

เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

1. NAME OF THE MEDICINAL PRODUCT

INVEGA SUSTENNA®

PRODUCT NAME

INVEGA SUSTENNA® (25 mg paliperidone as 39 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA SUSTENNA® (50 mg paliperidone as 78 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA SUSTENNA® (75 mg paliperidone as 117 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA SUSTENNA® (100 mg paliperidone as 156 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA SUSTENNA® (150 mg paliperidone as 234 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

International Non-proprietary Name

Paliperidone palmitate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INVEGA SUSTENNA contains 25, 50, 75, 100, or 150 mg paliperidone (as 39, 78, 117, 156, or 234 mg of paliperidone palmitate, respectively).

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

3. PHARMACEUTICAL FORM

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

For excipients, see *List of Excipients*.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INVEGA SUSTENNA is indicated for the treatment of schizophrenia and for the prevention of recurrence of symptoms of schizophrenia.

INVEGA SUSTENNA is indicated for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.

4.2 Posology and method of administration

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.

Dosage

Schizophrenia: Recommended initiation of INVEGA SUSTENNA is with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Schizoaffective disorder: Recommended initiation of INVEGA SUSTENNA is with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is within the range of 50 to 150 mg adjusted based on tolerability and/or efficacy using available strengths. The 25 mg strength was not studied in schizoaffective disorder. Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

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

Missed dose(s)

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 timepoint. 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 timepoint.

If the target date for the second INVEGA SUSTENNA injection (one week \pm 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection.

Missed second initiation dose (< 4 weeks from first injection). If less than 4 weeks have elapsed since the first injection, then the patient should be administered the second injection of 100 mg in the deltoid muscle as soon as possible. A third INVEGA SUSTENNA injection of 75 mg in either the deltoid or gluteal muscles should be administered 5 weeks after the first injection (regardless of the timing of the second injection). The normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy should be followed thereafter.

Missed second initiation dose (4-7 weeks from first injection). If 4 to 7 weeks have elapsed since the first injection of INVEGA SUSTENNA, resume dosing with two injections of 100 mg in the following manner: a deltoid injection as soon as possible followed by another deltoid injection

one week later, then resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed second initiation dose (> 7 weeks from first injection). If more than 7 weeks have elapsed since the first injection of INVEGA SUSTENNA, initiate dosing as described for the initial recommended initiation of INVEGA SUSTENNA above.

Missed Maintenance Dose (1 Month to 6 Weeks). After initiation, the recommended injection cycle of INVEGA SUSTENNA is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed Maintenance Dose (> 6 Weeks to 6 Months). If more than 6 weeks have elapsed since the last injection of INVEGA SUSTENNA, the recommendation is as follows:

For patients stabilized with doses of 25 to 100 mg:

1. A deltoid injection as soon as possible at the same dose the patient was previously stabilized on.
2. Another deltoid injection (same dose) one week later (day 8).
3. Resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

For patients stabilized with 150 mg:

1. A deltoid injection as soon as possible at the 100 mg dose.
2. Another deltoid injection one week later (day 8) at the 100 mg dose.
3. Resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed Maintenance Dose (> 6 Months). If more than 6 months have elapsed since the last injection of INVEGA SUSTENNA, initiate dosing as described for the initial recommended initiation of INVEGA SUSTENNA above.

Administration information

INVEGA SUSTENNA is intended for intramuscular use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

The recommended needle size for administration of INVEGA SUSTENNA into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg (≥ 200 lb), the 1½-inch, 22-gauge needle is recommended. For those < 90 kg (< 200 lb), the 1-inch, 23 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. Administration should be made into the upper-outer quadrant

of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Special populations

Pediatrics (less than 18 years of age)

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

Elderly (65 years of age and older)

In general, recommended dosing of INVEGA SUSTENNA for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. As elderly patients may have reduced renal function, see *Renal impairment* below for dosing recommendations in patients with renal impairment.

Renal impairment

INVEGA SUSTENNA has not been systematically studied in patients with renal impairment (see *Pharmacokinetic Properties*). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), recommended initiation of INVEGA SUSTENNA is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 50 mg in either the deltoid or gluteal muscle, adjusted within the range of 25 to 100 mg based on patient tolerability and/or efficacy.

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

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 *Pharmacokinetic Properties*)

Other populations

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

Switching from other antipsychotic agents

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. 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 (see *Dosage and Administration*).

Previous oral antipsychotics can be immediately or gradually discontinued at the time of initiation of treatment with INVEGA SUSTENNA. INVEGA SUSTENNA should be initiated as described at the beginning of *Dosage and Administration* above.

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 at the beginning of *Dosage and Administration* above is not required.

Patients previously stabilized on different doses of paliperidone extended-release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA SUSTENNA monthly doses as depicted in Table 1.

Table 1: Doses of Paliperidone Extended-Release Tablets and INVEGA SUSTENNA Needed to Attain Similar Steady-State Paliperidone Exposure During Maintenance Treatment

Formulation	Previous Paliperidone Extended-Release Tablet Dose	INVEGA SUSTENNA Injection
Dosing Frequency	Once Daily	Once every 4 weeks
Dose (mg)	3 mg 6 mg 9 mg 12 mg	25-50 mg eq. 75 mg eq. 100 mg eq. 150 mg eq.

Patients previously stabilized on different doses of risperidone injection can attain similar active moiety steady-state exposure during maintenance treatment with INVEGA SUSTENNA monthly doses as depicted in Table 2.

Table 2: Doses of Risperidone Injection and INVEGA SUSTENNA Needed to Attain Similar Active Moiety Exposure at Steady-state

Previous Risperidone Injection Dose	INVEGA SUSTENNA Injection
25 mg every 2 weeks	50 mg eq. monthly
37.5 mg every 2 weeks	75 mg eq. monthly
50 mg every 2 weeks	100 mg eq. monthly

Discontinuation of the previous antipsychotic should be made in accordance with the appropriate prescribing information. 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.

Warnings and Precautions

Neuroleptic Malignant Syndrome

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

Tardive dyskinesia/extrapyramidal symptoms

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

Extrapyramidal symptoms and psychostimulants

Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered (see *Interactions*).

QT interval

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

Hypersensitivity reactions

Although tolerability with oral paliperidone or risperidone should be established prior to initiating treatment with INVEGA SUSTENNA, very rare cases of anaphylactic reactions have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone (see *Dosage and Administration* and *Adverse Reactions*).

