เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

INVEGA®

PRODUCT NAME

INVEGA® Extended-Release Tablets

International Non-proprietary Name

Paliperidone

DOSAGE FORMS AND STRENGTHS

INVEGA contains 3, 6 or 9 mg of paliperidone.

- 3 mg: white capsule-shaped tablet imprinted with "PAL 3"
- 6 mg: beige capsule-shaped tablet imprinted with "PAL 6"
- 9 mg: pink capsule-shaped tablet imprinted with "PAL 9"

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.

For excipients, see *List of Excipients*.

INVEGA utilizes osmotic drug-release technology, whereby osmotic pressure delivers paliperidone from the dosage form at a controlled rate. The system, which resembles a capsule-shaped tablet in appearance, comprises 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 strength is identified by a unique color overcoat and print markings. In an aqueous environment, such as the gastrointestinal tract, the water-dispersible color overcoat erodes quickly. Water is then imbibed through the semipermeable, rate-controlling membrane. The membrane controls the rate at which water enters the tablet core, which, in turn, controls 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.

CLINICAL INFORMATION

Indications

INVEGA is indicated for the treatment of schizophrenia in adults, including acute treatment and recurrence prevention.

INVEGA is indicated for the treatment of schizophrenia in adolescents 12-17 years of age.

INVEGA is indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder in adults.

INVEGA is indicated for the treatment of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers in adults.

Dosage and Administration

Dosage

Schizophrenia

Adults (≥ 18 years of age)

The recommended dose of INVEGA for the treatment of schizophrenia in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 5 days.

Adolescents (12-17 years of age)

The recommended dose of INVEGA for the treatment of schizophrenia in adolescents 12-17 years of age is 3 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from a higher dose of 6 mg to 12 mg/day. Dose increases should be made only after clinical reassessment and should occur at increments of 3 mg/day at intervals of more than 5 days.

Bipolar Disorder

Adults (≥ 18 years of age)

The recommended dose of INVEGA for the treatment of acute manic and mixed episodes associated with bipolar I disorder in adults is 9 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. A dose increase to 12 mg/day, if indicated, should occur at an interval of 2 days or more.

Schizoaffective Disorder

Adults (≥ 18 years of age)

The recommended dose of INVEGA for the treatment of schizoaffective disorder in adults is 6 mg once daily, administered in the morning. 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. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days.

Special populations

Adolescents and children

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 bipolar disorder or schizoaffective disorder in patients < 18 years of age have not been studied.

Elderly

Dosing recommendations for elderly patients with normal renal function (≥ 80 mL/min) are the same as for adults with normal renal function (see *Dosage*). However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see *Renal impairment*).

Renal impairment

For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), the recommended initial dose is 3 mg once daily. The dose may be increased to 6 mg once daily based on clinical response and tolerability.

For patients with moderate to severe renal impairment (creatinine clearance ≥ 10 to < 50 mL/min), the recommended dose of INVEGA is 3 mg every other day, which may then be increased to 3 mg once daily after clinical reassessment. As INVEGA has not been studied in patients with creatinine clearance < 10 mL/min, use is not recommended in such patients.

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. INVEGA has not been studied in patients with severe hepatic impairment.

Other populations

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

Switching to other antipsychotic agents

There are no systematically collected data to specifically address switching patients from INVEGA to other antipsychotic agents. Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

Administration

INVEGA is for oral administration and can be administered with or without food. INVEGA must be swallowed whole with the aid of liquids, and must 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.

Contraindications

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

Warnings and Precautions

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotic drugs, including paliperidone. Additional clinical

signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotic drugs, including INVEGA, 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, 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 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 physiology*).

Hyperglycemia and diabetes mellitus

Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment 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. Any patient treated with atypical antipsychotics, including INVEGA 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 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 should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Potential for gastrointestinal obstruction

Because the INVEGA tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, INVEGA should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. 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. Due to the controlled-release design of the dosage form, INVEGA should only be used in patients who are able to swallow the tablet whole. (See *Dosage and Administration - Administration*)

Elderly patients with dementia

INVEGA 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 leucopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including INVEGA. 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 should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue INVEGA 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 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, 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 to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

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

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 (see *Adverse Reactions*).

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

Interactions

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

Potential for INVEGA 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. *In vitro* studies indicated that paliperidone is not an inducer of CYP1A2, 2C19, or 3A4 activity.

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 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 is administered with other therapeutic agents that have this potential.

Pharmacokinetic interaction between INVEGA and lithium is unlikely.

Co-administration of INVEGA 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.

Potential for other drugs to affect INVEGA

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 Elimination*). In an interaction study in healthy subjects in which **INVEGA was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.**

Co-administration of INVEGA 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 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, 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 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.

Concomitant use of INVEGA with risperidone

Concomitant Use of INVEGA with risperidone has not been studied. Since paliperidone is an active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is coadministered with INVEGA.

