last dose of INVEGA HAFYERA, do not administer the next dose of INVEGA HAFYERA. Instead, use the re-initiation regimen shown in Table 4:

Table 4. Re-initiation Regimen for Missed Dose (8 months up to and including 11 months since last dose)

Last dose of INVEGA HAFYERA	Administer PP1M Product* into deltoid muscle		Administer INVEGA HAFYERA into gluteal muscle
	Day 1	Day 8	1 month after Day 8
1,092 mg	156 mg	156 mg	1,092 mg
1,560 mg	156 mg	156 mg	1,560 mg

* PP1M: Once-a-month paliperidone palmitate extended-release injectable suspension

More than 11 Months Since Last Dose

If more than 11 months have elapsed since the last dose of INVEGA HAFYERA, re-initiate treatment with a PP1M product as described in the prescribing information for that product. INVEGA HAFYERA can then be resumed after the patient has been adequately treated with a PP1M product for at least 4 months.

2.4 Dosage Recommendations in Patients with Renal Impairment

INVEGA HAFYERA has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), adjust dosage and stabilize the patient using PP1M before transitioning from PP1M to INVEGA HAFYERA, or from PP1M to PP3M before transitioning to INVEGA HAFYERA *(see Table 1) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].* Refer to the Prescribing Information of PP1M or PP3M product for the recommended PP1M or PP3M dosage in patients with mild renal impairment.

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

2.5 Instructions for Preparation and Administration

- To be prepared and administered by a healthcare provider only.
- Read the instructions for preparation and administration below and consider referring to the separate Healthcare Provider "Instructions for Use" for preparation and administration considerations.
- For gluteal intramuscular injection only. Do not inject by any other route. As a universal precaution, always wear gloves.
- Inspect INVEGA HAFYERA for particulate matter and discoloration prior to administration.
- Do not mix with any other product or diluent.
- After shaking, INVEGA HAFYERA should appear uniform, thick and milky white.
- Do not use needles from the PP1M or PP3M products or other commercially-available needles to reduce the risk of blockage.
- Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the upper-outer quadrant of the gluteal muscle. Future injections should be alternated between the two gluteal muscles.

Incomplete Administration

- Proper shaking can reduce the likelihood for an incomplete injection. Storing the carton in a horizontal orientation improves the ability to resuspend this highly concentrated product *[see How Supplied/Storage and Handling (16)]*.
- Follow the full instructions for preparation and administration to avoid an incomplete injection.
- In the event of an incompletely administered dose, do not re-inject the dose remaining in the syringe and do not administer another dose of INVEGA HAFYERA.
- Closely monitor and treat the patient with oral paliperidone supplementation as clinically appropriate until the next scheduled 6-month injection of INVEGA HAFYERA. See Prescribing Information of the oral paliperidone product for the recommended dosage of these products.

Administer every 6 months

INVEGA HAFYERA (paliperidone palmitate)
Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds.

For Gluteal Intramuscular injection only.

Preparation

INVEGA HAFYERA requires **longer and faster shaking** than once-a-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA SUSTENNA).
INVEGA HAFYERA must be administered by a healthcare professional as a single injection. Do not divide dose into multiple injections.
INVEGA HAFYERA is intended for gluteal intramuscular use only. Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.

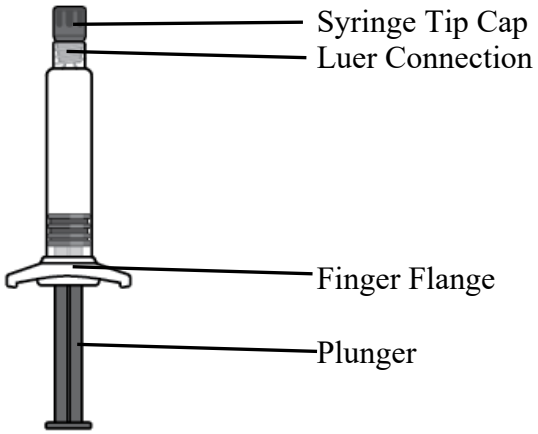
Dosing

Administer INVEGA HAFYERA **once every 6 months**.

Thin Wall Safety Needle

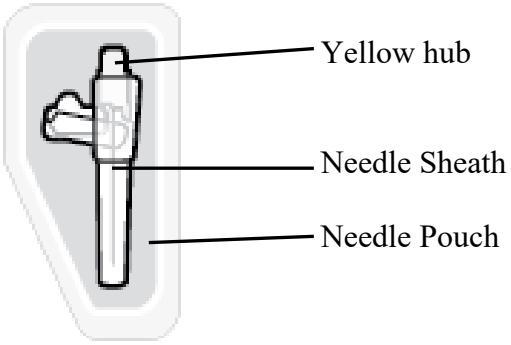
Thin wall safety needle is designed to be used with INVEGA HAFYERA. Therefore, it is important to **only use the needle provided in the INVEGA HAFYERA suspension kit.**

Dose pack contents
Prefilled Syringe



Thin Wall Safety Needle

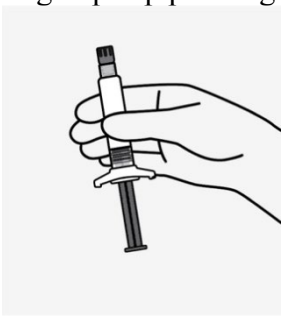
20G × 1½"
Only use the needle included in this kit



1. Prepare for the injection: this highly concentrated product requires specific steps to resuspend

Hold syringe with the tip cap pointing up

Syringe tip cap pointing up



Shake syringe VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds

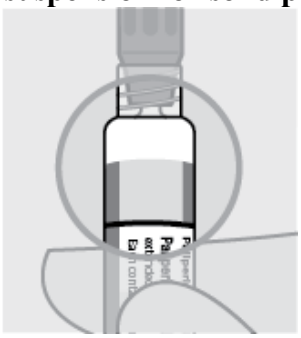
To ensure complete resuspension shake syringe with:

- **Short, VERY FAST up and down motion**
- **Loose wrist**

If more than <u>5 minutes</u> pass before injection, shake the syringe VERY FAST with the tip cap pointing up again for at least 30 seconds to resuspend INVEGA HAFYERA

Proceed to the next step immediately after shaking.

Check suspension for solid product



Mixed well

- Uniform, thick and milky white
- It is normal to see air bubbles

Not mixed well

STOP

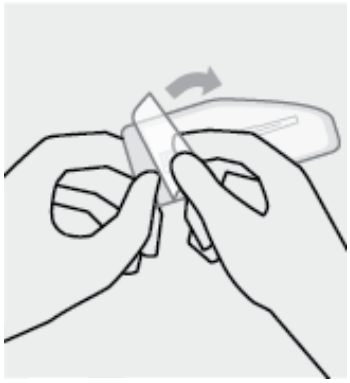
- Solid product on sides and top of syringe
- Uneven mix
- Thin liquid

Product may clog.

Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest, then shake again for 15 seconds.

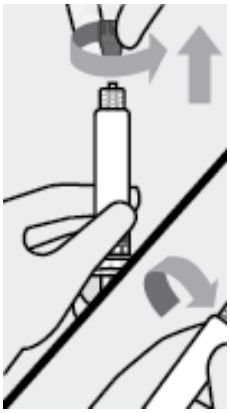
Open needle pouch

Peel off the pouch cover. Place pouch with the needle inside on a clean surface.



Remove syringe tip cap and attach needle

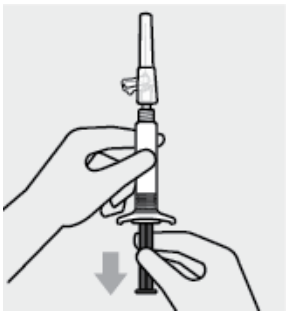
Hold the syringe with the tip cap pointing up.
Twist and pull off the cap.
Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage.
Always check for signs of damage



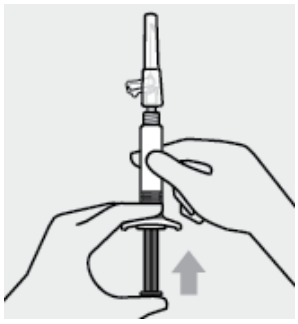
Only use the needle included in this kit.

or leakage prior
to administration.

Pull back plunger
Hold the syringe upright.
Gently pull back the plunger to clear the syringe tip of any solid product. This will make pressing the plunger easier during the injection.

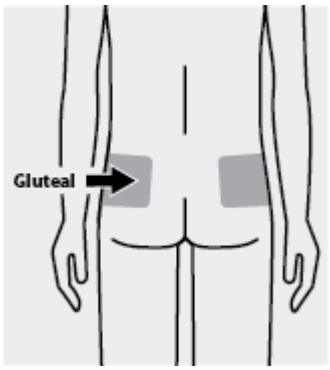


Remove air bubbles
Press the plunger carefully until a drop of liquid comes out of the needle tip.

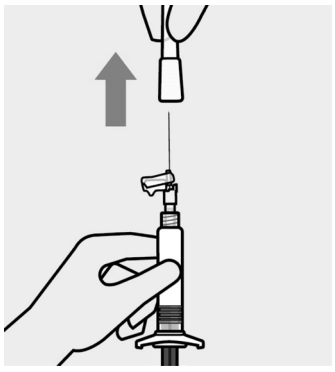


2. Slowly inject entire content and confirm

Select and clean a gluteal injection site
Wipe the gluteal site with an alcohol swab and allow it to dry.
Do not touch, fan or blow on the injection site after you have cleaned it.



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.



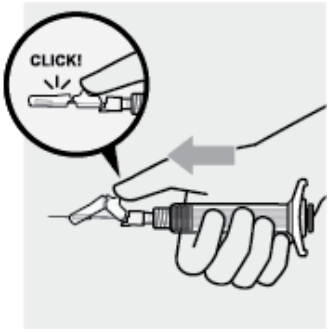
Slowly inject and confirm
Use slow, firm, consistent pressure to press the plunger **completely**. This should take approximately 30 seconds.

Continue to press the plunger if you feel resistance. This is normal.

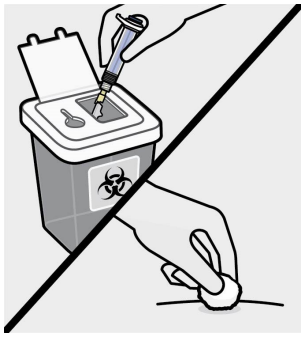
Remove needle from the muscle.

3. After the 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 you hear a “click” sound.



Dispose of properly and check injection site
Dispose of the syringe in an approved sharps container.
There may be a small amount of blood or liquid at the injection site. Hold pressure over the skin with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage.



3 DOSAGE FORMS AND STRENGTHS

INVEGA HAFYERA is a white to off-white aqueous extended-release injectable suspension for gluteal intramuscular injection in dose strengths of 1,092 mg/3.5 mL and 1,560 mg/5 mL paliperidone palmitate in single-dose prefilled syringes.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA HAFYERA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular

accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, the 1-month paliperidone palmitate extended-release injectable suspension, the 3-month paliperidone extended-release injectable suspension or INVEGA HAFYERA in elderly patients with dementia. These medications are not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone.

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

If NMS is suspected, discontinue INVEGA HAFYERA and provide symptomatic treatment and monitoring.

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of *Torsades de pointes* and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter Thorough QT study with oral paliperidone in adult patients, and in four fixed-dose efficacy studies and one maintenance study of the 1-month paliperidone palmitate injectable product.

In the Thorough QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD (QT interval corrected for heart rate using the population specified linear derived method) of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$=113 ng/mL) was approximately 1.3-fold the exposure with the maximum recommended 1,560 mg dose of INVEGA HAFYERA administered in the gluteal muscle (mean $C_{max\ md}$=89.3 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$=35 ng/mL, showed an

increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the four fixed-dose efficacy studies of the 1-month paliperidone palmitate injectable product, no subject had a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of >500 msec at any time point. In the maintenance study, no subject had a QTcLD change >60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

In the INVEGA HAFYERA randomized double-blind active controlled study in subjects with schizophrenia, during the double-blind Phase, QTcLD exceeding 60 msec was observed in 2 subjects (0.4%) in the INVEGA HAFYERA treatment group and in 2 subjects (0.9%) in the PP3M treatment group. No subject had a QTcLD value of >480 msec at any point in the study.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

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

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

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

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia,

dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

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

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

Data from the randomized double-blind active controlled study with INVEGA HAFYERA in patients with schizophrenia are presented in Table 5.

Table 5. Change in Fasting Glucose from the randomized double-blind active controlled study with INVEGA HAFYERA in patients with schizophrenia

Total no. of patients[a]	**PP3M[1] N=195**	**INVEGA HAFYERA N=423**
Normal to high	3%	4%
Impaired glucose tolerance to high	4%	5%
Normal/impaired glucose tolerance to high	7%	9%
<126 mg/dL to >=140 mg/dL	4%	5%
<126 mg/dL to >=200 mg/dL	0	1%
<126 mg/dL to >=300 mg/dL	0	<1%

[1] PP3M – Every-three-month paliperidone palmitate extended-release injectable suspension

(a) The number of subjects with paired fasting data (baseline and any post baseline assessment).
Using the conversion factor (1 mg/dL=0.05551 mmol/L) the ADA specified limits are as follows:
Normal: <100 mg/dL (<5.551 mmol/L)
Impaired: ≥100 mg/dL (≥5.551 mmol/L) to <126 mg/dL (<6.994 mmol/L)
High: ≥126 mg/dL (≥6.994 mmol/L)
126 mg/dL=6.994 mmol/L; 140 mg/dL=7.771 mmol/L; 200 mg/dL=11.102 mmol/L; 300 mg/dL=16.653 mmol/L

Dyslipidemia

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

Shifts in lipid parameters from the randomized double-blind active controlled study with INVEGA HAFYERA in patients with schizophrenia are presented in Table 6.

Table 6. Shifts in Fasting Lipids in the Double-Blind Phase from the randomized active controlled study with INVEGA HAFYERA in patients with schizophrenia

	PP3M[1] N=194	INVEGA HAFYERA N=423
Fasting Cholesterol (mg/dL)		
<200 mg/dL to >=240 mg/dL	2 (1%)	3 (0.7%)
Fasting HDL Cholesterol (mg/dL)		
>=40 mg/dL to <40 mg/dL	28 (14%)	55 (13%)
Fasting LDL Cholesterol (mg/dL)		
<100 mg/dL to >=160 mg/dL	1 (0.5%)	2 (0.5%)
Fasting Triglycerides (mg/dL)		
<150 mg/dL to >=200 mg/dL	22 (11%)	22 (5%)

[1] PP3M – Every-three-month paliperidone palmitate extended-release injectable suspension.
For each fasting parameter, subjects with both Baseline (DB) record and any post baseline (DB) record during Double-Blind Phase are included in the denominator.