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

Hyperglycemia and diabetes mellitus

Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with 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 or schizoaffective disorder and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Any patient treated with atypical antipsychotics, including INVEGA SUSTENNA should be monitored for symptoms of hyperglycemia and diabetes mellitus. (See *Adverse Reactions*)

Weight gain

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

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. INVEGA SUSTENNA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures

As with other antipsychotic drugs, INVEGA SUSTENNA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Elderly patients with dementia

INVEGA SUSTENNA has not been studied in elderly patients with dementia.

Overall mortality

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

Cerebrovascular adverse events

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

Leukopenia, neutropenia, and agranulocytosis

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

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

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10⁹/L) should discontinue INVEGA SUSTENNA and have their WBC followed until recovery.

Venous thromboembolism

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

Parkinson's disease and dementia with Lewy bodies

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

Priapism

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

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA 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.

Antiemetic effect

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

Administration

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

Intraoperative floppy iris syndrome

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Potential for INVEGA SUSTENNA to affect other drugs

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are

metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

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

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

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

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

Pharmacokinetic interaction between INVEGA SUSTENNA and lithium is unlikely.

Potential for other drugs to affect INVEGA SUSTENNA

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. *In vitro* studies have shown that paliperidone is a P-gp substrate.

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

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

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

Co-administration of a single dose of an oral paliperidone extended-release tablet 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone, likely the result of an

increased oral absorption. Since no significant effect on the systemic clearance was observed, a clinically significant interaction would not be expected between divalproex sodium extended-release tablets and INVEGA SUSTENNA intramuscular injection. This interaction has not been studied with INVEGA SUSTENNA.

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA is unlikely.

Concomitant use of INVEGA SUSTENNA 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.

Concomitant use of INVEGA SUSTENNA with psychostimulants

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

4.6 Pregnancy and lactation

Pregnancy

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

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

Laboratory animals treated with a high dose of oral paliperidone showed a slight increase in fetal deaths. Pregnancy parameters were not affected in rats given the intramuscular injection of paliperidone palmitate. The high doses were toxic to the mothers. The offspring was not affected at oral exposures 20- to 22-fold the maximum human exposure, or intramuscular exposures 6-fold the maximum human exposure.

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

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

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone palmitate based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone palmitate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The data described in this section are derived from clinical trial database consisting of a total of 3817 adult subjects (approximately 1705 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA in the recommended dose range of 25 to 150 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 long-term recurrence prevention 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 150 mg INVEGA SUSTENNA initiation dose followed by treatment with either 25 mg, 100 mg, or 150 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 adult subjects with schizoaffective disorder who participated in a long-term relapse prevention trial. 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).

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

Double-blind placebo-controlled data

Adverse reactions reported by $\geq 2\%$ of INVEGA SUSTENNA-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials are shown in Table 3.

Table 3: Adverse Reactions in $\geq 2\%$ of INVEGA SUSTENNA-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

System/Organ Class	Placebo ^a (N=510)	INVEGA SUSTENNA					
		25 mg (N=130)	50 mg (N=302)	100 mg (N=312)	150/25 mg ^b (N=160)	150/100 mg ^b (N=165)	150/150 mg ^b (N=163)
Adverse Reaction							
Total percentage of subjects with adverse reaction	46	54	50	52	44	43	47
Infections and infestations							
Upper respiratory tract infection	2	2	2	2	1	2	4
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Insomnia	15	15	15	13	12	10	13
Nightmare	<1	2	0	0	0	0	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
Vascular disorders							
Hypertension	1	2	1	1	1	1	0
Gastrointestinal disorders							
Abdominal pain upper	1	0	1	2	1	1	1
Constipation	5	3	5	5	2	4	1
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
Musculoskeletal and connective tissue disorders							
Pain in extremity	1	0	2	2	2	3	0
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site pain ^c	2	0	3	5	9	7	8
Investigations							
Weight increased	1	4	4	1	1	1	2

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

^b Initial deltoid injection of 150 mg followed by either 25 mg, 100 mg, or 150 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (25 mg, 50 mg, and 100 mg) are from studies involving only gluteal injection. (See *Pharmacodynamic Properties*)

^c Injection site pain includes injection site pain, pruritus, nodule, and induration.

In the long-term recurrence prevention trial, adverse reaction types, frequencies, and severities during the open-label phases of this study were generally comparable to those observed in the four 13-week and the 9-week placebo-controlled fixed-dose studies shown in Table 3. Adverse reactions reported during the double-blind phase of this study were generally similar in type and severity to those observed in the open-label phases.

Other clinical trial data

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

Adverse reactions reported with paliperidone and/or risperidone by $\geq 2\%$ of INVEGA SUSTENNA-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are shown in Table 4.

Table 4: Adverse Reactions Reported with Paliperidone and/or Risperidone by $\geq 2\%$ of INVEGA SUSTENNA-Treated Subjects in a Pooled Dataset of the 4 Double-Blind, Placebo-Controlled Schizophrenia Trials. The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class

Adverse Reaction

Psychiatric disorders

Anxiety

Nervous system disorders

Akathisia*, Parkinsonism*

Gastrointestinal disorders

Abdominal discomfort

Musculoskeletal and connective tissue disorders

Musculoskeletal pain

General disorders and administration site conditions

Injection site reaction

* **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **Parkinsonism includes:** akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness.

Adverse reactions reported with paliperidone and/or risperidone by $<2\%$ of INVEGA SUSTENNA-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are shown in Table 5.

Table 5: Adverse Reactions Reported with Paliperidone and/or Risperidone by <2% of INVEGA SUSTENNA-treated Subjects in a Pooled Dataset of the 4 Double-Blind, Placebo-Controlled Schizophrenia Trials. The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class

Adverse Reaction

Infections and infestations

Acarodermatitis, Bronchitis, Cellulitis, Ear infection, Eye infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Subcutaneous abscess, Tonsillitis, Urinary tract infection

Blood and lymphatic system disorders

Neutropenia, White blood cell count decreased

Immune system disorders

Hypersensitivity

Metabolism and nutritional disorders

Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycemia, Increased appetite, Polydipsia, Weight decreased

Psychiatric disorders

Depression, Sleep disorder

Nervous system disorders

Balance disorder, Cerebrovascular accident, Convulsion*, Disturbance in attention, Dizziness postural, Dysarthria, Dyskinesia*, Dystonia*, Hypoesthesia, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia, Tremor