Concomitant use of INVEGA with psychostimulants

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

Pregnancy and Breast-feeding

Pregnancy

The safety of 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 paliperidone showed a slight increase in fetal deaths. This high dose was toxic to the mothers. The offspring was not affected at exposures 20- to 34-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 should only be used during pregnancy if the benefits outweigh the risks. The effect of INVEGA 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 should not breast-feed infants.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone 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 safety of INVEGA in the treatment of schizophrenia was evaluated in 1205 adult subjects with schizophrenia who participated in 3 double-blind, placebo-controlled 6-week trials, of whom 850 subjects received INVEGA at fixed doses ranging from 3 mg to 12 mg once daily.

The safety of INVEGA was evaluated in 314 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 two Phase 3 studies, including 201 subjects in a 6-week, double-blind, placebo-controlled trial and subjects treated for up to 2 years in an open-label, single-arm safety trial.

The safety of INVEGA in the treatment of acute manic and mixed episodes associated with bipolar I disorder was evaluated in a total of 3 clinical trials in adults (n=1257). The conditions and duration of treatment with INVEGA varied across these studies and included (in overlapping categories) placebo- and active-controlled, double-blind, and fixed- and flexible-dose studies. Of the 1257 adult subjects, 739 subjects received INVEGA in the dose range of 3 mg to 12 mg once daily and 376 subjects received placebo.

The safety of INVEGA was also evaluated in 622 adult subjects with schizoaffective disorder who participated in two double-blind, placebo-controlled, 6-week 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 in combination with antidepressants and/or mood stabilizers.

The information in this section was derived from pooled data.

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

Double-blind, placebo-controlled data – schizophrenia - adults

Adverse reactions reported by ≥2% of INVEGA-treated subjects in the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia trials in adults are shown in Table 1.

Table 1: Adverse Reactions Reported by ≥ 2% of INVEGA-Treated Subjects with Schizophrenia in Three 6-Week Double-Blind, Placebo-Controlled, Fixed-Dose Clinical Trials in Adults

	Percentage of Patients				
System/Organ Class	**INVEGA 3 mg once daily (N=127)**	**INVEGA 6 mg once daily (N=235)**	**INVEGA 9 mg once daily (N=246)**	**INVEGA 12 mg once daily (N=242)**	**Placebo (N=355)**
Adverse Reaction	**%**	**%**	**%**	**%**	**%**
Nervous System Disorders					
Headache	11	12	14	14	12
Dizziness	6	5	4	5	4
Extrapyramidal disorder	5	2	7	7	2
Somnolence	5	3	7	5	3
Akathisia	4	3	8	10	4
Tremor	3	3	4	3	3
Hypertonia	2	1	4	3	1
Dystonia	1	1	4	4	1
Sedation	1	5	3	6	4
Parkinsonism	0	<1	2	1	0
Eye Disorders					
Oculogyric crisis	0	0	2	0	0
Cardiac Disorders					
Sinus tachycardia	9	4	4	7	4
Tachycardia	2	7	7	7	3
Bundle branch block	3	1	3	<1	2

Sinus arrhythmia	2	1	1	<1	0
Atrioventricular block first degree	2	0	2	1	1
Vascular Disorders					
Orthostatic hypotension	2	1	2	4	1
Gastrointestinal Disorders					
Vomiting	2	3	4	5	5
Dry mouth	2	3	1	3	1
Abdominal pain upper	1	3	2	2	1
Salivary hypersecretion	0	<1	1	4	<1
General disorders					
Asthenia	2	<1	2	2	1
Fatigue	2	1	2	2	1

Double-blind, placebo-controlled data - schizophrenia - adolescents

Adverse reactions reported by ≥ 2% of INVEGA-treated adolescent subjects 12-17 years of age with schizophrenia in a fixed-dose, placebo-controlled study are shown in Table 2.

Table 2: Adverse Reactions Reported by ≥ 2% of INVEGA-Treated Subjects with Schizophrenia in a Fixed-Dose, Placebo-Controlled Clinical Trial in Adolescents

	Percentage of Patients				
Body System/Organ Class	**INVEGA 1.5 mg once daily (N=54)**	**INVEGA 3 mg once daily (N=16)**	**INVEGA 6 mg once daily (N=45)**	**INVEGA 12 mg once daily (N=35)**	**Placebo (N=51)**
Adverse Reaction					

Infections and infestations					
Nasopharyngitis	4	0	4	0	2
Psychiatric disorders					
Insomnia	9	6	7	14	22
Anxiety	0	0	2	9	4
Nervous system disorders					
Somnolence	6	13	13	26	2
Akathisia	4	6	11	17	0
Headache	9	6	4	14	4
Tremor	2	6	7	11	0
Dystonia	2	0	4	9	0
Cogwheel rigidity	0	0	0	11	0
Dizziness	2	6	2	3	0
Dyskinesia	2	6	2	3	0
Sedation	4	0	2	0	2
Hypersomnia	0	0	4	0	0
Extrapyramidal disorder	0	6	0	0	0
Lethargy	0	0	0	3	0
Muscle contractions involuntary	0	0	0	3	0
Tongue paralysis	0	0	0	3	0
Eye disorders					
Oculogyric crisis	0	0	4	3	0
Vision blurred	0	0	0	3	0
Cardiac disorders					