Change in Body Weight

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. In the randomized active controlled clinical study of INVEGA HAFYERA, the overall mean weight change during the double-blind Phase was similar to PP3M.

5.7 Orthostatic Hypotension and Syncope

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

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

5.8 Falls

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

5.9 Leukopenia, Neutropenia, and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA HAFYERA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue INVEGA HAFYERA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.

Median prolactin levels remained relatively stable throughout the open-label and double-blind phases in male subjects, whereas in female subjects, median prolactin levels increased. During the double-blind phase, median prolactin levels continued to increase after dosing in both the INVEGA HAFYERA and PP3M groups, returning to baseline level at Month 6 and at Month 12 (end of double-blind phase).

During the double-blind phase, prolactin levels relative to reference range (>13.13 ng/mL in males and >26.72 ng/mL in females) from maintenance baseline were noted in a similar percentage of

subjects in the INVEGA HAFYERA and PP3M groups in both males (35% vs 36%) and females (29% vs. 30%). In the INVEGA HAFYERA group, 14 females (2.9%) and 4 males (0.8%) experienced potentially prolactin-related adverse reactions, while 6 females (2.7%) and 1 male (0.4%) in the PP3M experienced potentially prolactin-related adverse reactions.

5.11 Potential for Cognitive and Motor Impairment

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

5.12 Seizures

In the 6-month paliperidone palmitate extended-release injectable suspension double-blind active controlled trial there were no reports of seizures or convulsions, nor were any reports made in the long-term maintenance trial of PP3M. In the pivotal clinical studies with PP1M which included four fixed-dose, double-blind, placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with the PP1M experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA HAFYERA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.13 Dysphagia

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

5.14 Priapism

A case (0.2%) of priapism was reported in the clinical trial with INVEGA HAFYERA. Priapism has been reported with oral paliperidone during postmarketing surveillance. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Severe priapism may require surgical intervention.

5.15 Disruption of Body Temperature Regulation

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Patient Exposure

The data described in this section is derived from the randomized double-blind active controlled non-inferiority study of INVEGA HAFYERA and 3-month paliperidone palmitate extended-release injectable suspension. During the double-blind phase, 478 patients were randomized to receive 2 injection cycles of INVEGA HAFYERA over a 12-month duration. The mean (SD) duration of exposure was 329.8 (86.97) days in the INVEGA HAFYERA group and 336.4 (80.89) days in the PP3M group during the double-blind phase:

Adverse Reactions in the Double-Blind, Active-Controlled Clinical Trial

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence at least 5% in the double-blind Phase) of the INVEGA HAFYERA clinical trial were, upper respiratory tract infection, injection site reaction, weight increased, headache and parkinsonism.

Discontinuation of Treatment Due to Adverse Reactions: In the double-blind phase of the INVEGA HAFYERA clinical trial 1.3% of subjects in the INVEGA HAFYERA group and 0.4% of subjects in the 3-month paliperidone palmitate extended-release injectable suspension group discontinued due to adverse reactions.

Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA HAFYERA-Treated Patients: Table 7 lists the adverse reactions reported in the INVEGA HAFYERA clinical trial.

Table 7. Incidences of Adverse Reactions 2% or More of INVEGA HAFYERA-Treated Patients for the Double-Blind Phase of the Randomized Double-blind Active Controlled Trial in Patients with Schizophrenia

	Double Blind	
System Organ Class	**PP3M[1] (N=224) %**	**INVEGA HAFYERA (N=478) %**
Adverse Reaction		
Gastrointestinal disorders		
Diarrhea*	1	2
General disorders and administration site conditions		
Injection site reaction*	5	11
Infections and infestations		
Upper respiratory tract infection*	13	12
Urinary tract infection	1	3
Metabolism and nutrition disorders		
Weight increased	8	9
Musculoskeletal and connective tissue disorders		
Back pain*	1	3
Musculoskeletal pain*	1	3
Nervous system disorders		
Akathisia*	4	4
Headache	5	7
Extrapyramidal symptoms*	5	7
Psychiatric disorders		
Psychosis*	3	3
Anxiety	0	3
Insomnia*	2	3

[1] PP3M – Every-three-month paliperidone palmitate extended-release injectable suspension

* The following terms were combined:

Diarrhea includes: Diarrhea, Diarrhea infectious.

Injection site reaction: includes Injection site reaction, Injection site discomfort, Injection site erythema, Injection site hemorrhage, Injection site induration, Injection site nodule, Injection site oedema, Injection site pain, Injection site swelling.

Weight increased includes: Weight increased, Body mass index increased, Obesity, Waist circumference increased.

Upper respiratory tract infection includes: Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Rhinitis, Viral pharyngitis, Viral upper respiratory tract infection.

Back pain includes: Back pain, Neck pain, Spinal pain.

Musculoskeletal pain includes: Musculoskeletal pain, Musculoskeletal chest pain, Myalgia, Pain in extremity.

Akathisia includes: Akathisia, Restless legs syndrome, Restlessness.
Extrapyramidal symptoms includes: blepharospasms, bradykinesia, drooling, dyskinesia, dystonia, hypokinesia, musculoskeletal stiffness, muscle rigidity, muscle spasms, oculogyric crisis, Parkinsonism, Parkinsonism rest tremor, reduced facial expression, tardive dyskinesia.
Insomnia includes: Insomnia, Initial insomnia, Middle insomnia.
Psychosis includes: acute psychosis, delusion, delusion of reference, hallucination (auditory), psychotic disorder, psychotic symptom, and schizophrenia.

Demographic Differences

An examination of population subgroups in the INVEGA HAFYERA trial did not reveal any evidence of differences in safety on the basis of age, gender, or race alone.

Extrapyramidal Symptoms (EPS)

Data from the randomized double-blind active controlled study provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-Angus Rating Scale Global Score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale Global Clinical Rating Score which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale scores which evaluates dyskinesia, and (4) use of anticholinergic medications to treat EPS (Table 8) and (5) incidence of spontaneous reports of EPS (Table 9).

Table 8. Extrapyramidal Symptoms (EPS) Assessed by Rating Scales Incidence and Use of Anticholinergic Medication During the Double-blind Phase

	PP3M[1] (N=224) %	INVEGA HAFYERA (N=478) %
Use of Anticholinergic Medication[(a)]	13	15
Parkinsonism[(b)]	6	7
Akathisia[(c)]	3	3
Dyskinesia[(d)]	1	1

[1] PP3M - Every-three-month paliperidone palmitate extended-release injectable suspension
[(a)] Use of Anti-EPS Medication During the Double-blind Phase
[(b)] Percent of subjects with Simpson-Angus Scale Global Score >0.3(Global Score defined as total sum of items score divided by the number of items).
[(c)] Percent of subjects with Barnes Akathisia Rating Scale Global Clinical Rating Score ≥2
[(d)] Percent of subjects with a score ≥3 on any of the first seven items or a score ≥2 on two or more of any of the first seven items of the Abnormal Involuntary Movement Scale
Note: Percentages are calculated based on number of subjects in the DB Safety analysis set per treatment group.

Table 9. Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term

	Double-blind Phase	
	PP3M[1] (N=224)	INVEGA HAFYERA (N=478)
EPS Group	**%**	**%**
Overall percentage of subjects with EPS-related adverse events	9	10
Parkinsonism	4	5
Hyperkinesia	4	4
Tremor	0	<1
Dyskinesia	1	2
Dystonia	1	1

[1] PP3M – Every-three-month paliperidone palmitate extended-release injectable suspension
Parkinsonism group includes: Bradykinesia, drooling, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism, parkinsonian rest tremor, reduced facial expression
Hyperkinesia group includes: Akathisia, restlessness, restless legs syndrome

Dyskinesia group includes: Dyskinesia, muscle twitching, tardive dyskinesia
Dystonia group includes: Blepharospasm, dystonia, muscle spasms, oculogyric crisis

Dystonia

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

Pain Assessment and Local Injection Site Reactions

Investigator ratings of injection site. Induration, redness and swelling were observed in 13% in the INVEGA HAFYERA group and 9% in the PP3M group during the double-blind Phase. Investigator evaluation of tenderness was higher for subjects in the INVEGA HAFYERA group versus the 3-month paliperidone palmitate extended-release injectable suspension group (31% vs. 19%) during the double-blind Phase. Active INVEGA HAFYERA medication was given at double-blind baseline and Month 6, while placebo medication was given at the other injection times.

Subject ratings of injection site pain. The average score for the subject's evaluation of injection pain on a scale of 0 to 100 was approximately 16 at the open-label Phase end point and approximately 5 in both groups at the double-blind Phase end point.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA HAFYERA

The following additional adverse reactions were identified in the randomized double-blind active controlled study. The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications.

Blood and lymphatic system disorders: anemia

Cardiac disorders: bradycardia, tachycardia

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: constipation, nausea, vomiting

General disorders and administration site conditions: fatigue

Hepatobiliary disorders: transaminases increased

Infections and infestations: cystitis, respiratory tract infection, tonsillitis

Metabolism and nutritional disorders: decreased appetite, increased appetite, weight decreased

Psychiatric disorders: depression

Reproductive system and breast disorders: breast pain, menstrual disorder

Skin and subcutaneous tissue disorders: rash

Vascular disorders: hypertension

Additional Adverse Reactions Reported in Clinical Trials with the 1-Month and 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension

The following is a list of additional adverse reactions that have been reported in clinical trials with the 1-month and 3-month paliperidone palmitate extended-release injectable suspensions that are not listed elsewhere:

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

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

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

General disorders and administration site conditions: asthenia, chest discomfort

Immune system disorders: hypersensitivity

Investigations: electrocardiogram abnormal

Metabolism and nutrition disorders: hyperinsulinemia

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

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

Psychiatric disorders: agitation, nightmare

Reproductive system and breast disorders: breast discharge, erectile dysfunction, gynecomastia, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: cough

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

Vascular disorders: hypotension, orthostatic hypotension

Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

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

Cardiac disorders: bundle branch block left, sinus arrhythmia

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

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

Musculoskeletal and connective tissue disorders: arthralgia, torticollis, trismus

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

Psychiatric disorders: sleep disorder

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

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

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: ischemia

6.2 Postmarketing Experience

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

Cases of anaphylactic reaction after injection with the 1-month paliperidone palmitate extended-release suspension have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the *Adverse Reactions (6)* section of the Prescribing Information for those products.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with INVEGA HAFYERA

Because paliperidone palmitate is hydrolyzed to paliperidone, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential. In

addition, consider the 6-month dosing interval and the half-life of INVEGA HAFYERA *[see Clinical Pharmacology (12.3)]*.

Table 10 presents clinically significant drug interactions with INVEGA HAFYERA.

Table 10.	**Clinically Important Drug Interactions with INVEGA HAFYERA**
Centrally acting Drugs and Alcohol	
Clinical Rationale	Given the primary CNS effects of paliperidone, concomitant use of centrally acting drugs and alcohol may modulate the CNS effects of INVEGA HAFYERA.
Clinical Recommendation	INVEGA HAFYERA should be used with caution with other centrally acting drugs and alcohol.
Drugs with Potential for Inducing Orthostatic Hypotension	
Clinical Rationale	Because INVEGA HAFYERA has the potential for inducing orthostatic hypotension, an additive effect may occur when INVEGA HAFYERA is administered with other therapeutic agents that have this potential *[see Warnings and Precautions (5.7)]*.
Clinical Recommendation	Monitor orthostatic vital signs in patients who are vulnerable to hypotension *[see Warnings and Precautions (5.7)]*.
Strong Inducers of CYP3A4 and P-gp	
Clinical Rationale	The concomitant use of INVEGA HAFYERA and strong inducers of CYP3A4 and P-gp may decrease the exposure of paliperidone *[see Clinical Pharmacology (12.3)]*.
Clinical Recommendation	Avoid using CYP3A4 and/or P-gp inducers with INVEGA HAFYERA during the 6-month dosing interval, if possible. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets *[see Dosage and Administration (2.1)]*.
Examples	carbamazepine, rifampin, or St. John's Wort
Levodopa and Other Dopamine Agonists	
Clinical Rationale	Paliperidone may antagonize the effect of levodopa and other dopamine agonists.
Clinical Recommendation	Monitor and manage patient as clinically appropriate.

7.2 Drugs Having No Clinically Important Interactions with INVEGA HAFYERA

Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA HAFYERA is required when administered concomitantly with valproate *[see Clinical Pharmacology (12.3)]*. Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA HAFYERA *[see Clinical Pharmacology (12.3)]*.

Pharmacokinetic interaction between lithium and INVEGA HAFYERA is unlikely.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA HAFYERA during pregnancy *(see Clinical Considerations)*. Paliperidone has been detected in plasma in adult subjects up to 18 months after a single-dose administration of 3-month paliperidone palmitate extended-release injectable suspension. *[See Clinical Pharmacology (12.3)]*. The clinical significance of INVEGA HAFYERA administered before pregnancy or anytime during pregnancy is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

In animal reproduction studies, there were no treatment related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate or when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone *(see Animal Data)*.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

No developmental toxicity studies were conducted with the 6-month paliperidone palmitate extended-release injectable suspension.

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with 1-month paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is ~10 times the MRHD of 234 mg of the 1-month paliperidone palmitate extended-release injectable suspension based on mg/m^2 body surface area.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the oral MRHD of 12 mg based on mg/m^2 body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m^2 body surface area; maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m^2 body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m^2 body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or, to effects on the dams.

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant, or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone's parent compound, risperidone *(see Clinical Considerations)*. Paliperidone has been detected in plasma in adult subjects up to 18 months after a single-dose administration of 3-month paliperidone palmitate extended-release injectable suspension. The clinical significance on the breastfed infant is not known *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA HAFYERA and any potential adverse effects on the breastfed child from INVEGA HAFYERA or from the mother's underlying condition.

Clinical Considerations

Infants exposed to INVEGA HAFYERA through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of paliperidone (D_2 receptor antagonism), treatment with INVEGA HAFYERA may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.10)]*.

8.4 Pediatric Use

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

Juvenile Animal Studies

No juvenile animal studies were conducted with the 6-month paliperidone palmitate extended-release injectable suspension.

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

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

8.5 Geriatric Use

The clinical study of INVEGA HAFYERA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is substantially excreted by the kidney and clearance is decreased in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. Because elderly patients are more likely to have decreased renal function, INVEGA HAFYERA is not recommended to be used in elderly patients with mild, moderate or severe renal impairment *[see Use in Specific Populations (8.6)]*.