Eye disorders

Dry eye, Eye rolling, Lacrimation increased, Ocular hyperemia, Vision blurred

Ear and labyrinth disorders

Ear pain, Vertigo

Cardiac disorders

Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations, Postural orthostatic tachycardia syndrome, Sinus arrhythmia, Tachycardia

Vascular disorders

Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Cough, Dyspnea, Epistaxis, Nasal congestion, Pharyngolaryngeal pain, Pulmonary congestion, Respiratory tract congestion, Wheezing

Gastrointestinal disorders

Dyspepsia, Dysphagia, Fecal incontinence, Flatulence, Gastroenteritis, Swollen tongue

Hepatobiliary disorders

Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased

Skin and subcutaneous tissue disorder

Acne, Dry skin, Eczema, Erythema, Hyperkeratosis, Pruritus, Rash, Urticaria

Musculoskeletal and connective tissue disorders

Arthralgia, Back pain, Joint stiffness, Joint swelling, Muscle spasms, Neck pain

Renal and urinary disorders

Dysuria, Pollakiuria, Urinary incontinence

Reproductive system and breast disorders

Amenorrhea, Ejaculation disorder, Erectile dysfunction, Galactorrhea, Gynecomastia, Sexual dysfunction, Vaginal discharge

General disorders and administration site conditions

Chest discomfort, Chills, Edema*, Face edema, Gait abnormal, Induration, Malaise, Pyrexia, Thirst

Injury, poisoning and procedural complications

Fall

* **Convulsion includes:** grand mal convulsion; **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; **Dystonia includes:** blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Edema includes:** generalized edema, edema peripheral, pitting edema.

Adverse reactions reported with paliperidone and/or risperidone in other clinical trials but not reported by INVEGA SUSTENNA-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are shown in Table 6.

Table 6: Adverse Reactions Reported with Paliperidone and/or Risperidone in Other Clinical Trials but not Reported by INVEGA SUSTENNA-Treated Subjects in a Pooled Dataset of the 4 Double-Blind, Placebo-Controlled Schizophrenia Trials. The Terms within each System Organ Class are Sorted Alphabetically

System/Organ Class

Adverse Reaction

Infections and infestations

Cystitis

Blood and lymphatic system disorders

Anemia, Eosinophil count increased, Hematocrit decreased

Immune system disorders

Anaphylactic reaction

Endocrine disorders

Glucose urine present, Hyperprolactinemia

Metabolism and nutritional disorders

Hyperinsulinemia

Psychiatric disorders

Anorgasmia, Blunted affect, Confusional state, Libido decreased

Nervous system disorders

Cerebrovascular disorder, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Unresponsive to stimuli

Eye disorders

Conjunctivitis, Eye movement disorder, Glaucoma, Photophobia

Ear and labyrinth disorders

Tinnitus

Vascular disorders

Flushing, Hypotension, Ischemia

Respiratory, thoracic and mediastinal disorders

Dysphonia, Hyperventilation, Pneumonia aspiration, Rales

Gastrointestinal disorders

Cheilitis, Fecaloma, Intestinal obstruction

Skin and subcutaneous tissue disorders

Drug eruption, Seborrheic dermatitis, Skin discoloration

Musculoskeletal and connective tissue disorders

Blood creatine phosphokinase increased, Muscular weakness, Posture abnormal, Rhabdomyolysis

Reproductive system and breast disorders

Breast discharge, Breast discomfort, Breast engorgement, Breast enlargement, Menstrual disorder*, Menstruation delayed

General disorders and administration site conditions

Body temperature decreased, Body temperature increased, Drug withdrawal syndrome

* **Menstrual disorder includes:** menstruation irregular, oligomenorrhea.

Schizoaffective disorder

The safety profile of INVEGA SUSTENNA in patients with schizoaffective disorder is similar to that observed in patients with schizophrenia.

Events of particular interest to the class

Extrapyramidal symptoms (EPS). Pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled schizophrenia trials (see *Clinical efficacy*) showed no differences in treatment-emergent EPS between placebo and INVEGA SUSTENNA. Evaluation of EPS included a pooled analysis of the following EPS groups: dyskinesia, dystonia, hyperkinesia, parkinsonism, and tremor. The results from the 13-week schizophrenia study involving the 150 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled schizophrenia trial, and across all phases of the long-term recurrence prevention trials in subjects with schizophrenia and schizoaffective disorder exhibited comparable findings.

Weight gain. The proportions of subjects meeting a weight gain criterion of $\geq 7\%$ of body weight in the 13-week schizophrenia study involving 150 mg initiation dosing, weight increases from baseline of $\geq 7\%$ were more common among subjects in the INVEGA SUSTENNA groups than in the placebo group. The proportion of subjects with an abnormal weight increase $\geq 7\%$ showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA SUSTENNA 25 mg, 100 mg, and 150 mg groups, respectively.

In the two 13-week, fixed-dose, double-blind, placebo-controlled schizophrenia trials (pooled data), the proportions of subjects meeting a weight gain criterion of $\geq 7\%$ of body weight were 6%, 9%, and 10% in the INVEGA SUSTENNA 25, 50, and 100 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled schizophrenia trial, 8% and 6% in the INVEGA SUSTENNA 50 and 100 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label transition/maintenance period of the long-term recurrence prevention schizophrenia trial, 12% of INVEGA SUSTENNA-treated subjects met this criterion (weight gain of $\geq 7\%$ from double-blind phase to endpoint); the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion

was met by 6% of INVEGA SUSTENNA-treated subjects (median duration 171 days [range 1-407 days]) compared with 3% of placebo-treated subjects (median duration 105 days [range 8-441 days]); the mean (SD) weight change from double-blind baseline was +0.5 (3.83) kg for INVEGA SUSTENNA compared with -1.0 kg (3.08) for placebo. Similar results were observed in the open-label extension phase of this study.

During the initial 25-week open-label period of the 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 $\geq 7\%$ (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 $\geq 7\%$ (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 $\geq 7\%$ (n=168).

Laboratory tests: serum prolactin. Based on pooled data from the two 13-week, fixed-dose double-blind, placebo-controlled trials (see *Clinical efficacy*), median increases in serum prolactin were observed in subjects of both genders who received INVEGA SUSTENNA. The results from the 13-week study involving 150 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the recurrence prevention trial exhibited comparable findings.

Postmarketing data

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

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

In Table 7, adverse reactions are presented by frequency category based on spontaneous reporting rates.

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

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

Very rarely, 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.

4.9 Overdose

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

Symptoms and signs

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

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX13.