Tachycardia	0	6	7	6	0
Sinus tachycardia	0	0	2	0	0
Respiratory, thoracic and mediastinal disorders					
Epistaxis	0	0	2	0	0
Gastrointestinal disorders					
Vomiting	0	6	11	3	10
Nausea	0	0	2	9	12
Salivary hypersecretion	2	6	2	0	0
Abdominal pain upper	2	0	2	0	2
Dry mouth	0	0	0	3	2
Swollen tongue	0	0	0	3	0
Musculoskeletal and connective tissue disorders					
Muscle rigidity	0	0	2	3	0
Muscle contracture	0	0	0	3	0
Torticollis	0	0	2	0	0
Reproductive system and breast disorders					
Galactorrhea	0	0	4	0	0
Amenorrhea	0	6	0	0	0
Breast swelling	0	0	0	3	0
General disorders					

Fatigue	4	0	2	3	0
Asthenia	0	0	2	3	0
Investigations					
Weight increased	7	6	2	3	0

Double-blind, placebo-controlled data – bipolar disorder - adults

Adverse reactions reported by ≥ 2% of INVEGA-treated subjects in the three double-blind, placebo-controlled bipolar disorder trials in adults are shown in Table 3.

Table 3: Adverse Reactions Reported by ≥ 2% of INVEGA-Treated Subjects with Bipolar I Disorder in Three Double-Blind, Placebo-Controlled Clinical Trials in Adults

	Percentage of Patients	
System/Organ Class	**INVEGA 3-12 mg once daily (N=739)**	**Placebo (N=376)**
Adverse Reaction	**%**	**%**
Metabolism and Nutrition Disorders		
Increased appetite	3	1
Psychiatric Disorders		
Agitation	3	3
Nervous System Disorders		
Headache	14	10
Somnolence	8	5
Akathisia	7	2
Sedation	7	3
Dizziness	6	2
Tremor	5	3
Extrapyramidal disorder	4	2
Drooling	4	1
Hypertonia	3	2
Dystonia	2	0
Eye Disorders		

Vision blurred	2	<1
Cardiac Disorders		
Tachycardia	2	1
Gastrointestinal Disorders		
Constipation	6	4
Vomiting	4	3
Nausea	4	6
Dyspepsia	4	2
General Disorders		
Fatigue	3	1
Investigations		
Weight increased	4	2

Double-blind, placebo-controlled data – schizoaffective disorder - adults

Adverse reactions reported by ≥ 2% of INVEGA-treated subjects in the two placebo-controlled schizoaffective disorder trials in adults are shown in Table 4.

Table 4: Adverse Reactions Reported by ≥ 2% of INVEGA-Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials in Adults

	Percentage of Patients	
	INVEGA 3-12 mg once daily	**Placebo**
System/Organ Class	**(N=420)***	**(N=202)**
Adverse Reaction	**%**	**%**
Infections and Infestations		
Nasopharyngitis	3	1

Metabolism and Nutrition Disorders		
Increased appetite	2	<1
Nervous System Disorders		
Tremor	8	3
Akathisia	5	4
Sedation	5	3
Somnolence	5	2
Hypertonia	5	2
Drooling	2	0
Dysarthria	2	0
Gastrointestinal Disorders		
Nausea	6	6
Dyspepsia	5	2
Constipation	4	2
Musculoskeletal and Connective Tissue Disorders		
Myalgia	2	<1
Investigations		
Weight increased	4	1

* Among the 420 subjects treated with INVEGA, 230 (55%) received INVEGA as monotherapy and 190 (45%) received INVEGA in combination with antidepressants and/or mood stabilizers.

Monotherapy versus combination 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 in combination with antidepressants and/or mood stabilizers. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥3% difference) in subjects receiving INVEGA as monotherapy.

Dose-related adverse reactions

In the placebo-controlled, 6-week high- and low-dose study in adult subjects with schizoaffective disorder, dystonia, dysarthria, and nasopharyngitis occurred more frequently (i.e., a difference of at least 3%) in subjects who received higher doses of INVEGA compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of INVEGA compared with subjects who received higher doses.

Other clinical trial data

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 ≥ 2% of INVEGA-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 5.

Table 5: Adverse Reactions Reported with Paliperidone and/or Risperidone by ≥2% of INVEGA-Treated Subjects in a Pooled Dataset of the 9 Double-Blind, Placebo-Controlled Schizophrenia, Bipolar Disorder, and Schizoaffective Disorder Trials (8 in adults and 1 in adolescent subjects). The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class
Adverse Reaction
Infections and Infestations
Upper respiratory tract infection
Psychiatric Disorders
Insomnia*
Nervous System Disorders
Akathisia*, Dystonia*, Parkinsonism*
Gastrointestinal Disorders
Abdominal discomfort, Diarrhea
Musculoskeletal and Connective Tissue Disorders
Musculoskeletal pain

* **Insomnia includes:** initial insomnia, middle insomnia; **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **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; **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-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 6.