8.6 Renal Impairment

Use of INVEGA HAFYERA is not recommended for use in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min). Use of INVEGA HAFYERA in patients with mild renal impairment (creatinine clearance ≥50 mL/min to <80 mL/min) is based on the patient's previous dose of PP1M or PP3M before transitioning to INVEGA HAFYERA *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

INVEGA HAFYERA has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to INVEGA HAFYERA. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA HAFYERA contains paliperidone, which is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

10 OVERDOSAGE

Human Experience

No cases of overdose were reported in premarketing studies with paliperidone palmitate injection.

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

Paliperidone is the major active metabolite of risperidone. Refer to the *OVERDOSAGE* section of the risperidone prescribing information for overdose experience with risperidone.

Management of Overdosage

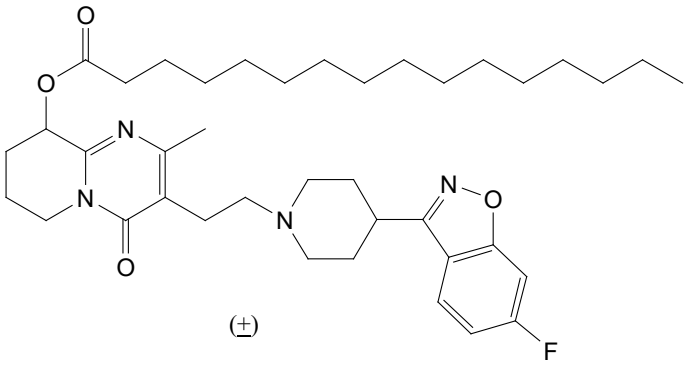
Contact a Certified Poison Control Center for the most up to date information on the management of paliperidone and INVEGA HAFYERA overdosage (1-800-222-1222 or www.poison.org). Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed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

Consider the extended-release characteristics of INVEGA HAFYERA and the half-life of paliperidone when assessing treatment needs and recovery.

11 DESCRIPTION

INVEGA HAFYERA® contains a racemic mixture of (+)- and (-)- paliperidone palmitate. Paliperidone palmitate is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical name is (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimadin-9-yl

hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



(±)

Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.

INVEGA HAFYERA is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 1,092 mg and 1,560 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 700 mg, and 1,000 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20 (10 mg/mL), polyethylene glycol 4000 (75 mg/mL), citric acid monohydrate (7.5 mg/mL), sodium dihydrogen phosphate monohydrate (6 mg/mL), sodium hydroxide (5.4 mg/mL), and water for injection.

INVEGA HAFYERA is provided in a single-dose prefilled syringe (cyclic-olefin-copolymer) prefilled with either 700 mg (3.5 mL), or 1,000 mg (5.0 mL) paliperidone (as 1,092 mg, or 1,560 mg paliperidone palmitate) suspension with a tip cap, plunger rod, backstop and a thin walled 20G, 1½-inch safety needle.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone is unclear. However, its efficacy in the treatment of schizophrenia could be mediated through a combination of central dopamine D_2 and serotonin $5HT_{2A}$ receptor antagonism.

12.2 Pharmacodynamics

In vitro, paliperidone acts as an antagonist at the central dopamine D_2 and serotonin $5HT_{2A}$ receptors with binding affinities (Ki values) of 1.6-2.8 nM and 0.8-1.2 nM, respectively. Paliperidone also acts as an antagonist at histamine H_1 and α_1 and α_2 adrenergic receptors with binding affinities of 32 nM, 4 nM, and 17 nM, respectively. Paliperidone has no appreciable affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar.

12.3 Pharmacokinetics

The pharmacokinetics for INVEGA HAFYERA presented below are based on gluteal administration only.

INVEGA HAFYERA delivers paliperidone over a 6-month period, compared to the 1-month or 3-month products which are administered every month or every three months, respectively. INVEGA HAFYERA doses of 1,092 mg and 1,560 mg result in paliperidone total exposure ranges that are encompassed within the exposure range for corresponding doses of 1-month paliperidone palmitate injections (PP1M) (156 mg and 234 mg) or corresponding doses of 3-month paliperidone palmitate (PP3M) injections (546 mg and 819 mg, respectively) or to corresponding once daily doses of paliperidone extended-release tablets. However, mean trough concentrations (C_{trough}) at the end of the dosing interval were approximately 20 - 25% lower for INVEGA HAFYERA as compared to corresponding doses of 3-month paliperidone palmitate. The mean peak concentration (C_{max}) was higher (1.4 to 1.5-fold) for INVEGA HAFYERA as compared to corresponding doses of 3-month paliperidone palmitate.

Inter-subject variability in paliperidone PK parameters for INVEGA HAFYERA ranged from 42 to 48% for $AUC_{6months}$ and ranged from 56 to 103% for C_{max}. Because of the difference in pharmacokinetic profiles among the four paliperidone products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Absorption

Due to its extremely low water solubility, the 6-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 is predicted to last longer than 18 months.

Following gluteal injection(s) of INVEGA HAFYERA at doses of 1,092 or 1,560 mg plasma concentrations of paliperidone rise to reach maximum concentrations at a median T_{max} of 29 to 32 days. The release profile and dosing regimen of INVEGA HAFYERA results in sustained concentrations over 6 months. The total and peak dose-normalized exposures of paliperidone following INVEGA HAFYERA administration were comparable between 1,092 mg and 1,560 mg dose levels. The median steady-state peak:trough ratio for an INVEGA HAFYERA dose is 3.1 and 3.0 following gluteal administration of 1,092 and 1,560 mg respectively.

Distribution

Following administration of INVEGA HAFYERA, the apparent volume of distribution of paliperidone is 1,960 L.

The plasma protein binding of racemic paliperidone is 74%.

Elimination

Metabolism

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

Excretion

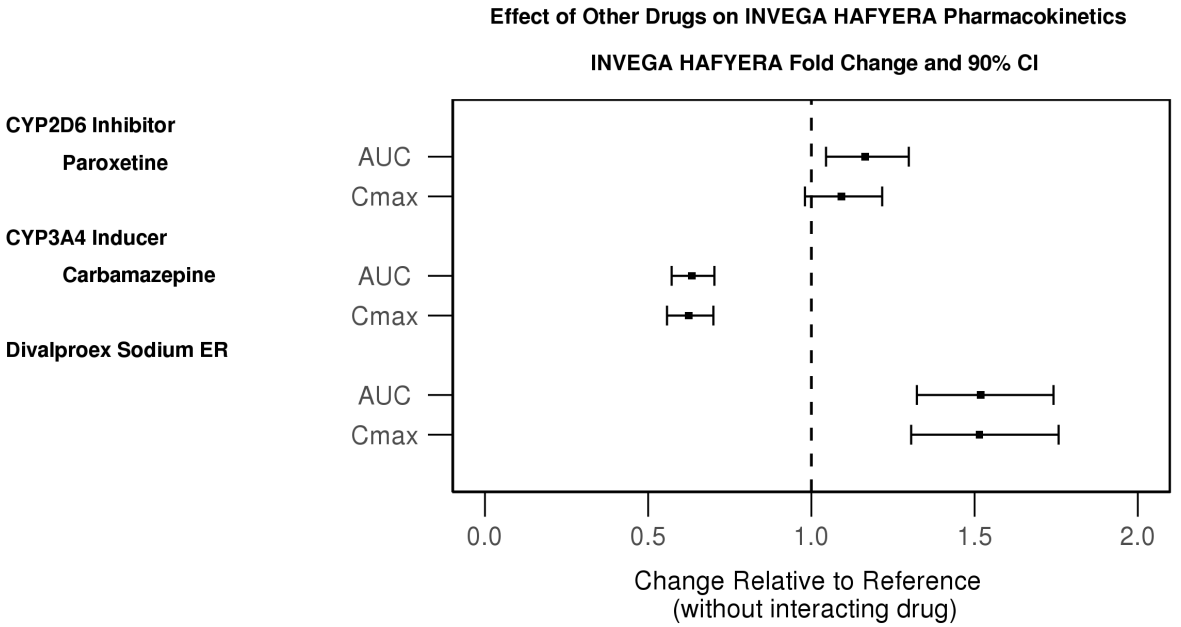
The median apparent half-life of paliperidone following a single INVEGA HAFYERA of either 1,092 or 1,560 mg was 148 and 159 days respectively. the concentration of paliperidone remaining in the circulation 18 months after dosing of 1,560 mg 6-month paliperidone palmitate extended-release injectable suspension stopped is estimated to be 18% of the average steady-state levels.

Drug Interaction Studies

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

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

Figure 1: Effects of Other Drugs on INVEGA HAFYERA Pharmacokinetics



In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism, however, there is no evidence *in vivo* that inhibitors of these enzymes significantly affect the metabolism of paliperidone; they contribute to only a small fraction of total body clearance. *In vitro* studies demonstrated that paliperidone is a substrate of P-glycoprotein (P-gp) *[see Drug Interactions (7.2)]*.

Co-administration of a single dose of an oral paliperidone extended-release tablet 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. 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 HAFYERA. This interaction has not been studied with INVEGA HAFYERA.

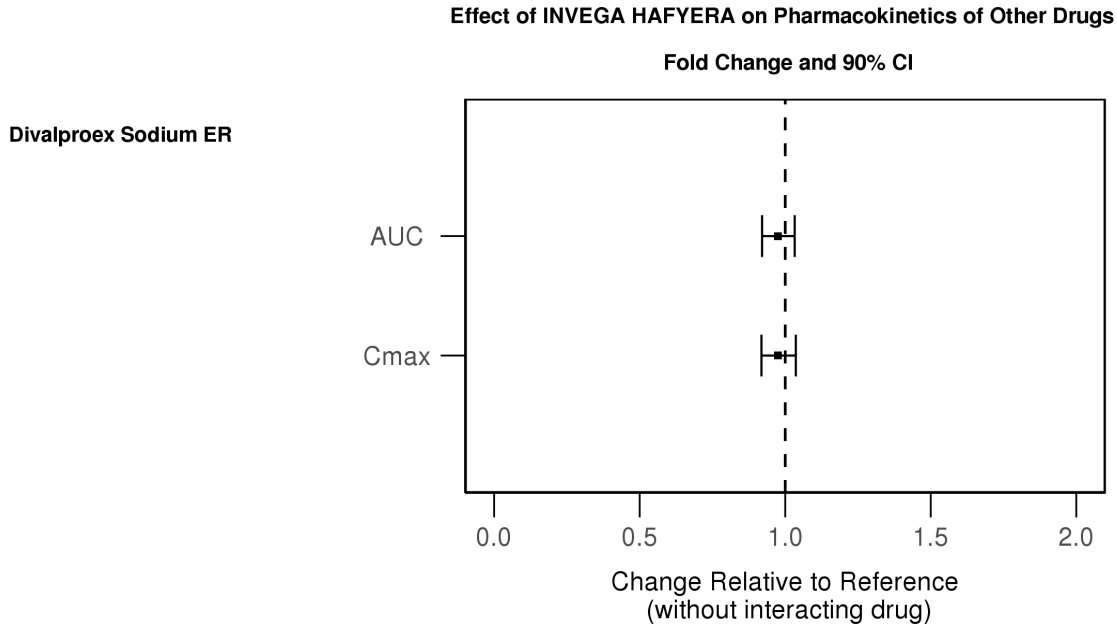
In vitro studies in human liver microsomes demonstrated that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available, and the clinical relevance is unknown.

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

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

Figure 2: Effects of INVEGA HAFYERA on Pharmacokinetics of Other Drugs



Specific Populations

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

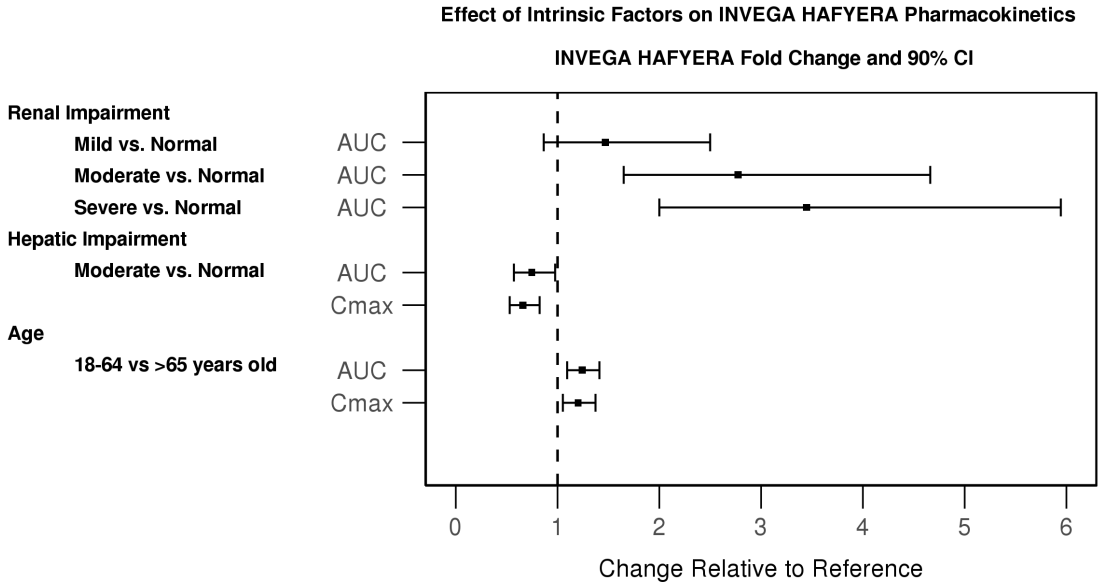
Patients with Hepatic Impairment

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

Geriatric Patients

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

Figure 3: Effects of Intrinsic factors on Paliperidone Pharmacokinetics



Smokers

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.

Male and Female Patients

Slower absorption was observed in females in a population pharmacokinetic analysis. At apparent steady-state with 6-month paliperidone palmitate extended-release injectable suspension the trough concentrations were similar between males and females.

Obese Patients

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity studies were conducted with the 6-month paliperidone palmitate extended-release injectable suspension.

The carcinogenic potential of intramuscularly injected 1-month paliperidone palmitate extended-release injectable suspension was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg/kg/month, which are ~0.7, 2 and 4 times, respectively, the MRHD of 234 mg of the 1-month paliperidone palmitate extended-release suspension based on mg/m^2 body surface area. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at ~2 and 4 times the MRHD of 234 mg of the 1-month paliperidone palmitate extended-release suspension based on mg/m^2 body surface area. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies with risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone based on mg/m^2 body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear *[see Warnings and Precautions (5.10)]*.