Mechanism of action

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

Paliperidone palmitate is hydrolyzed to paliperidone (see *Non-clinical Information*). Paliperidone is a centrally active dopamine D₂ antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H₁ histaminergic receptors. 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.

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

Effect on QT/QTc interval and cardiac electrophysiology

The effects of oral paliperidone on the QT interval were evaluated in two randomized, double-blind, multicenter, phase 1 studies 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 first phase 1 study (n=141), subjects were randomized to receive either 7 days of immediate-release oral paliperidone once daily (titrated from 4 to 8 mg) or a single dose of moxifloxacin (400 mg). The 8 mg once daily dose of immediate-release oral paliperidone (n=50, $C_{max\ ss}=113$ ng/mL) achieved a mean steady-state maximum plasma concentration greater than 2-fold the exposure observed with the maximum recommended 150 mg dose of INVEGA SUSTENNA administered in the deltoid muscle (predicted median $C_{max\ ss}$ 50 ng/mL). In the model-adjusted day-averaged linear-derived QT correction (QTcLD), there was a mean increase of 5.5 msec (90% CI: 3.66; 7.25) in the INVEGA SUSTENNA treatment group (n=50).

In the second phase 1 study (n=109), subjects were randomized to receive either placebo, the maximum recommended dose of oral extended-release paliperidone (12 mg once daily), subsequently titrated to a dose above the recommended range (18 mg once daily), or an active control from the same pharmacologic class of drugs (400 mg quetiapine twice daily). The primary comparison in this 10-day noninferiority study was between extended-release paliperidone 12 mg and quetiapine. The least squares mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 5.1 ms lower for 12 mg extended-release paliperidone (mean C_{max} 34 ng/mL) compared with 400 mg quetiapine twice daily (mean C_{max} 1183 ng/mL) (90% CI: -9.2; -0.9), meeting the prespecified noninferiority criterion of 10 ms. The mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 2.3 ms lower for 18 mg extended-release paliperidone (mean C_{max} 53 ng/mL) compared with 400 mg quetiapine twice daily (mean C_{max} 1183 ng/mL) (90% CI: -6.8; 2.3).

The mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 1.5 ms higher (90% CI: -3.3; 6.2) for 12 mg extended-release paliperidone and 8.0 ms higher (90% CI: 3.1; 12.9) for 400 mg quetiapine twice daily compared with the mean change from baseline in QTcLD at median observed t_{max} (of the active drug in the comparison) in the concurrent placebo arm. The mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 4.9 ms higher (90% CI: -0.5; 10.3) for extended-release paliperidone 18 mg and 7.5 ms higher (90% CI: 2.5; 12.5) for quetiapine 400 mg twice daily compared with the mean

change from baseline in QTcLD at median observed t_{max} (of the active drug in the comparison) in the concurrent placebo arm.

None of the subjects had a change from baseline exceeding 60 msec or a QTcLD exceeding 500 msec at any time during either of these studies.

In the three fixed-dose efficacy studies of oral extended-release paliperidone in subjects with schizophrenia, extensive electrocardiography (ECG) measurements were taken at 15 time points on specified days (including the times of expected C_{max}) using a standardized methodology. Mean QTcLD increase did not exceed 5 msec in any treatment group at any time point, based on pooled data from 836 subjects treated with extended-release paliperidone, 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the extended-release paliperidone 12 mg and olanzapine groups had a change exceeding 60 msec at one time-point during these studies (increases of 62 and 110 msec, respectively).

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 long-term recurrence prevention 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 patient also had a heart rate of 45 beats per minute.

Clinical efficacy

Schizophrenia

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 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. Functioning was 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: work and study, personal and social relationships, self-care, and disturbing and aggressive behaviors. The severity of dysfunctioning in social, personal, and self-care is measured by level of difficulty (absent, mild, manifest, marked, severe) in performing such activities with and without the help of other people. Similarly, severity of dysfunctioning in aggressive behaviors is measured by the presence or absence of aggressive behaviors (e.g., rudeness, insulting others in public, breaking objects, verbal threats, physical assault) and the frequency in which these behaviors occur.

In a 13-week study (n=636) comparing three fixed doses of INVEGA SUSTENNA (initial deltoid injection of 150 mg followed by 3 gluteal or deltoid doses of either 25 mg/4 weeks, 100 mg/4 weeks or 150 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA were superior to placebo in improving the PANSS total score. In this study, both the 100 mg/4 weeks and 150 mg/4 weeks, but not the 25 mg/4 weeks, treatment groups demonstrated statistical superiority to placebo for the PSP score. These results support efficacy across the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 25 mg and 150 mg INVEGA SUSTENNA groups by day 8.

In another 13-week study (n=349) comparing three fixed doses of INVEGA SUSTENNA (50 mg/4 weeks, 100 mg/4 weeks, and 150 mg/4 weeks) to placebo, only 100 mg/4 weeks of INVEGA SUSTENNA was superior to placebo in improving the PANSS total score. In this study, both the 50 mg/4 weeks and the 100 mg/4 weeks doses were superior to placebo in improving the PSP score. Although a 150 mg dose was included in this study, there were insufficient numbers of subjects receiving this dose to allow definitive conclusions concerning the efficacy of this dose.

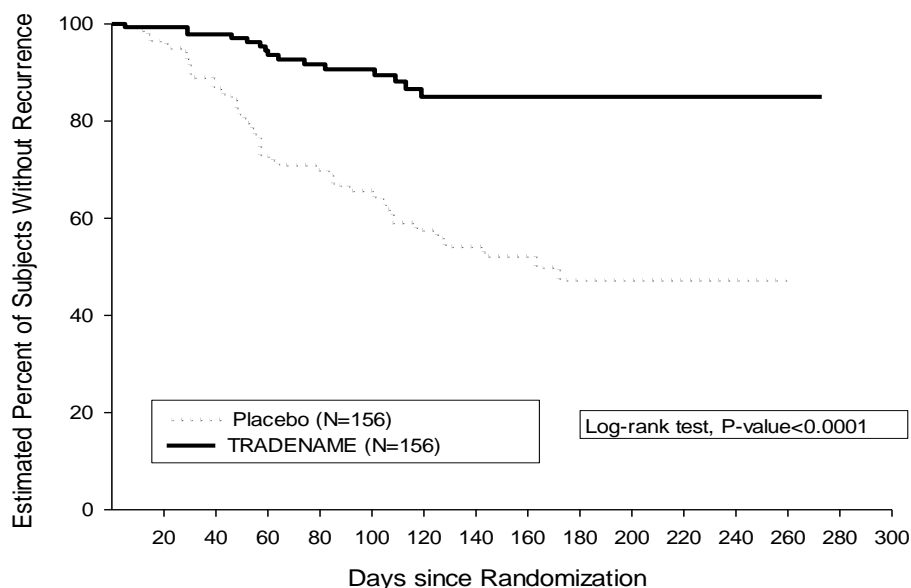
In a third 13-week study (n=513) comparing three fixed doses of INVEGA SUSTENNA (25 mg/4 weeks, 50 mg/4 weeks, and 100 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA were superior to placebo in improving the PANSS total score. In this study, none of the paliperidone dose groups achieved statistical significance when compared with placebo for the PSP score.