Table 6: Adverse Reactions Reported with Paliperidone and/or Risperidone by <2% of INVEGA-Treated Subjects in a Pooled Dataset of the 9 Double-Blind, Placebo-Controlled Schizophrenia, Bipolar Disorder, and Schizoaffective Disorder Trials (8 in adults and 1 in adolescent subjects). The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class
Adverse Reaction
Infections and Infestations
Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Ear infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Tonsillitis, Urinary tract infection
Blood and Lymphatic System Disorders
Anemia, Hematocrit decreased, Neutropenia, White blood cell count decreased
Immune System Disorders
Anaphylactic reaction, Hypersensitivity
Endocrine Disorders
Hyperprolactinemia
Metabolism and Nutritional Disorders
Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycemia, Weight decreased
Psychiatric Disorders
Anorgasmia, Depression, Libido decreased, Nightmare, Sleep disorder
Nervous System Disorders
Cerebrovascular accident, Convulsion*, Disturbance in attention, Dizziness postural, Dyskinesia*, Hypoesthesia, Loss of consciousness, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia
Eye Disorders
Conjunctivitis, Dry eye, Lacrimation increased, Photophobia

Ear and Labyrinth Disorders

Ear pain, Tinnitus, Vertigo

Cardiac Disorders

Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations

Vascular Disorders

Flushing, Hypertension, Hypotension, Ischemia

Respiratory, Thoracic and Mediastinal Disorders

Cough, Dyspnea, Hyperventilation, Nasal congestion, Pharyngolaryngeal pain, Wheezing

Gastrointestinal Disorders

Cheilitis, Dysphagia, Fecal incontinence, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue, Toothache

Hepatobiliary Disorders

Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased

Skin and Subcutaneous Tissue Disorder

Acne, Dry skin, Eczema, Erythema, Pruritus, Rash, Seborrheic dermatitis, Skin discoloration

Musculoskeletal and Connective Tissue Disorders

Arthralgia, Back pain, Blood creatine phosphokinase increased, Joint stiffness, Joint swelling, Muscle spasms, Muscular weakness, Neck pain

Renal and Urinary Disorders

Dysuria, Pollakiuria, Urinary incontinence

Reproductive System and Breast Disorders

Breast discharge, Breast discomfort, Breast engorgement, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge

General Disorders

Body temperature increased, Chest discomfort, Chills, Face edema, Gait abnormal, Edema*, Pyrexia, Thirst

Injury, Poisoning and Procedural Complications

Fall

* **Convulsion includes:** grand mal convulsion; **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; **Menstrual disorder includes:** menstruation irregular, oligomenorrhea**; 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 (3-12 mg)-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 7.

Table 7: Adverse Reactions Reported with Paliperidone and/or Risperidone in Other Clinical Trials but not Reported by INVEGA (3-12 mg)-treated Subjects in a Pooled Dataset of the 9 Double-blind, Placebo-Controlled Schizophrenia, Bipolar Disorder, and Schizoaffective Disorder Trials (8 in adults and 1 in adolescent subjects). The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class	Adverse Reaction
Infections and Infestations	Eye infection
Blood and Lymphatic System Disorders	Eosinophil count increased
Endocrine Disorders	Glucose urine present
Metabolism and Nutritional Disorders	Hyperinsulinemia, Polydipsia
Psychiatric Disorders	Blunted affect, Confusional state

Nervous System Disorders

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

Eye Disorders

Eye movement disorder, Eye rolling, Glaucoma, Ocular hyperemia

Cardiac Disorders

Postural orthostatic tachycardia syndrome

Respiratory, Thoracic and Mediastinal Disorders

Dysphonia, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory tract congestion

Gastrointestinal Disorders

Fecaloma

Skin and Subcutaneous Tissue Disorders

Drug eruption, Hyperkeratosis, Urticaria

Musculoskeletal and Connective Tissue Disorders

Posture abnormal, Rhabdomyolysis

Reproductive System and Breast Disorders

Breast enlargement, Menstruation delayed

General Disorders

Body temperature decreased, Drug withdrawal syndrome, Induration, Malaise

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Elderly

The safety of INVEGA was evaluated in 81 elderly subjects with schizophrenia (65 years of age and older) who received either flexible doses (n=76) or fixed doses (n=5) of INVEGA in a range of 3 to 12 mg once daily for a duration of up to 6 weeks during double-blind, placebo-controlled trials. Although this dataset does not allow for a systematic direct comparison between elderly and non-elderly subjects, the safety profile was similar in the two populations. However, based on these limited data and consistent with general clinical practice, a greater sensitivity of older individuals to adverse reactions cannot be ruled out.