Mutagenesis

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

Impairment of Fertility

No fertility studies were conducted with the 6-month paliperidone palmitate extended-release injectable suspension.

In an oral paliperidone study of fertility, the percentage of treated female rats that became pregnant was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day which is 2 times the oral MRHD of 12 mg based on mg/m^2 body surface area. However, pre- and post-implantation loss was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that

also caused slight maternal toxicity. These parameters were not affected at an oral dose of 0.63 mg/kg, which is half of the oral MRHD of 12 mg based on mg/m^2 body surface area.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2 times the oral MRHD of 12 mg/day based on mg/m^2 body surface area, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration (0.6 to 10 times the MRHD of 16 mg/day for risperidone, based on mg/m^2 body surface area). Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

13.2 Animal Toxicology and/or Pharmacology

Injection site toxicity was assessed in minipigs injected intramuscularly with the 6-month paliperidone palmitate extended-release injectable suspension at doses up to 2,115 mg, which is slightly above the MRHD. Injection site inflammatory reactions were greater and more advanced than reactions to the 1-month paliperidone palmitate extended-release injectable suspension. Reversibility of these findings was not examined.

14 CLINICAL STUDIES

The efficacy of INVEGA HAFYERA for the treatment of schizophrenia in patients who had previously been stably treated with either PP1M for at least 4 months or PP3M for at least one 3-month injection cycle was evaluated in a randomized, double-blind, active-controlled, interventional, parallel-group, multicenter, non-inferiority study designed to evaluate time to relapse in adults with a DSM-5 diagnosis of schizophrenia.

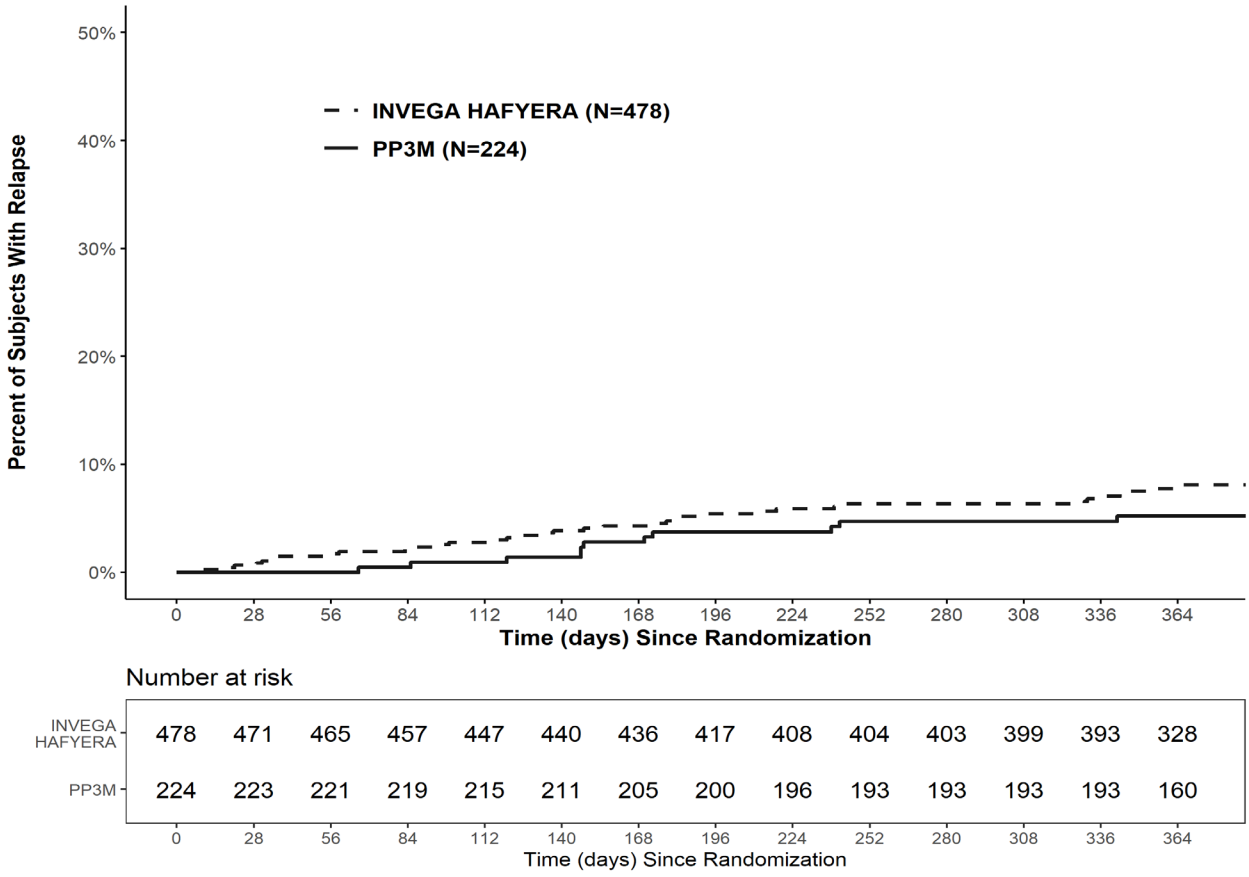
Patients could enter the study if previously treated with PP1M at dosages of 156 or 234 mg, PP3M at dosages of 546 or 819 mg, injectable risperidone at dosages of 50 mg, or any oral antipsychotic with a reason to change (e.g., efficacy, safety, tolerability, or a preference for a long-acting injectable medication) and with a PANSS total score of <70 points.

After establishing tolerability with PP1M (at dosages of 156 or 234 mg) or PP3M (at dosages of 546 or 819 mg) and clinical stability, defined by having a PANSS total score of <70 points for the previous 2 assessments prior to the double-blind phase, patients were randomized in a 2:1 ratio to receive INVEGA HAFYERA (478 patients) or PP3M (224 patients).

The primary efficacy variable was time to first relapse in the double-blind phase. The primary efficacy analysis was based on the difference in Kaplan-Meier 12-month estimates of percentage of subjects remaining relapse-free between INVEGA HAFYERA and 3-month paliperidone palmitate extended-release injectable suspension. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥25% increase (if the baseline score was >40) or a 10-point increase (if the baseline score was ≤40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation: a score of ≥5 (if the maximum baseline score was ≤3) or ≥6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items.

A relapse event was experienced by 7.5% and 4.9% of patients in the INVEGA HAFYERA and PP3M treatment groups, respectively, with the Kaplan-Meier estimated difference (INVEGA HAFYERA – PP3M) of 2.9% (95% CI: -1.1 to 6.8). The upper bound of the 95% CI (6.8%) was less than 10%, the prespecified non-inferiority margin. The study demonstrated non-inferiority of INVEGA HAFYERA to PP3M. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 4.

Figure 4: Kaplan-Meier Plot of Cumulative Proportion of Patients with Relapse Over Time



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

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA HAFYERA® is available as a white to off-white sterile aqueous extended-release suspension for gluteal intramuscular injection in dose strengths of 1,092 mg/3.5 mL and 1,560 mg/5 mL paliperidone palmitate. The kit contains a single-dose prefilled syringe and a 20G, 1½-inch safety needle.

1,092 mg paliperidone palmitate kit (NDC 50458-611-01)

1,560 mg paliperidone palmitate kit (NDC 50458-612-01)

Storage and Handling

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

Ship and store in a horizontal position. See arrows on product carton for proper orientation.

17 PATIENT COUNSELING INFORMATION

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

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal side effect referred to as Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Patients should contact their health care provider or report to the emergency room if they experience the following signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

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

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness), and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Orthostatic Hypotension

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

Leukopenia/Neutropenia

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

Hyperprolactinemia

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

Interference with Cognitive and Motor Performance

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

Priapism

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

Heat Exposure and Dehydration

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

Concomitant Medication

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

Pregnancy

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

Lactation

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

Infertility

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

INVEGA HAFYERA (paliperidone palmitate) Extended-Release Injectable Suspension

INVEGA TRINZA, INVEGA SUSTENNA, RISPERDAL, and RISPERDAL CONSTA are trademarks of Janssen Pharmaceuticals, Inc.

Product of Ireland

Manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

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

For patent information: www.janssenpatents.com

PATIENT INFORMATION
INVEGA HAFYERA® (in-VAY-guh HAF-ye-RA)
(paliperidone palmitate)
extended-release injectable suspension

What is the most important information I should know about INVEGA HAFYERA?

INVEGA HAFYERA may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis.** INVEGA HAFYERA increases the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). INVEGA HAFYERA is not for the treatment of people with dementia-related psychosis.

What is INVEGA HAFYERA?

INVEGA HAFYERA is a prescription medicine given by injection by a healthcare provider 1 time every 6 months and used for the treatment of schizophrenia in adults who have been adequately treated with either:

- A 1 time each month paliperidone palmitate extended-release injectable suspension for at least 4 months.
- A 1 time every 3 months paliperidone palmitate extended-release injectable suspension for at least 3 months.

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

Do not receive INVEGA HAFYERA if you are allergic to paliperidone palmitate, risperidone, or any of the ingredients in INVEGA HAFYERA. See the end of this Patient Information leaflet for a complete list of ingredients in INVEGA HAFYERA.

Before receiving INVEGA HAFYERA, tell your healthcare provider about all your medical conditions, including if you:

- have had Neuroleptic Malignant Syndrome (NMS)
- have or have had heart problems, including a heart attack, heart failure, abnormal heart rhythm, or long QT syndrome
- have or have had low levels of potassium or magnesium in your blood
- have or have had uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)
- have or have had kidney or liver problems
- have diabetes or have a family history of diabetes
- have Parkinson's disease or a type of dementia called Lewy Body Dementia
- have had a low white blood cell count
- have had problems with dizziness or fainting or are being treated for high blood pressure
- have or have had seizures or epilepsy
- are pregnant or plan to become pregnant. It is not known if INVEGA HAFYERA will harm your unborn baby.
    - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with INVEGA HAFYERA.
    - If you become pregnant while receiving INVEGA HAFYERA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
    - Babies born to mothers who receive INVEGA HAFYERA during their third trimester of pregnancy may develop agitation, low muscle tone (floppy baby syndrome) tremors, excessive sleepiness, breathing problems, and feeding problems. Tell your healthcare provider right away if your baby develops any of these symptoms.
- are breastfeeding or plan to breastfeed. INVEGA HAFYERA can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with INVEGA HAFYERA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

INVEGA HAFYERA and other medicines may affect each other causing possible serious side effects. INVEGA HAFYERA may affect the way other medicines work, and other medicines may affect how INVEGA HAFYERA works.

Your healthcare provider can tell you if it is safe to receive INVEGA HAFYERA with your other medicines. Do not start or stop any medicines during treatment with INVEGA HAFYERA without talking to your healthcare provider first.

Know the medicines you take. Keep a list of them to show to your healthcare provider or pharmacist when you get a new medicine.

How will I receive INVEGA HAFYERA?

- Follow your INVEGA HAFYERA treatment schedule exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much INVEGA HAFYERA you will receive and when you will receive it.
- INVEGA HAFYERA is given as an injection by your healthcare provider into the muscle (intramuscularly) of your buttocks, 1 time every 6 months.

What should I avoid while receiving INVEGA HAFYERA?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how INVEGA HAFYERA affects you. INVEGA HAFYERA may affect your judgment, thinking, or motor skills.
- Avoid getting too hot or dehydrated.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of INVEGA HAFYERA?

INVEGA HAFYERA may cause serious side effects, including:

- See **"What is the most important information I should know about INVEGA HAFYERA?"**
- **Cerebrovascular problems (including stroke) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic Malignant Syndrome (NMS), a serious condition that can lead to death.** Call your healthcare provider or go to your nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - confusion
  - changes in your breathing, pulse, heart rate, and blood pressure
  - stiff muscles
  - sweating
- **Problems with your heartbeat.** These heart problems can cause death. Call your healthcare provider right away if you have any of these symptoms:
  - passing out or feeling like you will pass out
  - dizziness
  - feeling as if your heart is pounding or missing beats
- **Uncontrolled body movements (tardive dyskinesia).** INVEGA HAFYERA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving INVEGA HAFYERA. Tardive dyskinesia may also start after you stop receiving INVEGA HAFYERA.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes**. Increases in blood sugar can happen in some people who receive INVEGA HAFYERA. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start and regularly during treatment with INVEGA HAFYERA.

Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with INVEGA HAFYERA:

- feel very thirsty
- feel very hungry
- feel sick to your stomach
- need to urinate more than usual
- feel weak or tired
- feel confused, or your breath smells fruity

  - **increased fat levels (cholesterol and triglycerides) in your blood.** Your healthcare provider should check the fat levels in your blood before you start and regularly during treatment with INVEGA HAFYERA.
  - **weight gain.** You and your healthcare provider should check your weight before you start and often during treatment with INVEGA HAFYERA.

- **Decreased blood pressure (orthostatic hypotension) and fainting.** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position, especially early in treatment or when the dose is changed.
- **Falls.** INVEGA HAFYERA may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Low white blood cell count.** Your healthcare provider may do blood tests during the first few months of treatment with INVEGA HAFYERA.
- **Increased prolactin levels in your blood (hyperprolactinemia).** INVEGA HAFYERA may cause a rise in the blood levels of a hormone called prolactin (hyperprolactinemia) that may cause side effects including missed menstrual periods, a reversible reduction in fertility in females who are able to become pregnant, leakage of milk from the breasts, development of breasts in men, or problems with erection.
- **INVEGA HAFYERA can make you sleepy or dizzy, and can slow your thinking and motor skills.** Do not drive, operate heavy machinery, or do other dangerous activities until you know how INVEGA HAFYERA affects you.
- **Seizures (convulsions).**
- **Difficulty swallowing** that can cause food or liquid to get into your lungs.
- **Prolonged or painful erection lasting more than 4 hours (priapism).** Call your healthcare provider or go to your nearest emergency room right away if you have an erection that lasts more than 4 hours.
- **Problems controlling your body temperature so that you feel too warm.** See, "What should I avoid while receiving INVEGA HAFYERA?"

The most common side effects of INVEGA HAFYERA include:

- upper respiratory tract infections
- weight gain
- feeling restlessness or difficulty sitting still
- tremors
- shuffling walk
- injection site reactions
- headache
- slow movements
- stiffness

These are not all the possible side effects of INVEGA HAFYERA.

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

General information about INVEGA HAFYERA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about INVEGA HAFYERA that is written for health professionals.

What are the ingredients in INVEGA HAFYERA?