In the 9-week study (n=197) comparing two fixed doses of INVEGA SUSTENNA (50 mg/4 weeks and 100 mg/4 weeks) to placebo, both doses of INVEGA SUSTENNA were superior to placebo in improving PANSS total score.

The efficacy of INVEGA SUSTENNA in maintaining symptomatic control and delaying relapse of schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving 849 non-elderly adult subjects who met DSM-IV criteria for schizophrenia. This study included a 33-week open-label acute treatment and stabilization phase, a randomized, placebo-controlled phase to observe for relapse and a 52-week open-label extension period. In this study, doses of INVEGA SUSTENNA included 25, 50, 75, and 100 mg administered monthly; the 75 mg dose was allowed only in the 52-week open-label extension. Subjects initially received flexible doses (25-100 mg) of INVEGA SUSTENNA during a 9-week transition period. In order to enter the 24-week maintenance period, subjects were required to have a PANSS score of ≤ 75 . Dosing adjustments were only allowed in the first 12 weeks of the maintenance period. During the variable length double-blind phase, patients were randomized to either the same dose of INVEGA SUSTENNA (median duration 171 days [range 1 day - 407 days]) they received during the stabilization phase, administered every 4 weeks, or to placebo (median duration 105 days [range 8 days - 441 days]). 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, $\geq 25\%$ increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline

score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness). The primary efficacy variable was time to relapse. A pre-planned interim analysis (after 68 recurrence events occurred), showed a significantly longer time to relapse in patients treated with INVEGA SUSTENNA compared to placebo (Figure 1), and the study was stopped early because maintenance of efficacy was demonstrated.

Figure 1: Kaplan-Meier Plot of Time to Recurrence - Interim Analysis (Intent-to-Treat Analysis Set)

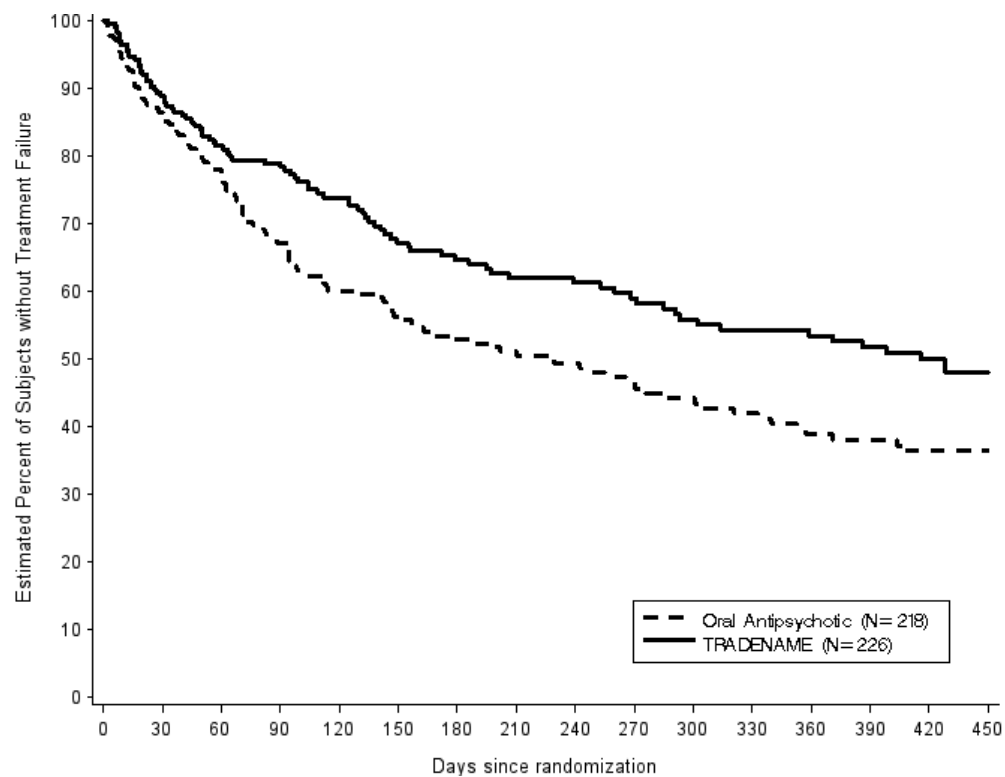


The result of the analysis based on the final data, including all data up to the date of study termination, was consistent with that of the primary efficacy analysis based on the interim data.

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

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 2. The frequencies of first treatment failure events by type are shown in Table 8. 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 2: Kaplan-Meier Plot of Time to First Treatment Failure

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

Table 8: Components of Composite Endpoint

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.

Schizoaffective disorder

The efficacy of INVEGA SUSTENNA in the treatment of subjects with schizoaffective disorder was established in a long-term double-blind, placebo-controlled, flexible-dose relapse prevention study involving 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 50 mg, 75 mg, 100 mg, or 150 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 Clinical Global Impression-Severity for Schizoaffective Disorder (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, relapse prevention period. For the 164 subjects who were randomized to INVEGA SUSTENNA, dose distribution was 50 mg (4.9%), 75 mg (9.8%), 100 mg (47.0%), and 150 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: $\geq 25\%$ 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.

Maintenance of 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.

There was a significant difference in the time to relapse (p-value <0.001) 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 percentage of subjects meeting relapse criteria was statistically significantly lower in subjects in the INVEGA SUSTENNA group (15.2%) than in the placebo group (33.5%). The risk (hazard) of relapse of schizoaffective symptoms for a placebo treated subject was 2.49 times that of a INVEGA SUSTENNA-treated subject.