Events of particular interest to the class

Extrapyramidal symptoms (EPS). Pooled data from the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia studies (see *Pharmacodynamic Properties - Clinical Efficacy*) showed no differences in treatment-emergent EPS between placebo (11%) and INVEGA 3 and 6 mg doses (13% and 10%, respectively). Dose-relatedness for EPS was seen with the two higher doses of INVEGA (25% and 26% for the 9 and 12 mg doses, respectively). EPS included a pooled analysis of the following terms: dyskinesia, dystonia, hyperkinesia, Parkinsonism, and tremor. Pooled data from the two 6-week, double-blind, placebo-controlled studies in subjects with schizoaffective disorder (see *Pharmacodynamic Properties - Clinical Efficacy*) showed similar results.

Weight gain. In the pooled data from the three placebo-controlled, 6-week, fixed-dose adult schizophrenia studies (see *Pharmacodynamic Properties - Clinical Efficacy*), the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were compared, revealing a similar incidence of weight gain for INVEGA 3 mg and 6 mg (7% and 6%, respectively) compared with placebo (5%), and a higher incidence of weight gain for INVEGA 9 mg and 12 mg (9% and 9%, respectively).

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. In the double-blind, placebo-controlled study, a higher percentage of INVEGA low dose (6%), medium dose (13%), and high dose (13%) treated subjects (see *Pharmacodynamic Properties*) had an increase in body weight of ≥ 7% from baseline compared with placebo-treated subjects (2%). 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, 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 of normative data). Based on comparison to the normative data, these changes are not considered to be clinically significant.

In the pooled data from the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder (see *Pharmacodynamic Properties - Clinical Efficacy*), 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.

Laboratory tests: serum prolactin. Based on pooled data from the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia studies (see *Pharmacodynamic Properties - Clinical Efficacy*), increases in serum prolactin were observed in subjects of both genders who received INVEGA. Maximum mean increases of serum prolactin concentrations were generally observed on Day 15 of treatment, but remained above baseline levels at study endpoint.

Clinical trials: Adverse reactions in a long-term, placebo-controlled study

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 *Pharmacodynamic*

Properties - Clinical Efficacy). In general, the types, frequencies, and severities of adverse reactions reported during the initial 14-week open-label phase of this study were comparable to those reported in the 6-week, placebo-controlled, fixed-dose studies. The 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, but occurred at generally lower frequencies.

Postmarketing data

In addition to the adverse reactions reported during clinical trials and listed above, the following adverse reactions have been reported during postmarketing experience with paliperidone and/or risperidone (Tables 8). In the table, the frequencies are provided according to the following convention:

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

In Table 8, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 8: Adverse Reactions Identified During Postmarketing Experience with paliperidone and/or risperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Paliperidone

Blood and Lymphatic System Disorders	
Very rare	Agranulocytosis, Thrombocytopenia
Endocrine Disorders	
Not known	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia
Not known	Water intoxication
Psychiatric Disorders	
Very rare	Catatonia, Mania, Somnambulism
Not known	Sleep-related eating disorder
Nervous System Disorders	
Very rare	Dysgeusia
Eye Disorders	
Not known	Floppy iris syndrome (intraoperative)
Cardiac Disorders	
Very rare	Atrial fibrillation
Vascular Disorder	
Very rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal Disorders	
Very rare	Pancreatitis
Very rare	Ileus

Hepatobiliary Disorders	
Not known	Jaundice
Skin and Subcutaneous Tissue Disorders	
Rare	Angioedema
Very rare	Alopecia
Not known	Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and Urinary Disorders	
Very rare	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
Very rare	Priapism
General Disorders	
Very rare	Hypothermia

Overdose

Signs and symptoms

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. 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 the product 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. Administration of activated charcoal together with a laxative should be considered. In case of severe extrapyramidal

symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antipsychotics, other antipsychotics, ATC code: N05AX13.

Mechanism of action

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

Paliperidone is a centrally active dopamine D_2 antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or 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, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_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.

Polysomnography

Centrally-acting medications through their mechanism of action, drug-release profile, and/or time of dose administration may affect sleep. To evaluate the impact of morning dosing of INVEGA on sleep architecture and continuity, a placebo-controlled study was conducted in 36 subjects with schizophrenia in which INVEGA 9 mg or placebo was administered once daily for 14 days. The following observations were made (mean data compared with placebo): reduced latency to persistent sleep by 41.0 (SE 18.70) minutes, decreased sleep onset latency by 35.2 (SE 14.99) minutes, decreased number of awakenings after sleep onset by 7.0 (SE 3.88) events, increased total sleep time by 52.8 (SE 24.01) minutes, increased sleep period time by 41.7 (SE 18.75) minutes, and increased sleep efficiency index by 11.0% (SE 5.00). There was also a statistically significant decrease (relative to placebo) in Stage 1 sleep of 11.9 (SE 4.44) minutes and increase in Stage 2 sleep of 50.7 (SE 17.67) minutes. No clinically relevant effect on REM sleep was observed.