Active ingredient: paliperidone palmitate

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

Manufactured by: Janssen Pharmaceutica N.V. Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560, USA

For more information, go to www.invegahafyerahcp.com or call 1-800-526-7736.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: September 2024

INSTRUCTIONS FOR USE

INVEGA HAFYERA®

in-VAY-guh HAF-ye-RA
(paliperidone palmitate)
extended-release injectable
suspension

For Gluteal Intramuscular
Injection Only

Administer every 6 months

Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds

INSTRUCTIONS FOR USE

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Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds

Important

⚠ **Shipping and storing the carton in a horizontal orientation improves the ability to resuspend this highly concentrated product.**

Preparation

INVEGA HAFYERA requires **longer and faster shaking** than once-a-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA SUSTENNA).

INVEGA HAFYERA must be administered by a healthcare professional as a single injection. **Do not** divide dose into multiple injections.

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

Dosing

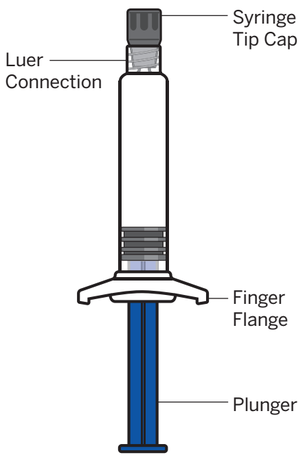
Administer INVEGA HAFYERA **once every 6 months.**

Thin Wall Safety Needle

Thin wall safety needle is designed to be used with INVEGA HAFYERA. Therefore, it is important to **only use the needle provided in the INVEGA HAFYERA suspension kit.**

Dose pack contents

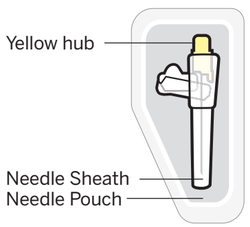
Prefilled Syringe



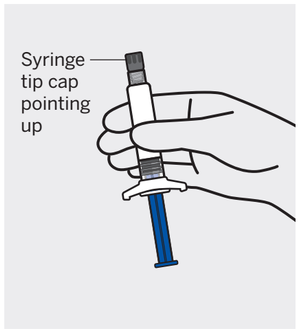
Thin Wall Safety Needle

20G×1½"

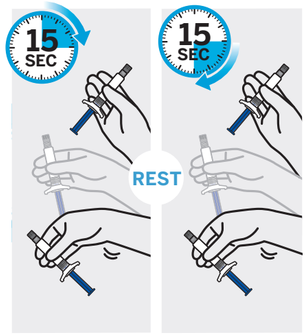
⚠ **Only use the needle included in this kit.**



1 Prepare for the injection: this highly concentrated product requires specific steps to resuspend



Hold syringe with the tip cap pointing up



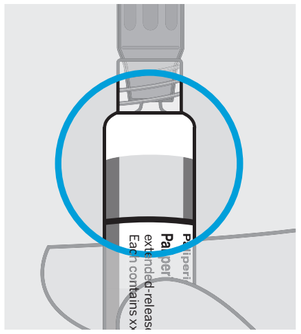
Shake syringe VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds

To ensure complete resuspension shake syringe with:

- **Short, VERY FAST up and down motion**
- **Loose wrist**

If more than 5 minutes pass before injection, shake the syringe VERY FAST with the tip cap pointing up again for at least 30 seconds to resuspend INVEGA HAFYERA

Proceed to the next step immediately after shaking.



Check suspension for solid product

Mixed well

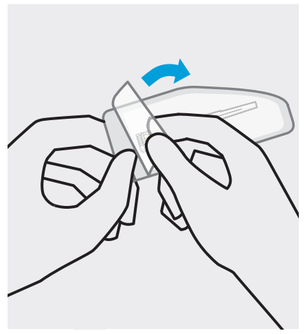
- Uniform, thick and milky white
- It is normal to see air bubbles

Not mixed well

- Solid product on sides and top of syringe
- Uneven mix
- Thin liquid

⚠ STOP

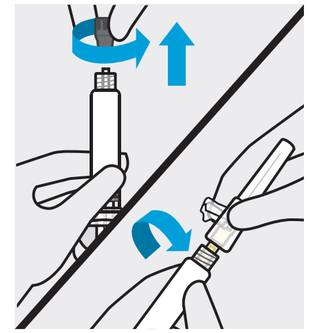
Product may clog. Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest, then shake again for 15 seconds.



Open needle pouch

Peel off the pouch cover.

Place pouch with the needle inside on a clean surface.



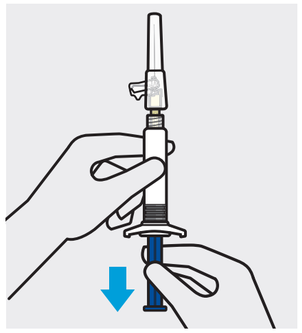
Remove syringe tip cap and attach needle

Hold the syringe with the tip cap pointing up. Twist and pull off the cap.

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

⚠ **Only use the needle included in this kit.**

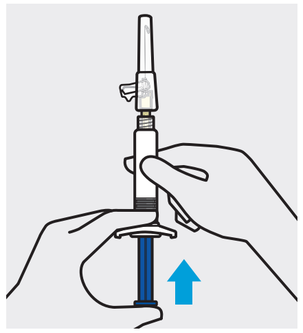
2 Slowly inject entire content and confirm



Pull back plunger

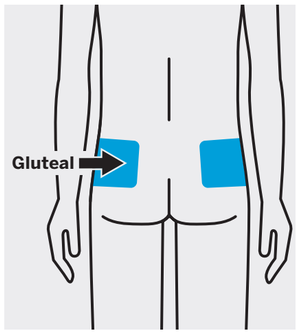
Hold the syringe upright.

Gently pull back the plunger to clear the syringe tip of any solid product. This will make pressing the plunger easier during the injection.



Remove air bubbles

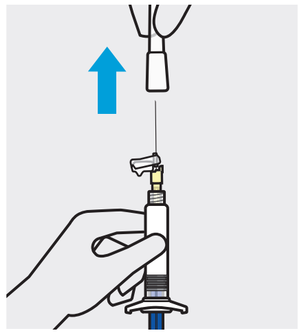
Press the plunger carefully until a drop of liquid comes out of the needle tip.



Select and clean a gluteal injection site

Wipe the gluteal site with an alcohol swab and allow it to dry.

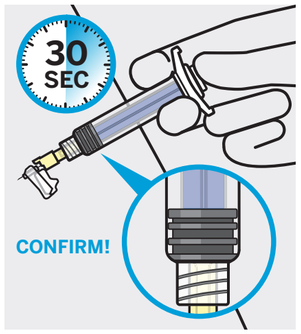
Do not touch, fan or blow on the injection site after you have cleaned it.



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.



Slowly inject and confirm

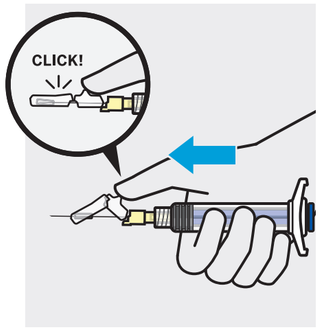
Use slow, firm, consistent pressure to press the plunger **completely**. This should take approximately **30 seconds**.

Continue to press the plunger if you feel resistance. This is normal.

While the needle is in the gluteal muscle, confirm that the entire content of the syringe has been injected.

Remove needle from the muscle.

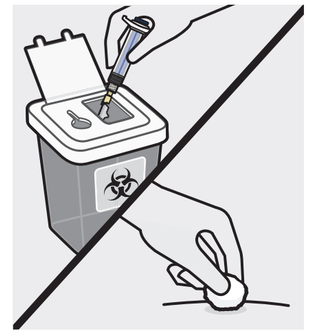
3 After the injection



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 you hear a "click" sound.



Dispose of properly and check injection site

Dispose of the syringe in an approved sharps container.

There may be a small amount of blood or liquid at the injection site. Hold pressure over the skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 9/2024

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

For patent information:
www.janssenpatents.com

Reference ID: 5517951

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA® safely and effectively. See full prescribing information for INVEGA®.

INVEGA® (paliperidone) Extended-Release Tablets
Initial U.S. Approval: 2006

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

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.5)	1/2025
Warnings and Precautions (5.7)	1/2025

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

INVEGA is an atypical antipsychotic agent indicated for

Treatment of schizophrenia (1.1)

- Adults: Efficacy was established in three 6-week trials and one maintenance trial. (14.1)
- Adolescents (ages 12-17): Efficacy was established in one 6-week trial. (14.1)

Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants. (1.2)

- Efficacy was established in two 6-week trials in adult patients. (14.2)

----------DOSAGE AND ADMINISTRATION----------

		Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia - adults (2.1)		6 mg/day	3 - 12 mg/day	12 mg/day
Schizophrenia-adolescents (2.1)	Weight < 51kg	3 mg/day	3 - 6 mg/day	6 mg/day
	Weight ≥ 51kg	3 mg/day	3 - 12 mg/day	12 mg/day
Schizoaffective disorder - adults (2.2)		6 mg/day	3 - 12 mg/day	12 mg/day

- Tablet should be swallowed whole and should not be chewed, divided, or crushed. (2.3)

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

Tablets: 3 mg, 6 mg, and 9 mg (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions:* An increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotics. (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *QT Prolongation:* Increase in QT interval, avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. (5.4)
- *Tardive Dyskinesia:* Discontinue drug if clinically appropriate. (5.5)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.6)
    - *Hyperglycemia and Diabetes Mellitus:* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
    - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.6)
    - *Weight Gain:* Significant weight gain has been reported. Monitor weight gain. (5.6)
- *Hyperprolactinemia:* Prolactin elevations occur and persist during chronic administration. (5.7)
- *Gastrointestinal Narrowing:* Obstructive symptoms may result in patients with gastrointestinal disease. (5.8)
- *Orthostatic Hypotension and Syncope:* Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension. (5.9)
- *Leukopenia, Neutropenia, and Agranulocytosis:* has been reported with antipsychotics, including INVEGA. Patients with a history of a clinically significant low white blood cell count (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 should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.11)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.12)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.13)

----------ADVERSE REACTIONS----------

Commonly observed adverse reactions (incidence ≥ 5% and at least twice that for placebo) were (6)

- Adults with schizophrenia: extrapyramidal symptoms, tachycardia, and akathisia.
- Adolescents with schizophrenia: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia.
- Adults with schizoaffective disorder: extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

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

----------DRUG INTERACTIONS----------

- Centrally-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol. (7.1)
- Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with INVEGA. (7.1)
- Strong CYP3A4/P-glycoprotein (P-gp) inducers: It may be necessary to increase the dose of INVEGA when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA. (7.2)
- Co-administration of divalproex sodium increased C_{max} and AUC of paliperidone by approximately 50%. Adjust dose of INVEGA if necessary based on clinical assessment. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Renal impairment: Dosing must be individualized according to renal function status. (2.5)
- Elderly: Same as for younger adults (adjust dose according to renal function status). (2.4)
- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Pediatric Use: Safety and effectiveness in the treatment of schizophrenia not established in patients less than 12 years of age. Safety and effectiveness in the treatment of schizoaffective disorder not established in patients less than 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

1.1 Schizophrenia

INVEGA (paliperidone) Extended-Release Tablets are indicated for the treatment of schizophrenia *[see Clinical Studies (14.1)]*.

The efficacy of INVEGA in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents, as well as one maintenance trial in adults.

1.2 Schizoaffective Disorder

INVEGA (paliperidone) Extended-Release Tablets are indicated for the treatment of schizoaffective disorder as monotherapy and an adjunct to mood stabilizers and/or antidepressant therapy *[see Clinical Studies (14.2)]*.

The efficacy of INVEGA in schizoaffective disorder was established in two 6-week trials in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended dose of INVEGA (paliperidone) Extended-Release Tablets for the treatment of schizophrenia in adults is 6 mg administered once daily. Initial dose titration is not required. Although it has not been systematically established that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse reactions. Thus, some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

In a longer-term study, INVEGA has been shown to be effective in delaying time to relapse in patients with schizophrenia who were stabilized on INVEGA for 6 weeks *[see Clinical Studies (14)]*. INVEGA should be prescribed at the lowest effective dose for maintaining clinical stability and the physician should periodically reevaluate the long-term usefulness of the drug in individual

patients.

Adolescents (12-17 years of age)

The recommended starting dose of INVEGA (paliperidone) Extended-Release Tablets for the treatment of schizophrenia in adolescents 12-17 years of age is 3 mg administered once daily. Initial dose titration is not required. Dose increases, if considered necessary, should be made only after clinical reassessment and should occur at increments of 3 mg/day at intervals of more than 5 days. Prescribers should be mindful that, in the adolescent schizophrenia study, there was no clear enhancement to efficacy at the higher doses, i.e., 6 mg for subjects weighing less than 51 kg and 12 mg for subjects weighing 51 kg or greater, while adverse events were dose-related.

2.2 Schizoaffective Disorder

The recommended dose of INVEGA (paliperidone) Extended-Release Tablets for the treatment of schizoaffective disorder in adults is 6 mg administered once daily. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended dose range of 3 to 12 mg once daily. A general trend for greater effects was seen with higher doses. This trend must be weighed against dose-related increase in adverse reactions. Dosage adjustment, if indicated, should occur only after clinical reassessment. Dose increases, if indicated, generally should occur at intervals of more than 4 days. When dose increases are indicated, increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

2.3 Administration Instructions

INVEGA can be taken with or without food.

INVEGA must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

2.4 Use with Risperidone

Concomitant use of INVEGA with risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is coadministered with INVEGA.

2.5 Dosage in Special Populations

Renal Impairment

Dosing must be individualized according to the patient's renal function status. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), the recommended initial dose of INVEGA is 3 mg once daily. The dose may then be increased to a maximum of 6 mg once daily based on clinical response and tolerability. For patients with moderate to severe renal impairment (creatinine clearance ≥ 10 mL/min to < 50 mL/min), the recommended initial dose of INVEGA is 3 mg every other day, which may be increased to a maximum of 3 mg once daily after clinical reassessment. As INVEGA has not been studied in patients with creatinine clearance below 10 mL/min, use is not recommended in such patients. *[See Clinical Pharmacology (12.3)]*

Hepatic Impairment

For patients with mild to moderate hepatic impairment, (Child-Pugh Classification A and B), no dose adjustment is recommended *[see Clinical Pharmacology (12.3)]*. INVEGA has not been studied in patients with severe hepatic impairment.