Figure 3. Kaplan-Meier Plot of Time to Relapse

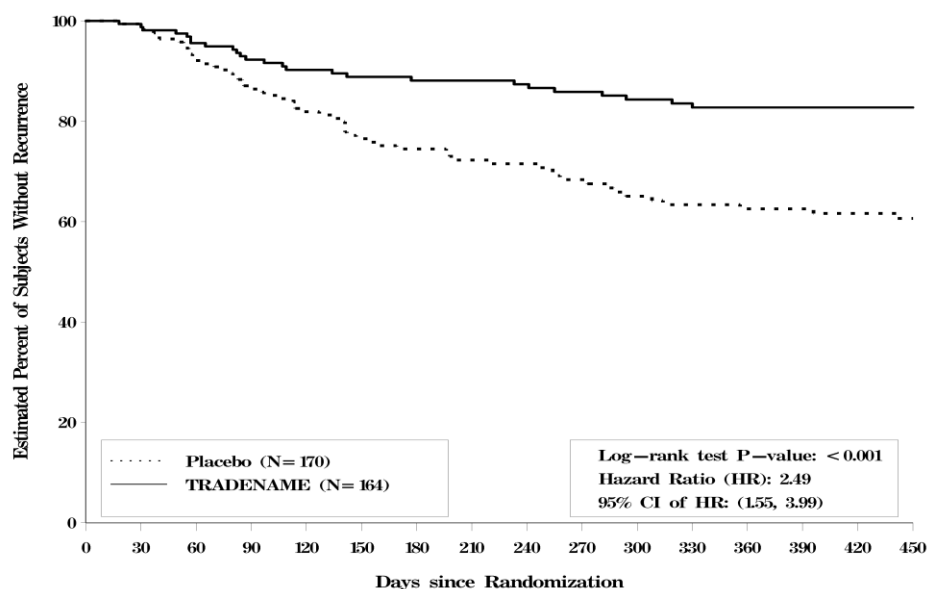


Table 9 summarizes the relapse rates and risk of relapse of the overall population, subgroup analysis (monotherapy and adjunctive therapy groups), relapse with psychotic symptoms, and relapse with mood symptoms. Analysis of the subgroup of subjects showed that the risk of relapse was 3.38- or 2.03-times greater with the placebo group in monotherapy or in adjunctive antidepressants or mood stabilizers treatment, respectively. In addition, relapse of psychotic symptoms and mood symptoms (manic, depressive or mixed) were further evaluated. The risk of relapse due to psychotic symptoms, manic and depressive mood symptoms was significantly higher for subjects in the placebo group than for subjects continuing INVEGA SUSTENNA treatment.

Table 9: Summary of Relapse Rates and Risk of Relapse (Hazard Ratios).

	Number (percent) of Subjects who relapsed	Risk of Relapse (Placebo vs. INVEGA SUSTENNA)^a	95% CI of Risk of Relapse^a	p-value^a
Placebo	INVEGA SUSTENNA			
N=170	N=164			

All Subjects	57 (33.5%)	25 (15.2%)	2.49	(1.55, 3.99)	<0.001
Monotherapy subset	N=73 24 (32.9%)	N=78 9 (11.5%)	3.38	(1.57, 7.28)	0.002
Adjunct to Antidepressants or Mood Stabilizers subset	N=97 33 (34.0%)	N=86 16 (18.6%)	2.03	(1.11, 3.68)	0.021
Psychotic Symptoms^b	53 (31.2%)	21 (12.8%)	2.82	(1.70, 4.67)	<0.001
Mood Symptoms^c					
Any Mood Symptoms	48 (28.2%)	18 (11.0%)	2.93	(1.70, 5.04)	<0.001
Manic	16 (9.4%)	5 (3.0%)	3.62	(1.32, 9.89)	0.012
Depressive	23 (13.5%)	8 (4.9%)	3.12	(1.39, 6.98)	0.006
Mixed	9 (5.3%)	5 (3.0%)	1.93	(0.65, 5.78)	0.238

^a The instantaneous risk (hazard) of relapse for a placebo treated subjects compared to INVEGA SUSTENNA-treated subjects. Risk of relapse, corresponding p-values, and 95% CIs are from separate Cox proportional hazards regression models.

^b 8 subjects experienced a relapse without psychotic symptoms.

^c 16 subjects experienced a relapse without any mood symptoms.

INVEGA SUSTENNA was superior to placebo in maintaining functioning as measured by the PSP scale.

5.2 Pharmacokinetic properties

Absorption and distribution

Due to its extremely low water solubility, 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 (25-150 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 150 mg on day 1 and 100 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA SUSTENNA results in sustained therapeutic concentrations. The total exposure of paliperidone following INVEGA SUSTENNA administration was dose-proportional over a 25-150 mg dose range, and less than dose-proportional for C_{\max} for doses exceeding 50 mg. The mean steady-state peak:trough ratio for a INVEGA SUSTENNA dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. The median apparent half-life of paliperidone following INVEGA SUSTENNA administration over the dose range of 25-150 mg ranged from 25-49 days.

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 excretion

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 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

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

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. Figure 4 presents the median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA SUSTENNA administration using the recommended initiation regimen compared to the administration of an oral extended-release tablet (6 mg or 12 mg). The initiation regimen for INVEGA SUSTENNA (150 mg/100 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.