Effect on QT/QTc interval and cardiac electrophysiology

The effects of 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=44) achieved a mean steady-state peak plasma concentration greater than twice the exposure observed with the maximum recommended INVEGA dose of 12 mg ($C_{max\ ss}$ = 113 and 45 ng/mL, respectively). 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 treatment group (n=44).

In the second phase 1 study (n=109), subjects were randomized to receive either placebo, the maximum recommended INVEGA dose (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 INVEGA 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 INVEGA (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 INVEGA (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 INVEGA 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 paliperidone ER 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.

For the three fixed-dose efficacy studies, 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 INVEGA, 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the INVEGA 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).

Clinical efficacy

Schizophrenia - adults

The efficacy of INVEGA was established in three placebo-controlled, double-blind, 6-week trials in subjects who met DSM-IV criteria for schizophrenia. An active control (olanzapine) was included for assay sensitivity purposes. INVEGA doses, which varied across the three studies, ranged from 3 to 15 mg once daily. Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS); the primary endpoint was decrease in total PANSS scores. An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of age, race, or gender. Secondary endpoints were also assessed, including Personal and Social Performance (PSP) and the Clinical Global Impression - Severity (CGI-S) scale. The PSP is a validated clinician-rated scale that measures four areas of personal and social functioning (socially useful activities including work and study, personal and social relationships, self care, and disturbing and aggressive behaviors). The CGI-S is an independent investigator-rated assessment of overall severity of illness. In a pooled analysis of these three

studies, each dose of INVEGA was superior to placebo on the PSP and CGI-S. In addition, the effect on PSP was distinct from the improvement in symptoms as measured by the primary endpoint, total PANSS. Further evaluation of the open-label extensions of these three studies showed that flexibly-dosed INVEGA (3 to 15 mg once daily) for up to 52 weeks was associated with continued improvement on PSP.

In a long-term trial designed to assess the maintenance of effect, INVEGA was significantly more effective than placebo in maintaining symptom control and delaying recurrence of schizophrenia. In this study, adults who met DSM-IV criteria for schizophrenia and who remained clinically stable on an established dose of INVEGA during an 8-week period of open-label treatment (doses ranging from 3 to 15 mg once daily) after having been treated for an acute episode for the previous 6 weeks with INVEGA (doses ranging from 3 to 15 mg once daily) were then randomized in a double-blind manner to either continue on INVEGA at their achieved stable dose or to placebo until they experienced a recurrence of schizophrenia symptoms. The trial was stopped early for efficacy reasons based on an interim analysis that achieved predefined criteria by showing a significantly longer time to recurrence in patients treated with INVEGA compared to placebo ($p=0.0053$). Based on final analysis (including also those patients included after the cut-off point for the interim analysis), the rate of recurrence events was 22.1% in the INVEGA group compared with 51.5% in the placebo group. A significant improvement in symptoms was achieved at the end of the open-label stabilization phase (decrease in PANSS total scores of 38 [SD ±16.03] points), but after randomization to double-blind treatment, the patients receiving placebo deteriorated significantly more than those on INVEGA ($p<0.001$). INVEGA was also significantly more effective than placebo in maintaining personal and social performance. During the double-blind phase of this study as measured by the CGI-S scale, there was worsening on the overall severity of psychosis in the placebo group, while patients treated with INVEGA remained clinically stable.

Schizophrenia – 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. Subjects were 12-17 years of age and met 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. This study demonstrated the efficacy of INVEGA in adolescent subjects with schizophrenia when given at daily doses of 3, 6, and 12 mg in body weight-based treatment groups. The minimum effective dose for INVEGA in this population was 3 mg/day.

Bipolar disorder

The efficacy of INVEGA in the treatment of acute manic episodes was established in two multicenter, placebo-controlled, double-blind trials in subjects who met DSM-IV criteria for Bipolar I Disorder, most recent episode manic or mixed. One study evaluated the efficacy and safety of INVEGA over a flexible dose range of 3-12 mg relative to placebo and quetiapine *[an established antimanic agent]* over a 12-week period, while the other study evaluated the efficacy and safety of fixed doses of INVEGA (3 mg, 6 mg, and 12 mg) relative to placebo over a 3-week period.

INVEGA over a flexible dose range of 3 to 12 mg and at a fixed dose of 12 mg was superior to placebo with regard to the primary efficacy variable, change in YMRS total score from baseline at the 3-week endpoint. Superiority to placebo was established as early as Day 2, and antimanic efficacy compared to placebo was maintained at every subsequent assessment for up to 3 weeks. After 3 weeks of treatment, over one-half of subjects treated with INVEGA were rated as treatment responders. Flexibly dosed INVEGA was statistically superior to placebo with regard to both the rate of response and remission at Week 3. The efficacy observed for the primary efficacy variable was supported by improvements in secondary efficacy variables such as global measures of disease severity (CGI-BP-S) and function (GAF), as well as psychotic symptoms (PANSS).