Elderly

Because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status. In general, recommended dosing for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. For patients with moderate to severe renal impairment (creatinine clearance 10 mL/min to < 50 mL/min), the maximum recommended dose of INVEGA is 3 mg once daily *[see Renal Impairment above]*.

3 DOSAGE FORMS AND STRENGTHS

INVEGA Extended-Release Tablets are available in the following strengths and colors: 3 mg (white), 6 mg (beige), and 9 mg (pink). All tablets are capsule shaped and are imprinted with either "PAL 3", "PAL 6", or "PAL 9".

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA (paliperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA was not marketed at the time these studies were performed. INVEGA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

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

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

5.4 QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class

1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA ($C_{max\ ss}$ = 113 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.

For the three fixed-dose efficacy studies in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA had a QTcLD exceeding 500 msec at any time in any of these three studies.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear

to increase with duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, INVEGA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on INVEGA, drug discontinuation should be considered. However, some patients may require treatment with INVEGA despite the presence of the syndrome.

5.6 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA. 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. Because INVEGA was not

marketed at the time these studies were performed, it is not known if INVEGA is associated with this increased risk.

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

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia are presented in Table 1a.

Table 1a. Change in Fasting Glucose from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

		INVEGA			
	Placebo	**3 mg/day**	**6 mg/day**	**9 mg/day**	**12 mg/day**
		Mean change from baseline (mg/dL)			
	n=322	**n=122**	**n=212**	**n=234**	**n=218**
Serum Glucose					
Change from baseline	0.8	-0.7	0.4	2.3	4.3
		Proportion of Patients with Shifts			
Serum Glucose					
Normal to High	5.1%	3.2%	4.5%	4.8%	3.8%
(<100 mg/dL to ≥126 mg/dL)	(12/236)	(3/93)	(7/156)	(9/187)	(6/157)

In the uncontrolled, longer-term open-label extension studies, INVEGA was associated with a mean change in glucose of +3.3 mg/dL at Week 24 (n=570) and +4.6 mg/dL at Week 52 (n=314).

Data from the placebo-controlled 6-week study in adolescent subjects (12-17 years of age) with schizophrenia are presented in Table 1b.

Table 1b. Change in Fasting Glucose from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia

		INVEGA			
	Placebo	**1.5 mg/day**	**3 mg/day**	**6 mg/day**	**12 mg/day**
		Mean change from baseline (mg/dL)			
	n=41	**n=44**	**n=11**	**n=28**	**n=32**
Serum Glucose Change from baseline	0.8	-1.4	-1.8	-0.1	5.2
		Proportion of Patients with Shifts			
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	3% (1/32)	0% (0/34)	0% (0/9)	0% (0/20)	11% (3/27)

Dyslipidemia

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

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia are presented in Table 2a.

Table 2a. Change in Fasting Lipids from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

		INVEGA			
	Placebo	**3 mg/day**	**6 mg/day**	**9 mg/day**	**12 mg/day**
		Mean change from baseline (mg/dL)			
Cholesterol	**n=331**	**n=120**	**n=216**	**n=236**	**n=231**
Change from baseline	-6.3	-4.4	-2.4	-5.3	-4.0
LDL	**n=322**	**n=116**	**n=210**	**n=231**	**n=225**
Change from baseline	-3.2	0.5	-0.8	-3.9	-2.0
HDL	**n=331**	**n=119**	**n=216**	**n=234**	**n=230**
Change from baseline	0.3	-0.4	0.5	0.8	1.2
Triglycerides	**n=331**	**n=120**	**n=216**	**n=236**	**n=231**
Change from baseline	-22.3	-18.3	-12.6	-10.6	-15.4
		Proportion of Patients with Shifts			
Cholesterol					
Normal to High	2.6%	2.8%	5.6%	4.1%	3.1%
(<200 mg/dL to ≥240 mg/dL)	(5/194)	(2/71)	(7/125)	(6/147)	(4/130)
LDL					
Normal to High	1.9%	0.0%	5.0%	3.7%	0.0%
(<100 mg/dL to ≥160 mg/dL)	(2/105)	(0/44)	(3/60)	(3/81)	(0/69)
HDL					
Normal to Low	22.0%	16.3%	29.1%	23.4%	20.0%
(≥40 mg/dL to <40 mg/dL)	(44/200)	(13/80)	(39/134)	(32/137)	(27/135)
Triglycerides					
Normal to High	5.3%	11.0%	8.8%	8.7%	4.3%
(<150 mg/dL to ≥200 mg/dL)	(11/208)	(9/82)	(12/136)	(13/150)	(6/139)

In the uncontrolled, longer-term open-label extension studies, INVEGA was associated with a mean change in (a) total cholesterol of -1.5 mg/dL at Week 24 (n=573) and -1.5 mg/dL at Week 52 (n=317), (b) triglycerides of -6.4 mg/dL at Week 24 (n=573) and -10.5 mg/dL at Week 52 (n=317); (c) LDL of -1.9 mg/dL at Week 24 (n=557) and -2.7 mg/dL at Week 52 (n=297); and (d) HDL of +2.2 mg/dL at Week 24 (n=568) and +3.6 mg/dL at Week 52 (n=302).

Data from the placebo-controlled 6-week study in adolescent subjects (12-17 years of age) with schizophrenia are presented in Table 2b.

Table 2b. Change in Fasting Lipids from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia

		INVEGA			
	Placebo	**1.5 mg/day**	**3 mg/day**	**6 mg/day**	**12 mg/day**
	Mean change from baseline (mg/dL)				
Cholesterol	**n=39**	**n=45**	**n=11**	**n=28**	**n=32**
Change from baseline	-7.8	-3.3	12.7	3.0	-1.5
LDL	**n=37**	**n=40**	**n=9**	**n=27**	**n=31**
Change from baseline	-4.1	-3.1	7.2	2.4	0.6
HDL	**n=37**	**n=41**	**n=9**	**n=27**	**n=31**
Change from baseline	-1.9	0.0	1.3	1.4	0.0
Triglycerides	**n=39**	**n=44**	**n=11**	**n=28**	**n=32**
Change from baseline	-8.9	3.2	17.6	-5.4	3.9
	Proportion of Patients with Shifts				
Cholesterol					
Normal to High	7%	4%	0%	6%	11%
(<170 mg/dL to ≥200 mg/dL)	(2/27)	(1/26)	(0/6)	(1/18)	(2/19)
LDL					
Normal to High	3%	4%	14%	0%	9%
(<110 mg/dL to ≥130 mg/dL)	(1/32)	(1/25)	(1/7)	(0/22)	(2/22)
HDL					
Normal to Low	14%	7%	29%	13%	23%
(≥40 mg/dL to <40 mg/dL)	(4/28)	(2/30)	(2/7)	(3/23)	(5/22)
Triglycerides					
Normal to High	3%	5%	13%	8%	7%
(<150 mg/dL to ≥200 mg/dL)	(1/34)	(2/38)	(1/8)	(2/26)	(2/28)

Weight Gain

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

Schizophrenia Trials

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥ 7% of body weight from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects are presented in Table 3a.

Table 3a. Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥ 7% Gain in Body Weight from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

		INVEGA			
	Placebo	3 mg/day	6 mg/day	9 mg/day	12 mg/day
	n=323	n=112	n=215	n=235	n=218
Weight (kg)					
Change from baseline	-0.4	0.6	0.6	1.0	1.1
Weight Gain					
≥ 7% increase from baseline	5%	7%	6%	9%	9%

In the uncontrolled, longer-term open-label extension studies, INVEGA was associated with a mean change in weight of +1.4 kg at Week 24 (n=63) and +2.6 kg at Week 52 (n=302).

Weight gain in adolescent subjects with schizophrenia was assessed in a 6-week, double-blind, placebo-controlled study and an open-label extension with a median duration of exposure to INVEGA of 182 days. Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥ 7% of body weight *[see Clinical Studies (14.1)]* from the placebo-controlled 6-week study in adolescent subjects (12-17 years of age) are presented in Table 3b.

Table 3b. Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥ 7% Gain in Body Weight from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia

		INVEGA			
	Placebo	1.5 mg/day	3 mg/day	6 mg/day	12 mg/day
	n=51	n=54	n=16	n=45	n=34
Weight (kg)					
Change from baseline	0.0	0.3	0.8	1.2	1.5
Weight Gain					
≥ 7% increase from baseline	2%	6%	19%	7%	18%

In the open-label long-term study the proportion of total subjects treated with INVEGA with an increase in body weight of ≥ 7% from baseline was 33%. When treating adolescent patients with INVEGA, weight gain should be assessed against that expected with normal growth. When taking into consideration the median duration of exposure to INVEGA in the open-label study (182 days) along with expected normal growth in this population based on age and gender, an assessment of standardized scores relative to normative data provides a more clinically relevant measure of changes in weight. The mean change from open-label baseline to endpoint in standardized score for weight was 0.1 (4% above the median for normative data). Based on comparison to the normative data, these changes are not considered to be clinically significant.

Schizoaffective Disorder Trials

In the pooled data from the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder, a higher percentage of INVEGA-treated subjects (5%) had an increase in body weight of ≥ 7% compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of ≥ 7% was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

5.7 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.

5.8 Potential for Gastrointestinal Obstruction

Because the INVEGA tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA should only be used in patients who are able to swallow the tablet whole *[see Dosage and Administration (2.3) and*

Patient Counseling Information (17)].

A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract.

5.9 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA (3 mg, 6 mg, 9 mg, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo.

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

5.10 Falls

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

5.11 Leukopenia, Neutropenia, and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA in patients

with severe neutropenia (absolute neutrophil count < 1000/mm^3) and follow their WBC until recovery.

5.12 Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA *[see Adverse Reactions (6.2)]*. Antipsychotics, including INVEGA, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.13 Seizures

During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. Like other antipsychotic drugs, INVEGA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.14 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 and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.15 Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with INVEGA during postmarketing surveillance. Severe priapism may require surgical intervention.

5.16 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 to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic changes *[see Warnings and Precautions (5.6)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.7)]*
- Potential for gastrointestinal obstruction *[see Warnings and Precautions (5.8)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.9)]*
- Falls *[see Warnings and Precautions (5.10)]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.11)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Dysphagia *[see Warnings and Precautions (5.14)]*
- Priapism *[see Warnings and Precautions (5.15)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

The most common adverse reactions in clinical trials in adult subjects with schizophrenia (reported in 5% or more of subjects treated with INVEGA and at least twice the placebo rate in any of the dose groups) were extrapyramidal symptoms, tachycardia, and akathisia. The most common adverse reactions in clinical trials in adult patients with schizoaffective disorder (reported in 5%

or more of subjects treated with INVEGA and at least twice the placebo rate) were extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

The most common adverse reactions that were associated with discontinuation from clinical trials in adult subjects with schizophrenia (causing discontinuation in 2% of INVEGA-treated subjects) were nervous system disorders. The most common adverse reactions that were associated with discontinuation from clinical trials in adult subjects with schizoaffective disorder were gastrointestinal disorders, which resulted in discontinuation in 1% of INVEGA-treated subjects. *[See Adverse Reactions (6)]*.

The safety of INVEGA was evaluated in 1205 adult subjects with schizophrenia who participated in three placebo-controlled, 6-week, double-blind trials, of whom 850 subjects received INVEGA at fixed doses ranging from 3 mg to 12 mg once daily. The information presented in this section was derived from pooled data from these three trials. Additional safety information from the placebo-controlled phase of the long-term maintenance study, in which subjects received INVEGA at daily doses within the range of 3 mg to 15 mg (n=104), is also included.

The safety of INVEGA was evaluated in 150 adolescent subjects 12-17 years of age with schizophrenia who received INVEGA in the dose range of 1.5 mg to 12 mg/day in a 6-week, double-blind, placebo-controlled trial.

The safety of INVEGA was also evaluated in 622 adult subjects with schizoaffective disorder who participated in two placebo-controlled, 6-week, double-blind trials. In one of these trials, 206 subjects were assigned to one of two dose levels of INVEGA: 6 mg with the option to reduce to 3 mg (n=108) or 12 mg with the option to reduce to 9 mg (n=98) once daily. In the other study, 214 subjects received flexible doses of INVEGA (3-12 mg once daily). Both studies included subjects who received INVEGA either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. 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.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of INVEGA (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for INVEGA often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia in Adults and Adolescents

Adult Patients with Schizophrenia

Table 4 enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies in adults, listing those that occurred in 2% or more of subjects treated with INVEGA in any of the dose groups, and for which the incidence in INVEGA-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

Table 4. Adverse Reactions Reported by ≥ 2% of INVEGA-Treated Adult Subjects with Schizophrenia in Three Short-Term, Fixed-Dose, Placebo-Controlled Clinical Trials *

	Percentage of Patients				
		INVEGA			
Body System or Organ Class Dictionary-Derived Term	**Placebo (N=355)**	**3 mg once daily (N=127)**	**6 mg once daily (N=235)**	**9 mg once daily (N=246)**	**12 mg once daily (N=242)**
Total percentage of subjects with adverse reactions	37	48	47	53	59
Cardiac disorders					
Atrioventricular block first degree	1	2	0	2	1
Bundle branch block	2	3	1	3	<1
Sinus arrhythmia	0	2	1	1	<1
Tachycardia	7	14	12	12	14
Gastrointestinal disorders					
Abdominal pain upper	1	1	3	2	2
Dry mouth	1	2	3	1	3
Salivary hypersecretion	<1	0	<1	1	4
General disorders					
Asthenia	1	2	<1	2	2
Fatigue	1	2	1	2	2
Nervous system disorders					
Akathisia	4	4	3	8	10
Dizziness	4	6	5	4	5
Extrapyramidal symptoms	8	10	7	20	18
Headache	12	11	12	14	14
Somnolence	7	6	9	10	11
Vascular disorders					
Orthostatic hypotension	1	2	1	2	4

* Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies; one study included once-daily INVEGA doses of 3 mg and 9 mg, the second study included 6 mg, 9 mg, and 12 mg, and the third study included 6 mg and 12 mg *[see Clinical Studies (14)]*. Extrapyramidal symptoms includes the terms dyskinesia, dystonia, extrapyramidal disorder, hypertonia, muscle rigidity, oculogyration, parkinsonism, and tremor. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Adverse reactions for which the INVEGA incidence was equal to or less than placebo are not listed in the table, but included the following: vomiting.