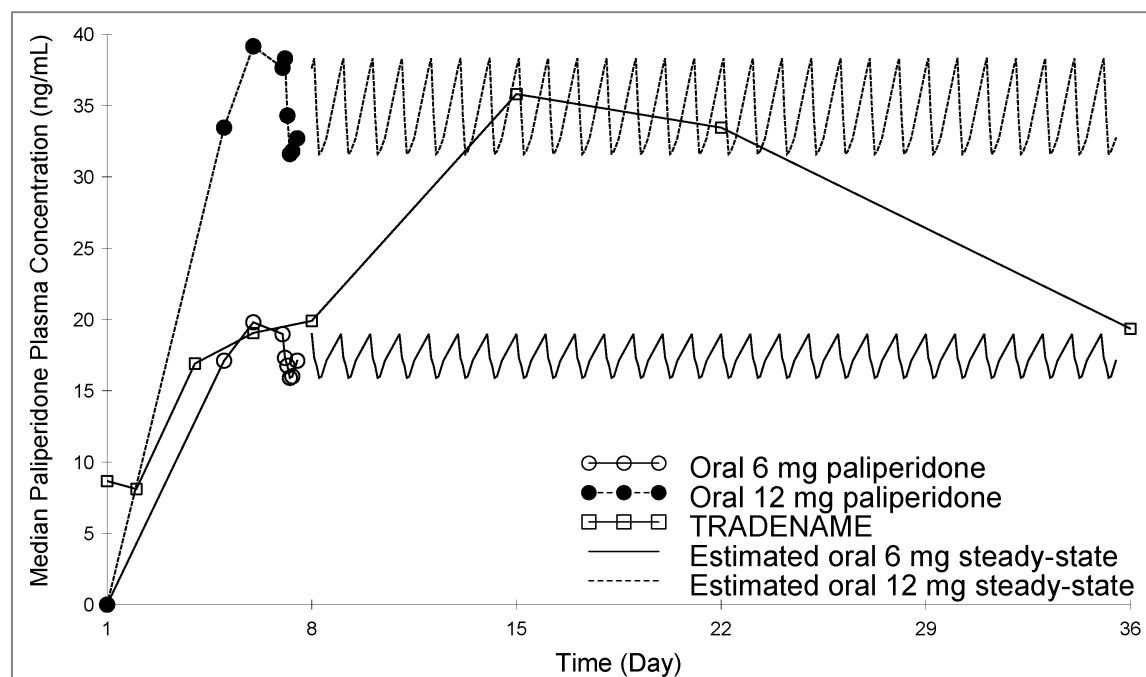


Figure 4. Median plasma concentration-time profiles following median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA SUSTENNA administration using the recommended initiation regimen (initiating with paliperidone palmitate equivalent to paliperidone 150 mg/100 mg in the deltoid muscle on Day 1/Day 8) compared to the daily administration of an oral extended-release tablet (6 mg or 12 mg).

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.

Special populations

Elderly (65 years of age and older)

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

Renal impairment

The dose of INVEGA SUSTENNA should be reduced in patients with mild renal impairment; INVEGA SUSTENNA is not recommended for use in patients with moderate or severe renal impairment (see *Dosage and Administration*). The disposition of a single oral dose paliperidone 3 mg extended-release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA SUSTENNA in subjects with mild renal impairment and pharmacokinetic simulations, the recommended initiation of INVEGA SUSTENNA for patients with mild renal impairment is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle; thereafter, follow with monthly (every 4 weeks) injections of 50 mg in either the deltoid or gluteal muscle, adjusted within the range of 25 to 100 mg based on patient tolerability and/or efficacy (see *Dosage and Administration*).

Hepatic impairment

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

Race

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

Gender

No clinically significant differences were observed between men and women.

Smoking status

Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

5.3 PRECLINICAL SAFETY DATA

Toxicology

As with other drugs that antagonize dopamine D₂ receptors, intramuscularly-injected paliperidone palmitate, as well as orally-dosed paliperidone, elevated serum prolactin levels in repeat-dose toxicity studies.

In a 7-week juvenile toxicity study in rats with oral doses of paliperidone of 0.16, 0.63, and 2.5 mg/kg/day, which are 0.12, 0.5, and 1.8 times the maximum recommended human oral dose of 12 mg/day for adolescents on a mg/m² basis, no effects on growth, sexual maturation, and reproductive performance were observed. Oral doses up to 2.5 mg/kg/day did not impair neurobehavioral development in males and females, except for an effect on learning and memory in female rats treated at 2.5 mg/kg/day. This effect was not observed after discontinuation of treatment.

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

Carcinogenicity

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg/kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 1.2 and 2.2 times the exposure level at the maximum recommended human 150 mg dose of INVEGA SUSTENNA.

The carcinogenic potential of oral paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats. Risperidone was administered at doses up to 10 mg/kg/day for 18 months to mice and for 25 months to rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. An increase in mammary, pituitary, and endocrine pancreas tumors has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D₂ antagonism. The relevance of these tumor findings in rodents in terms of human risk is unknown.

Mutagenicity

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

Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Inactive ingredients in INVEGA SUSTENNA are citric acid monohydrate, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

6.2 Incompatibilities

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

6.3 Shelf Life

See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store above 30°C.

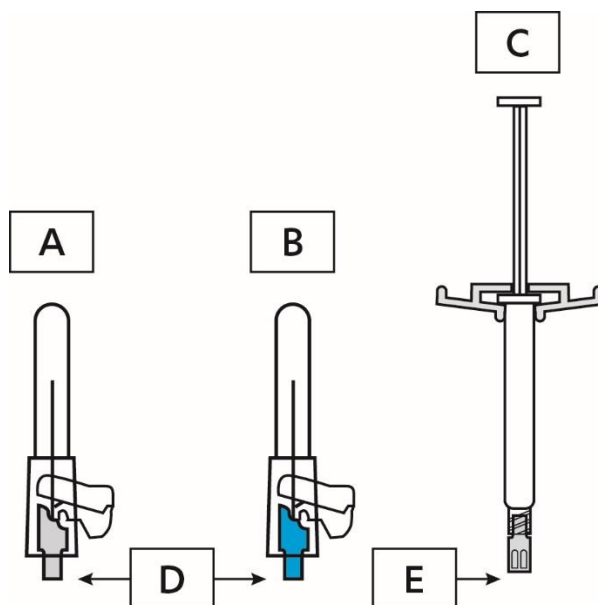
Keep out of the sight and reach of children.

6.5 Nature and Contents of Container

Kit containing a syringe (cyclic-olefin-copolymer) prefilled with either 25 mg (0.25 mL), 50 mg (0.5 mL), 75 mg (0.75 mL), 100 mg (1.0 mL), or 150 mg (1.5 mL) paliperidone (as 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg paliperidone palmitate) suspension with a plunger stopper and tip cap (bromobutyl rubber), backstop, a 1½-inch 22 gauge safety needle, and a 1-inch 23 gauge safety needle.

Instructions for Use and Handling and Disposal

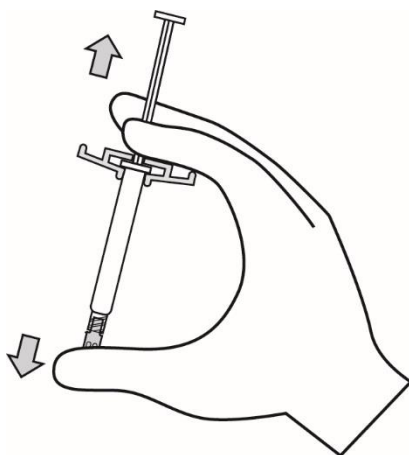
The kit contains a prefilled syringe and 2 safety needles (a 1½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.



A-22Gx1 1/2" Gray hub; B-23Gx1" Blue hub; C-Prefilled Syringe; D-Hub; E-Tip cap

INVEGA SUSTENNA is for single use only.