Over the 12-week double-blind treatment period of the flexible-dose study, INVEGA was shown noninferior to quetiapine (an established antimanic agent) in the authorized dose range for the primary efficacy variable using a predefined noninferiority margin.

In a separate multicenter, placebo-controlled, double-blind trial in subjects with Bipolar I Disorder, most recent episode manic or mixed, INVEGA was shown to be well tolerated when used in combination with the mood stabilizers, lithium or valproate, over a period of 6 weeks, while the incremental benefit of INVEGA as adjunctive therapy was not demonstrated in this study.

Schizoaffective disorder

The 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 who met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders. In one of these trials, 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. In the other study, efficacy was assessed in 211 subjects who received flexible doses of INVEGA (3-12 mg once daily). Both studies included subjects who received INVEGA either as monotherapy or in combination with antidepressants and/or mood stabilizers. Dosing was 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 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.

The higher dose group of INVEGA in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day), and the INVEGA group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) were each superior to placebo in the PANSS. 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 in combination with antidepressants and/or mood stabilizers. 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.

Pharmacokinetic Properties

Unless where otherwise stated, the pharmacokinetic information presented in this section are based on data from studies in adults.

The pharmacokinetics of paliperidone following INVEGA administration are dose proportional within the recommended clinical dose range (3 to 12 mg).

Absorption

Following a single dose of INVEGA, the plasma concentrations of paliperidone steadily rise to reach peak plasma concentration (C_{max}) in approximately 24 hours after dosing. With once-daily dosing of INVEGA, steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.

The release characteristics of INVEGA result in minimal peak-trough fluctuations as compared to those observed with immediate-release risperidone. In a study comparing the steady-state pharmacokinetics following once daily administration of 12 mg paliperidone (administered as extended-release [*prolonged-release*] tablets) with 4 mg immediate-release risperidone in schizophrenic subjects, the fluctuation indexes were 38% for paliperidone extended-release [*prolonged-release*] compared to 125% for risperidone immediate-release (see Figure 1).

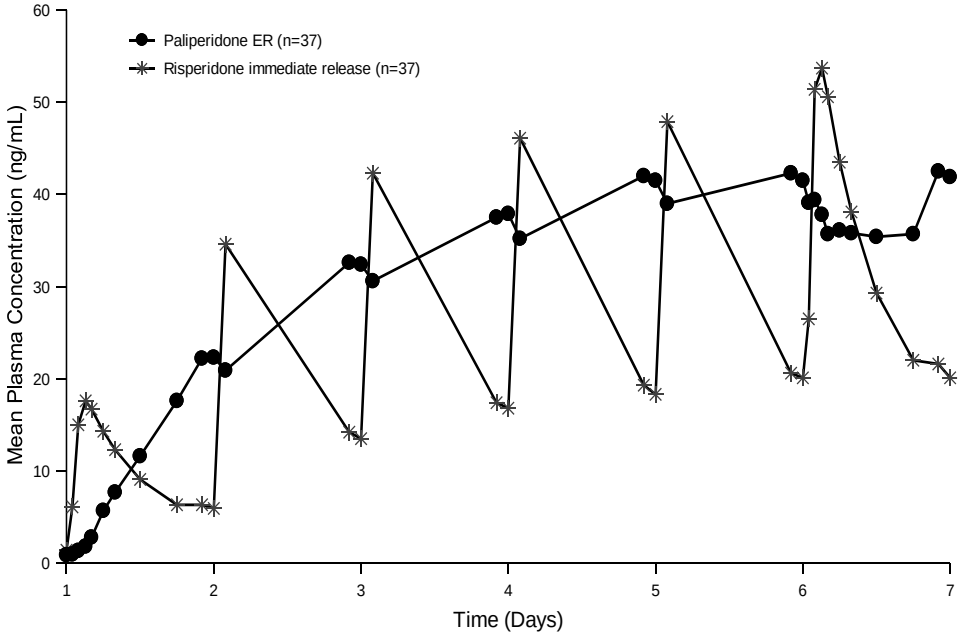

Figure 1. Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg extended-release [prolonged-release] tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release

administered as 2 mg once daily on Day 1 and 4 mg once daily on Days 2 to 6 (paliperidone+risperidone concentrations are represented).

Following administration of INVEGA, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6 at steady state. The absolute oral bioavailability of paliperidone following INVEGA administration is 28%.

Following administration of a single 15 mg paliperidone extended-release tablet to healthy subjects, confined to bed for 36 hours, with a standard high-fat/high-caloric meal, the C_{max} and AUC values increased by 42% and 46%, respectively, compared with administration under fasting conditions. In another study involving healthy ambulatory subjects, the C_{max} and AUC of paliperidone following administration of a single 12 mg paliperidone prolonged-release tablet with a standard high-fat/high-caloric meal resulted in increases of 60% and 54%, respectively, compared with administration under fasting conditions. Although the presence or absence of food at the time of INVEGA administration may increase or decrease exposure to paliperidone, these changes are not considered clinically relevant. Clinical trials establishing the safety and efficacy of INVEGA were carried out in subjects without regard to the timing of meals (see *Dosage and Administration*).