Adolescent Patients with Schizophrenia

Table 5 lists the adverse reactions reported in a fixed-dose, placebo-controlled study in adolescent subjects 12-17 years of age with schizophrenia, listing those that occurred in 2% or more of subjects treated with INVEGA in any of the dose groups, and for which the incidence in INVEGA-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

Table 5. Adverse Reactions Reported by ≥ 2% of INVEGA-Treated Adolescent Subjects with Schizophrenia in a Fixed-Dose, Placebo-Controlled Clinical Trial *

	Percentage of Patients				
		INVEGA			
Body System or Organ Class Dictionary-Derived Term	**Placebo (N=51)**	**1.5 mg once daily (N=54)**	**3 mg once daily (N=16)**	**6 mg once daily (N=45)**	**12 mg once daily (N=35)**
Total percentage of subjects with adverse reactions	43	37	50	58	74
Cardiac disorders					
Tachycardia	0	0	6	9	6
Eye disorders					
Vision blurred	0	0	0	0	3
Gastrointestinal disorders					
Dry mouth	2	0	0	0	3
Salivary hypersecretion	0	2	6	2	0
Swollen tongue	0	0	0	0	3
Vomiting	10	0	6	11	3
General disorders					
Asthenia	0	0	0	2	3
Fatigue	0	4	0	2	3
Infections and infestations					
Nasopharyngitis	2	4	0	4	0
Investigations					
Weight increased	0	7	6	2	3
Nervous system disorders					
Akathisia	0	4	6	11	17
Dizziness	0	2	6	2	3
Extrapyramidal symptoms	0	4	19	18	23
Headache	4	9	6	4	14
Lethargy	0	0	0	0	3

Body System or Organ Class Dictionary-Derived Term	Percentage of Patients Placebo (N=51)	INVEGA 1.5 mg once daily (N=54)	3 mg once daily (N=16)	6 mg once daily (N=45)	12 mg once daily (N=35)
Somnolence	4	9	13	20	26
Tongue paralysis	0	0	0	0	3
Psychiatric disorders					
Anxiety	4	0	0	2	9
Reproductive system and breast disorders					
Amenorrhea	0	0	6	0	0
Galactorrhea	0	0	0	4	0
Gynecomastia	0	0	0	0	3
Respiratory, thoracic and mediastinal disorders					
Epistaxis	0	0	0	2	0

* Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA dose groups and which occurred at greater incidence than in the placebo group. Extrapyramidal symptoms includes the terms oculogyric crisis, muscle rigidity, musculoskeletal stiffness, nuchal rigidity, torticollis, trismus, bradykinesia, cogwheel rigidity, dyskinesia, dystonia, extrapyramidal disorder, hypertonia, hypokinesia, muscle contractions involuntary, parkinsonian gait, parkinsonism, tremor, and restlessness. Somnolence includes the terms somnolence, sedation, and hypersomnia. Insomnia includes the terms insomnia and initial insomnia. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Hypertension includes the terms hypertension and blood pressure increased. Gynecomastia includes the terms gynecomastia and breast swelling.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizoaffective Disorder in Adults

Table 6 enumerates the pooled incidences of adverse reactions reported in the two placebo-controlled 6-week studies in adult subjects, listing those that occurred in 2% or more of subjects treated with INVEGA and for which the incidence in INVEGA-treated subjects was greater than the incidence in subjects treated with placebo.

Table 6. Adverse Drug Reactions Reported by ≥ 2% of INVEGA-Treated Adult Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials *

Body System or Organ Class Dictionary-Derived Term	Percentage of Patients Placebo (N=202)	INVEGA 3-6 mg once-daily fixed-dose range (N=108)	INVEGA 9-12 mg once-daily fixed-dose range (N=98)	INVEGA 3-12 mg once-daily flexible dose (N=214)
Total percentage of subjects with adverse reactions	32	48	50	43
Cardiac disorders				
Tachycardia	2	3	1	2
Gastrointestinal disorders				
Abdominal discomfort/Abdominal pain upper	1	1	0	3
Constipation	2	4	5	4
Dyspepsia	2	5	6	6
Nausea	6	8	8	5
Stomach discomfort	1	0	1	2
General disorders				
Asthenia	1	3	4	<1
Infections and Infestations				
Nasopharyngitis	1	2	5	3
Rhinitis	0	1	3	1
Upper respiratory tract infection	1	2	2	2
Investigations				
Weight increased	1	5	4	4
Metabolism and nutrition disorders				
Decreased appetite	<1	1	0	2
Increased appetite	<1	3	2	2
Musculoskeletal and connective tissue disorders				
Back pain	1	1	1	3
Myalgia	<1	2	4	1
Nervous system disorders				
Akathisia	4	4	6	6
Dysarthria	0	1	4	2
Extrapyramidal symptoms	8	20	17	12
Somnolence	5	12	12	8
Psychiatric disorders				
Sleep disorder	<1	2	3	0

Body System or Organ Class Dictionary-Derived Term	Placebo (N=202)	Percentage of Patients INVEGA 3-6 mg once-daily fixed-dose range (N=108)	INVEGA 9-12 mg once-daily fixed-dose range (N=98)	INVEGA 3-12 mg once-daily flexible dose (N=214)
Respiratory, thoracic and mediastinal disorders				
Cough	1	1	3	1
Pharyngolaryngeal pain	<1	0	2	1

* Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from two studies. One study included once-daily INVEGA doses of 6 mg (with the option to reduce to 3 mg) and 12 mg (with the option to reduce to 9 mg). The second study included flexible once-daily doses of 3 to 12 mg. Among the 420 subjects treated with INVEGA, 230 (55%) received INVEGA as monotherapy and 190 (45%) received INVEGA as an adjunct to mood stabilizers and/or antidepressants. Extrapyramidal symptoms includes the terms bradykinesia, drooling, dyskinesia, dystonia, hypertonia, muscle rigidity, muscle twitching, oculogyration, parkinsonian gait, parkinsonism, restlessness, and tremor. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased.

Monotherapy versus Adjunctive Therapy

The designs of the two placebo-controlled, 6-week, double-blind trials in adult subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received INVEGA as monotherapy and 190 (45%) subjects received INVEGA as an adjunct to mood stabilizers and/or antidepressants. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥ 3% difference) in subjects receiving INVEGA as monotherapy.

Discontinuations Due to Adverse Reactions

Schizophrenia Trials

The percentages of subjects who discontinued due to adverse reactions in the three schizophrenia placebo-controlled, 6-week, fixed-dose studies in adults were 3% and 1% in INVEGA- and placebo-treated subjects, respectively. The most common reasons for discontinuation were nervous system disorders (2% and 0% in INVEGA- and placebo-treated subjects, respectively).

Among the adverse reactions in the 6-week, fixed-dose, placebo-controlled study in adolescents with schizophrenia, only dystonia led to discontinuation (<1% of INVEGA-treated subjects).

Schizoaffective Disorder Trials

The percentages of subjects who discontinued due to adverse reactions in the two schizoaffective disorder placebo-controlled 6-week studies in adults were 1% and <1% in INVEGA- and placebo-treated subjects, respectively. The most common reasons for discontinuation were gastrointestinal disorders (1% and 0% in INVEGA- and placebo-treated subjects, respectively).

Dose-Related Adverse Reactions

Schizophrenia Trials

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

In the 6-week, fixed-dose, placebo-controlled study in adolescents with schizophrenia, among the adverse reactions that occurred with >2% incidence in the subjects treated with INVEGA, the incidences of the following adverse reactions increased with dose: tachycardia, akathisia, extrapyramidal symptoms, somnolence, and headache.

Schizoaffective Disorder Trials

In a placebo-controlled, 6-week, high- and low-dose study in adult subjects with schizoaffective disorder, akathisia, dystonia, dysarthria, myalgia, nasopharyngitis, rhinitis, cough, and pharyngolaryngeal pain occurred more frequently (i.e., a difference of at least 2%) in subjects who received higher doses of INVEGA compared with subjects who received lower doses.

Demographic Differences

An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia and in the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder did not reveal any evidence of clinically relevant differences in safety on the basis of gender or race alone; there was also no difference on the basis of age *[see Use in Specific Populations (8.5)]*.

Extrapyramidal Symptoms (EPS)

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to

treat emergent EPS (*Table 7*), and (4) incidence of spontaneous reports of EPS (*Table 8*). For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA 3 mg and 6 mg doses for any of these EPS measures.

Table 7. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

	Percentage of Patients				
		INVEGA			
EPS Group	**Placebo (N=355)**	**3 mg once daily (N=127)**	**6 mg once daily (N=235)**	**9 mg once daily (N=246)**	**12 mg once daily (N=242)**
Parkinsonism[a]	9	11	3	15	14
Akathisia[b]	6	6	4	7	9
Use of anticholinergic medications[c]	10	10	9	22	22

[a] For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items)
[b] For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2
[c] Percent of patients who received anticholinergic medications to treat emergent EPS

Table 8. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

	Percentage of Patients				
		INVEGA			
EPS Group	**Placebo (N=355)**	**3 mg once daily (N=127)**	**6 mg once daily (N=235)**	**9 mg once daily (N=246)**	**12 mg once daily (N=242)**
Overall percentage of patients with EPS-related AE	11	13	10	25	26
Dyskinesia	3	5	3	8	9
Dystonia	1	1	1	5	5
Hyperkinesia	4	4	3	8	10
Parkinsonism	2	3	3	7	6
Tremor	3	3	3	4	3

Dyskinesia group includes: Dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia
Dystonia group includes: Dystonia, muscle spasms, oculogyration, trismus
Hyperkinesia group includes: Akathisia, hyperkinesia
Parkinsonism group includes: Bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism
Tremor group includes: Tremor

Compared to data from the studies in adults subjects with schizophrenia, pooled data from the two placebo-controlled 6-week studies in adult subjects with schizoaffective disorder showed similar types and frequencies of EPS as measured by rating scales, anticholinergic medication use, and spontaneous reports of EPS-related adverse events. For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

Table 9 shows the EPS data from the pooled schizoaffective disorder trials.

Table 9. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies in Adults

	Percentage of Patients			
		INVEGA		
EPS Group	Placebo (N=202)	3-6 mg once-daily fixed-dose range (N=108)	9-12 mg once-daily fixed-dose range (N=98)	3-12 mg once-daily flexible dose (N=214)
Overall percentage of patients with EPS-related AE	11	23	22	17
Dyskinesia	1	3	1	1
Dystonia	1	2	3	2
Hyperkinesia	5	5	8	7
Parkinsonism	3	14	7	7
Tremor	3	12	11	5

Dyskinesia group includes: Dyskinesia, muscle twitching
Dystonia group includes: Dystonia, muscle spasms, oculogyration
Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness
Parkinsonism group includes: Bradykinesia, drooling, hypertonia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonian gait, parkinsonism
Tremor group includes: Tremor

The incidences of EPS-related adverse events in the adolescent schizophrenia studies showed a similar dose-related pattern to those in the adult studies. There were notably higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescent population as compared to the adult studies *(Table 10)*.

Table 10. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizophrenia Studies in Adolescent Subjects

	Percentage of Patients				
		INVEGA			
EPS Group	Placebo (N=51)	1.5 mg once daily (N=54)	3 mg once daily (N=16)	6 mg once daily (N=45)	12 mg once daily (N=35)
Overall percentage of patients with EPS-related AE	0	6	25	22	40
Hyperkinesia	0	4	6	11	17
Dystonia	0	2	0	11	14
Tremor	0	2	6	7	11
Parkinsonism	0	0	6	2	14
Dyskinesia	0	2	6	2	6

Hyperkinesia group includes: Akathisia
Dystonia group includes: Dystonia, muscle contracture, oculogyric crisis, tongue paralysis, torticollis
Tremor group includes: Tremor
Parkinsonism group includes: Cogwheel rigidity, extrapyramidal disorder, muscle rigidity
Dyskinesia group includes: Dyskinesia, muscle contractions involuntary

Dystonia

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

Laboratory Test Abnormalities

In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia and from the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder, between-group comparisons revealed no medically important differences between INVEGA and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA was associated with increases in serum prolactin *[see Warnings and Precautions (5.7)]*.

Other Adverse Reactions Observed During Premarketing Evaluation of INVEGA

The following additional adverse reactions occurred in < 2% of INVEGA-treated subjects in the above schizophrenia and schizoaffective disorder clinical trial datasets. The following also includes additional adverse reactions reported at any frequency by INVEGA-treated subjects who participated in other clinical studies.

Cardiac disorders: bradycardia, palpitations

Eye disorders: eye movement disorder

Gastrointestinal disorders: flatulence

General disorders: edema

Immune system disorders: anaphylactic reaction

Infections and infestations: urinary tract infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity

Nervous system disorders: opisthotonus

Psychiatric disorders: agitation, insomnia, nightmare

Reproductive system and breast disorders: breast discomfort, menstruation irregular, retrograde ejaculation

Respiratory, thoracic and mediastinal disorders: nasal congestion

Skin and subcutaneous tissue disorders: pruritus, rash

Vascular disorders: hypertension

The safety of INVEGA was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA in adults with schizophrenia *[see Clinical Studies (14)]*. In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of INVEGA; because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: angioedema, catatonia, ileus, priapism, somnambulism, swollen tongue, tardive dyskinesia, thrombotic thrombocytopenic purpura, urinary incontinence, urinary retention.

6.3 Adverse Reactions Reported with Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

7 DRUG INTERACTIONS

7.1 Potential for INVEGA to Affect Other Drugs

Given the primary CNS effects of paliperidone *[see Adverse Reactions (6.1, 6.2)]*, INVEGA 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, an additive effect may be observed when INVEGA is administered with other therapeutic agents that have this potential *[see Warnings and Precautions (5.9)]*.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Pharmacokinetic interaction between lithium and INVEGA is unlikely.

In a drug interaction study, co-administration of INVEGA (12 mg once daily for 5 days) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics (AUC_{24h} and $C_{max,ss}$) of valproate in 13 patients stabilized on valproate. In a clinical study, subjects on stable doses of valproate had comparable valproate average plasma concentrations when INVEGA 3-15 mg/day was added to their existing valproate treatment.

7.2 Potential for Other Drugs to Affect INVEGA

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so 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, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of INVEGA 6 mg once daily with carbamazepine, a strong inducer of both CYP3A4 and P-glycoprotein (P-gp), at 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology (12.3)]*. In an interaction study in healthy subjects in which a single 3 mg dose of INVEGA was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

Co-administration of a single dose of INVEGA 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. Dosage reduction for INVEGA should be considered when INVEGA is co-administered with valproate after clinical assessment.

Pharmacokinetic interaction between lithium and INVEGA is unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including INVEGA, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical

Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated with paliperidone during the period of organogenesis with up to 8 times the maximum recommended human dose (MRHD) based on mg/m^2 body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone, the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR= 1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m^2 body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleft palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m^2 body surface area; maternal toxicity occurred at 4 times the MHRD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m^2 body surface area, reached adulthood, learning was impaired. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m^2 body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams (see RISPERDAL package insert).