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

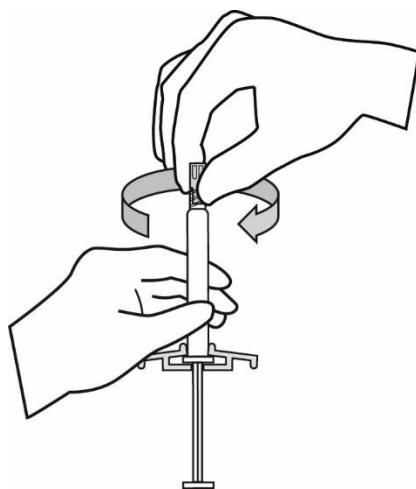


2. Select the appropriate needle.

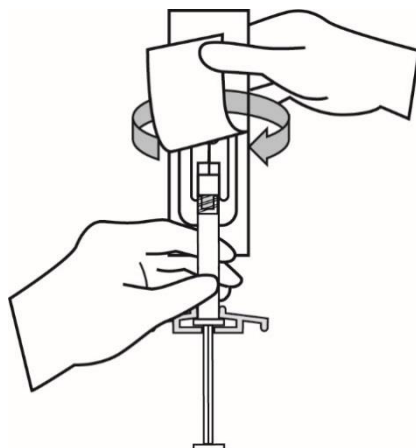
For DELTOID injection, if the patient weighs < 200 lb (< 90 kg), use the 1-inch **23** gauge needle (needle with **blue** colored hub); if the patient weighs \geq 200 lb (\geq 90 kg), use the 1½-inch **22** gauge needle (needle with **gray** colored hub).

For GLUTEAL injection, use the 1½-inch **22** gauge needle (needle with **gray** colored hub).

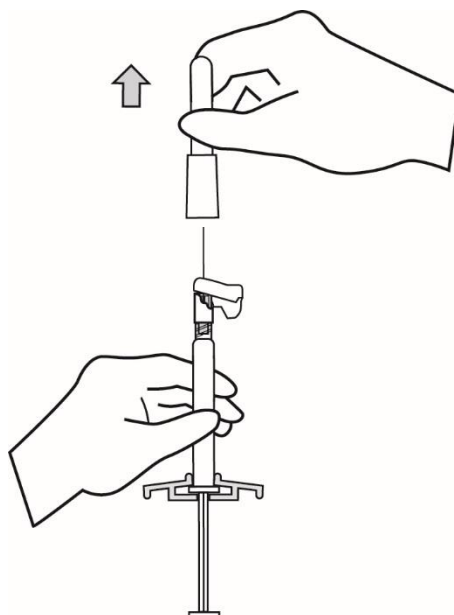
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



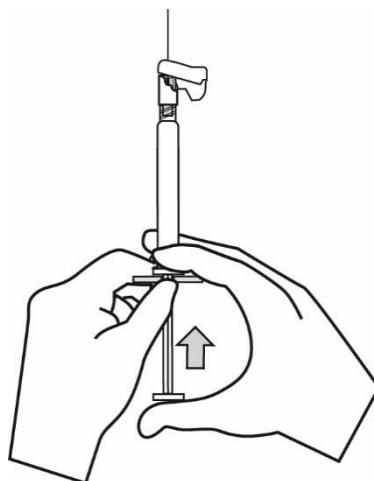
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



5. 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.

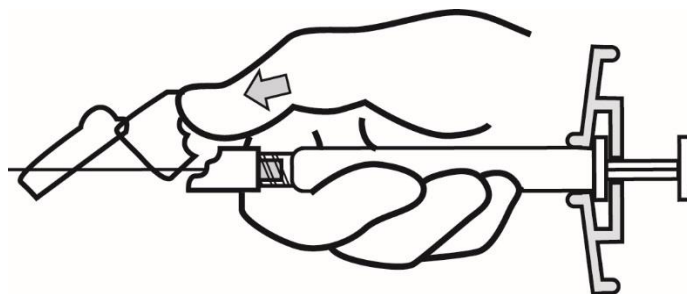
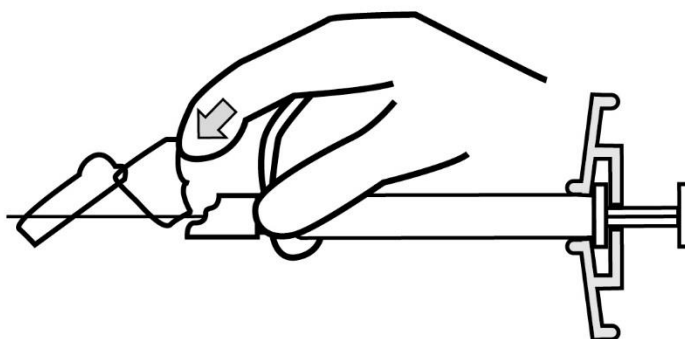
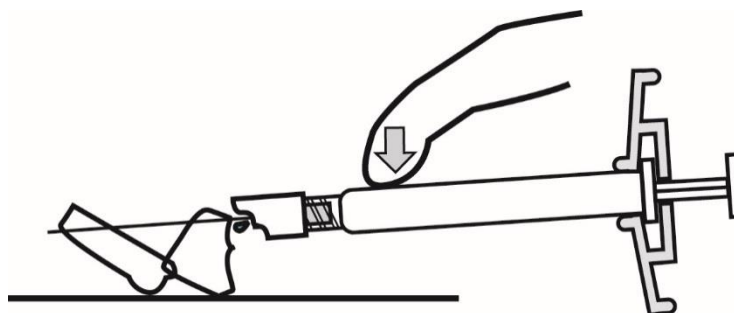


6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.



7. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**
8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle protection system. The needle protection system is fully activated when a 'click' is heard. Discard the syringe with needle appropriately.

8a

**8b****8c**

7. Marketing Authorisation Holder

See the end of the leaflet.

8. MARKETING AUTHORIZATION NUMBER

See table below.

9. DATE OF AUTHORIZATION

See table below.

Manufactured by	Marketing Authorization Number	Date of Authorization
Janssen Pharmaceutica N.V., Beerse, Kingdom of Belgium	1C 21/54 (N)	7 June 2011
Cilag AG Schaffhausen, Switzerland	1C XX/XX (N)	DD MMM YYYY

10.DATE OF REVISION OF THE TEXT

16-Feb-2021 (CCDS V.07 May 2018)

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