In the Phase 3 studies of INVEGA tablets in Bipolar I Disorder, median dose-normalized paliperidone plasma concentrations at 8 hours postdose after 6 days of treatment were comparable between fasted subjects and subjects who had consumed a standard continental or high-caloric breakfast between 2 hours before and 1 hour after their medication intake.

Distribution

Paliperidone is rapidly distributed. The apparent volume of distribution is 487 L. The plasma protein binding of paliperidone is 74%. It binds primarily to α_1-acid glycoprotein and albumin. *In vitro*, high therapeutic concentrations of diazepam (3 mcg/mL), sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused a slight increase in the free fraction of paliperidone at 50 ng/mL. These changes are not expected to be of clinical significance.

Metabolism and elimination

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. Despite the large variation in the general population with regard to the ability to metabolize CYP2D6 substrates, population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of INVEGA between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies using microsomal preparations of heterologous systems indicate that CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5 are not involved in the metabolism of paliperidone. The terminal elimination half-life of paliperidone is about 23 hours.

Special populations

Adolescents

Paliperidone systemic exposure in adolescent subjects was comparable to that in adults. In adolescents weighing < 51 kg (< 112 lbs), a 23% higher exposure was observed than in adolescents weighing ≥ 51 kg (≥ 112 lbs); this is considered not to be clinically significant. Age alone did not influence the paliperidone exposure.

Elderly

Data from a pharmacokinetic study in elderly subjects (≥ 65 years of age, n=26) indicated that the apparent steady-state clearance of paliperidone following INVEGA administration was 20% lower compared to that of adult subjects (18-45 years of age, n=28). However, there was no discernable effect of age in the population pharmacokinetic analysis involving schizophrenia subjects after correction of age-related decreases in CrCl.

Renal impairment

The dose should be reduced in patients with moderate and severe renal impairment (see *Dosage and Administration*). The disposition of paliperidone was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing creatinine clearance (CrCl). Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 mL/min).

Hepatic impairment

Paliperidone is not extensively metabolized in the liver. In a study 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

No dosage adjustment is recommended based on race. Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA administration. No differences in pharmacokinetics were observed in a pharmacokinetics study conducted in Japanese and Caucasian subjects.

Gender

The apparent clearance of paliperidone following INVEGA administration is approximately 19% lower in women than men. This difference is largely explained by differences in lean body mass and creatinine clearance between men and women, as a population pharmacokinetics evaluation revealed no evidence of clinically significant gender-related differences in the pharmacokinetics of paliperidone following INVEGA administration after correction for lean body mass and creatinine clearance.

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.

NON-CLINICAL INFORMATION

Toxicology

As with other drugs that antagonize dopamine D_2 receptors, paliperidone elevated serum prolactin levels in repeat-dose toxicity studies.

In a 7-week juvenile toxicity study 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 dose of 12 mg/day for adolescents on a mg/m^2 basis, no effects on growth, sexual maturation, and reproductive performance were observed. 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 paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats. Risperidone was administered at doses up to 10 mg/kg/day for 18 months to mice and for 25 months to rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. An increase in mammary, pituitary, and endocrine pancreas tumors has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism. The relevance of these tumor findings in rodents in terms of human risk is unknown.

Mutagenicity

No evidence of mutagenic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the rat micronucleus test.

Fertility

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

PHARMACEUTICAL INFORMATION

List of Excipients

Inactive ingredients of INVEGA are butyl hydroxytoluene (E321), carnauba wax, cellulose acetate, hydroxyethyl cellulose, hypromellose, iron oxides (E172), polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, and titanium dioxide (E171). The 3 mg tablets also contain lactose monohydrate and triacetin.

Incompatibilities

None.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Do not store above 30ºC. Protect from moisture.Keep out of the sight and reach of children.

Nature and Contents of Container

Blisters: 7 tablets/strip

- Blisters of 3 mg, 6 mg and 9 mg packed in oriented polyamide (OPA)-aluminum-polyvinyl chloride (PVC)/aluminum push-through child-resistant (CR) layer.

Instructions for Use and Handling [and Disposal]

No special requirements.

Manufactured by

Janssen-Cilag Manufacturing LLC., Gurabo, Puerto Rico

Marketing Authorization Numbers and Date of Authorization

Product name	**Marketing Authorization Number**	**Date of Authorization**
INVEGA (EXTENDED-RELEASE TABLETS, 3 MG)	1C 61/53(N)	31 August 2010
INVEGA (EXTENDED-RELEASE TABLETS, 6 MG)	1C 62/53(N)	31 August 2010
INVEGA (EXTENDED-RELEASE TABLETS, 9 MG)	1C 63/53(N)	31 August 2010

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Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com