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant, or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms

(tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone's parent compound, risperidone *(see Clinical Considerations)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA and any potential adverse effects on the breastfed child from INVEGA or from the mother's underlying condition.

Clinical Considerations

Infants exposed to INVEGA through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of paliperidone (D_2 receptor antagonism), treatment with INVEGA may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.7)]*.

8.4 Pediatric Use

Safety and effectiveness of INVEGA in the treatment of schizophrenia were evaluated in 150 adolescent subjects 12-17 years of age with schizophrenia who received INVEGA in the dose range of 1.5 mg to 12 mg/day in a 6-week, double-blind, placebo-controlled trial.

Safety and effectiveness of INVEGA for the treatment of schizophrenia in patients < 12 years of age have not been established. Safety and effectiveness of INVEGA for the treatment of schizoaffective disorder in patients < 18 years of age have not been studied.

Juvenile Animal Studies

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

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen

at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of INVEGA on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

The safety, tolerability, and efficacy of INVEGA were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA (3 mg to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA (3 mg to 15 mg once daily) *[see Clinical Studies (14)]*. There were no subjects ≥ 65 years of age in the schizoaffective disorder studies.

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA (n=1796), including those who received INVEGA or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment *[see Clinical Pharmacology (12.3)]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5)]*.

8.6 Renal Impairment

Dosing must be individualized according to the patient's renal function status *[see Dosage and Administration (2.5)]*.

8.7 Hepatic Impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. INVEGA has not been studied in patients with severe hepatic impairment.

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to INVEGA. Manifestations can include confusion, obtundation, postural instability

with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA (paliperidone) is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of INVEGA misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

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

10 OVERDOSAGE

10.1 Human Experience

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

10.2 Management of Overdosage

There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following

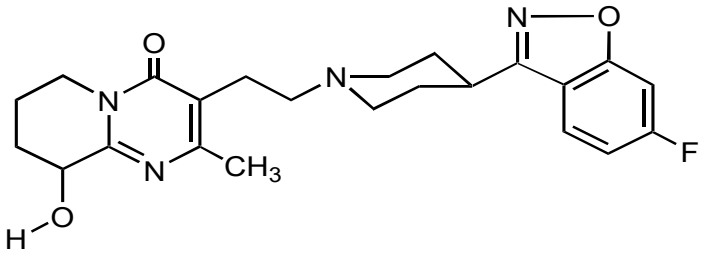
overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly, the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

11 DESCRIPTION

INVEGA® contains paliperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. INVEGA contains a racemic mixture of (+)- and (-)- paliperidone. The chemical name is (±)-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. Its molecular formula is $C_{23}H_{27}FN_4O_3$ and its molecular weight is 426.49. The structural formula is:



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.

INVEGA (paliperidone) Extended-Release Tablets are intended for oral administration and are available in)3 mg (white), 6 mg (beige), and 9 mg (pink) strengths. INVEGA utilizes OROS® osmotic drug-release technology.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

Delivery System Components and Performance

INVEGA uses osmotic pressure to deliver paliperidone at a controlled rate. The delivery system, which resembles a capsule-shaped tablet in appearance, consists of an osmotically active trilayer core surrounded by a subcoat and semipermeable membrane. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There are two precision laser-drilled orifices on the drug-layer dome of the tablet. Each tablet strength has a different colored water-dispersible overcoat and print markings. In an aqueous environment, such as the gastrointestinal tract, the water-dispersible color overcoat erodes quickly. Water then enters the tablet through the semipermeable membrane that controls the rate at which water enters the tablet core, which, in turn, determines the rate of drug delivery. The hydrophilic polymers of the core hydrate and swell, creating a gel containing paliperidone that is then pushed out through the tablet orifices. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone in schizophrenia is unclear. However, the drug's therapeutic effect in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

In vitro, paliperidone acts as an antagonist at the central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptors, with binding affinities (Ki values) of 1.6-2.8 nM for D_2 and 0.8-1.2 nM for $5HT_{2A}$ receptors. Paliperidone is also active as an antagonist at the α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro.*

12.3 Pharmacokinetics

Following a single dose, the plasma concentrations of paliperidone gradually rise to reach peak plasma concentration (C_{max}) approximately 24 hours after dosing. The pharmacokinetics of paliperidone following INVEGA administration are dose-proportional within the available dose range. The terminal elimination half-life of paliperidone is approximately 23 hours.

Steady-state concentrations of paliperidone are attained within 4-5 days of dosing with INVEGA in most subjects. The mean steady-state peak:trough ratio for an INVEGA dose of 9 mg was 1.7 with a range of 1.2-3.1.

Following administration of INVEGA, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6 at steady state.

Absorption and Distribution

The absolute oral bioavailability of paliperidone following INVEGA administration is 28%.

Administration of a 12 mg paliperidone extended-release tablet to healthy ambulatory subjects with a standard high-fat/high-caloric meal gave mean C_{max} and AUC values of paliperidone that were increased by 60% and 54%, respectively, compared with administration under fasting conditions. Clinical trials establishing the safety and efficacy of INVEGA were carried out in subjects without regard to the timing of meals. While INVEGA can be taken without regard to food, the presence of food at the time of INVEGA administration may increase exposure to paliperidone *[see Dosage and Administration (2.3)]*.

Based on a population analysis, the apparent volume of distribution of paliperidone is 487 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, *in vivo* results indicate that these isozymes play a limited role in the overall elimination of paliperidone *[see Drug Interactions (7)]*.

One week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone to 5 healthy volunteers, 59% (range 51% - 67%) of the dose was excreted unchanged into urine, 32% (26% - 41%) of the dose was recovered as metabolites, and 6% - 12% of the dose was not recovered. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four primary metabolic pathways have been identified *in vivo*, none of which could be shown to account for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission.

Population pharmacokinetic analyses found no difference in exposure or clearance of paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

Special Populations

Renal Impairment

The dose of INVEGA should be reduced in patients with moderate or severe renal impairment *[see Dosage and Administration (2.5)]*. The disposition of a single dose paliperidone 3 mg extended-release tablet was studied in adult 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 mL/min to < 80 mL/min), 64% in moderate (CrCl = 30 mL/min to < 50 mL/min), and 71% in severe (CrCl = 10 mL/min to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) 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 hours, 40 hours, 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).

Hepatic Impairment

In a study in adult subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Consequently, no dose adjustment is required in patients with mild or moderate hepatic impairment. INVEGA has not been studied in patients with severe hepatic impairment.

Adolescents (12-17 years of age)

Paliperidone systemic exposure in adolescents weighing ≥ 51 kg (≥ 112 lbs) was similar to that in adults. In adolescents weighing < 51 kg (< 112 lbs), a 23% higher exposure was observed; this is considered not to be clinically significant. Age did not influence the paliperidone exposure.

Elderly

No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance *[see Renal Impairment above and Dosage and Administration (2.1, 2.5)]*.

Race

No dosage adjustment is recommended based on race. No differences in pharmacokinetics were observed in a pharmacokinetic study conducted in Japanese and Caucasians.

Gender

No dosage adjustment is recommended based on gender. No differences in pharmacokinetics were observed in a pharmacokinetic study conducted in men and women.

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 should, therefore, not have an effect on the pharmacokinetics of paliperidone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies with paliperidone administered orally have not been performed.

Carcinogenicity studies with risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the MRHD of risperidone based on mg/m^2 body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear *[see Warnings and Precautions (5.7)]*.

Mutagenesis

No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test.

Impairment of Fertility

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

The fertility of male rats was not affected at oral doses of paliperidone of up to 2 times the MRHD of 12 mg/day based on mg/m^2 body surface area, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration

(0.6 to 10 times the MRHD of 16 mg/day for risperidone, based on mg/m^2 body surface area). Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

The acute efficacy of INVEGA (3 mg to 15 mg once daily) was established in three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose trials in non-elderly adult subjects (mean age of 37) who met DSM-IV criteria for schizophrenia. Studies were carried out in North America, Eastern Europe, Western Europe, and Asia. The doses studied among these three trials included 3 mg/day, 6 mg/day, 9 mg/day, 12 mg/day, and 15 mg/day. Dosing was in the morning without regard to meals.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Efficacy was also evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in the domains of socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors.

In all 3 studies (n=1665), INVEGA was superior to placebo on the PANSS at all doses. Mean effects at all doses were fairly similar, although the higher doses in all studies were numerically superior. INVEGA was also superior to placebo on the PSP in these trials.

An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age (there were few patients over 65), or geographic region. There were insufficient data to explore differential effects based on race.

In a longer-term trial, adult outpatients meeting DSM-IV criteria for schizophrenia who had clinically responded (defined as PANSS score ≤ 70 or ≤ 4 on pre-defined PANSS subscales, as well as having been on a stable fixed dose of INVEGA for the last two weeks of an 8-week run-in phase) were entered into a 6-week open-label stabilization phase where they received INVEGA (doses ranging from 3 mg to 15 mg once daily). After the stabilization phase, patients were randomized in a double-blind manner to either continue on INVEGA at their achieved stable dose, or to placebo, until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as significant increase in PANSS (or pre-defined PANSS subscales), hospitalization, clinically significant suicidal or homicidal ideation, or deliberate injury to self or others. An

interim analysis of the data showed a significantly longer time to relapse in patients treated with INVEGA compared to placebo, and the trial was stopped early because maintenance of efficacy was demonstrated.

Adolescents

The efficacy of INVEGA in adolescent subjects with schizophrenia was established in a randomized, double-blind, parallel-group, placebo-controlled, 6-week study using a fixed-dose weight-based treatment group design over the dose range of 1.5 to 12 mg/day. The study was carried out in the US, India, Romania, Russia, and Ukraine, and involved subjects 12-17 years of age meeting DSM-IV criteria for schizophrenia, with diagnosis confirmation using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL).

Eligible subjects were randomly assigned to 1 of 4 treatment groups: a placebo group or INVEGA Low, Medium, or High dose groups. Doses were administered based on body weight to minimize the risk of exposing lower-weight adolescents to high doses of INVEGA. Subjects weighing between 29 kg and less than 51 kg at the baseline visit were randomly assigned to receive placebo or 1.5 mg (Low dose), 3 mg (Medium dose), or 6 mg (High dose) of INVEGA daily, and subjects weighing at least 51 kg at the baseline visit were randomly assigned to receive placebo or 1.5 mg (Low dose), 6 mg (Medium dose), or 12 mg (High dose) of INVEGA daily. Dosing was in the morning without regard to meals.

Efficacy was evaluated using PANSS. Overall, this study demonstrated the efficacy of INVEGA in adolescents with schizophrenia in the dose range of 3 to 12 mg/day. Doses within this broad range were shown to be effective, however, there was no clear enhancement to efficacy at the higher doses, i.e., 6 mg for subjects weighing less than 51 kg and 12 mg for subjects weighing 51 kg or greater. Although paliperidone was adequately tolerated within the dose range of 3 to 12 mg/day, adverse events were dose related.

14.2 Schizoaffective Disorder

Adults

The acute efficacy of INVEGA (3 mg to 12 mg once daily) in the treatment of schizoaffective disorder was established in two placebo-controlled, 6-week trials in non-elderly adult subjects. Enrolled subjects 1) met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders, 2) had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 3) had prominent mood symptoms as confirmed by a score of at least 16 on the Young Mania Rating Scale and/or Hamilton Rating Scale for Depression. The population included subjects with schizoaffective bipolar and depressive types. In one of these trials, efficacy was assessed in 211 subjects who received flexible doses of INVEGA (3-12 mg once daily). In the other study, efficacy was assessed in 203 subjects who were

assigned to one of two dose levels of INVEGA: 6 mg with the option to reduce to 3 mg (n=105) or 12 mg with the option to reduce to 9 mg (n=98) once daily. Both studies included subjects who received INVEGA either as monotherapy [no mood stabilizers and/or antidepressants (55%)] or as an adjunct to mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. INVEGA was dosed in the morning without regard to meals. Studies were carried out in the United States, Eastern Europe, Russia, and Asia.

Efficacy was evaluated using the PANSS, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. As secondary outcomes, mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D-21) and the Young Mania Rating Scale (YMRS).

The INVEGA group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) and the higher dose group of INVEGA in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day) were each superior to placebo in the PANSS. Numerical improvements in mood symptoms were also observed, as measured by the HAM-D-21 and YMRS. In the lower dose group of the 2 dose-level study (6 mg/day with option to reduce to 3 mg/day), INVEGA was not significantly different from placebo as measured by the PANSS.

Taking the results of both studies together, INVEGA improved the symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age, or geographic region. There were insufficient data to explore differential effects based on race.

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA® (paliperidone) Extended-Release Tablets are available in the following strengths and packages. All tablets are capsule-shaped.

3 mg tablets are white and imprinted with “PAL 3”, and are available in bottles of 30 (NDC 50458-550-01) and hospital unit dose packs of 100 (NDC 50458-550-10).

6 mg tablets are beige and imprinted with “PAL 6”, and are available in bottles of 30 (NDC 50458-551-01) and hospital unit dose packs of 100 (NDC 50458-551-10).

9 mg tablets are pink and imprinted with “PAL 9”, and are available in bottles of 30 (NDC 50458-552-01) and hospital unit dose packs of 100 (NDC 50458-552-10).

Storage and Handling

Store up to 25 ºC (77 ºF); excursions permitted to 15 ºC to 30 ºC (59 ºF to 86 ºF) [see USP Controlled Room Temperature]. Protect from moisture.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact their healthcare provider or report to the emergency room if they experience signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status including delirium, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

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

Metabolic Changes

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

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension and syncope, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.9)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia they should have their CBC monitored while taking INVEGA *[see Warnings and Precautions (5.11)]*.

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of INVEGA. Advise them to seek medical attention if they experience any of the

following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males *[see Warnings and Precautions (5.7)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery, or operating a motor vehicle, until they are reasonably certain that INVEGA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.15)]*.

Heat Exposure and Dehydration

Counsel patients on the importance of avoiding overheating and dehydration *[see Warnings and Precautions (5.16)]*.

Concomitant Medication

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

Alcohol

Advise patients to avoid alcohol while taking INVEGA *[see Drug Interactions (7.1)]*.

Administration

Patients should be informed that INVEGA should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool *[see Dosage and Administration (2.3)]*.

Pregnancy

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

Lactation

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

Infertility

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

INVEGA (paliperidone) Extended-Release Tablets

Manufactured for:
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