

NAME OF THE MEDICINAL PRODUCT

Trade Name

INVEGA™ Extended-Release Tablets

International Non-Proprietary Name

Paliperidone

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended-release tablet contains 3, 6, 9, or 12 mg of paliperidone.

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

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”

12 mg: dark-yellow capsule-shaped tablet imprinted with “PAL 12”

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 PARTICULARS

Therapeutic Indications

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

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

Posology and Method of Administration

Adults (≥ 18 Years of Age)

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.

Schizophrenia

The recommended dose of INVEGA™ for the treatment of Schizophrenia is 6 mg once daily, administered in the morning with or without food. 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.

Schizoaffective Disorder

The recommended dose of INVEGA™ for the treatment of schizoaffective disorder 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.

Patients with 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.

Patients with 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 once daily. As INVEGA™ has not been studied in patients with creatinine clearance < 10 mL/min, use is not recommended in such patients.

Elderly

Dosing recommendations for elderly patients with normal renal function (≥ 80 mL/min) are the same as for adults with normal renal function (see first paragraph in Posology and Method of Administration above). However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Patients with Renal Impairment above).

Adolescents and Children

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

Other Special Populations

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

Contraindications

INVEGA™ 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™ is contraindicated in patients with a known hypersensitivity to risperidone.

Special Warnings and Special Precautions for Use

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

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.

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.

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 also Undesirable Effects)

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 also Posology and Method of 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 leukopenia, 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 10⁹/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 Undesirable Effects).

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 overdose with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Interactions with Other Medicinal Products and Other Forms of Interaction

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 Undesirable Effects), 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 Special Warnings and Special Precautions for Use: *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 CLINICAL PHARMACOLOGY: Pharmacokinetics: 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.

Pharmacokinetic interaction between lithium and INVEGA™ is unlikely.

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™.

Pregnancy and Lactation

Pregnancy

The safety of paliperidone for use during human pregnancy has not been established. No teratogenic effect was noted in any animal study. 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.

Lactation

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 Undesirable Effects). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Undesirable Effects

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 also evaluated in 622 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 ADRs were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data - Schizophrenia

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

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

System/Organ Class Adverse Reaction	Percentage of Patients				
	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) %
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 Disorder					
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

System/Organ Class Adverse Reaction	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)
	%	%	%	%	%
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 – Schizoaffective Disorder

ADRs reported by $\geq 2\%$ of INVEGA™-treated subjects in the two placebo-controlled schizoaffective disorder trials are shown in Table 2.

Table 2 Adverse Drug Reactions Reported by $\geq 2\%$ of INVEGA™-Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials in Adults

System/Organ Class Adverse Reaction	Percentage of Patients	
	INVEGA™ 3-12 mg once daily (N=420) %	Placebo (N=202) %
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 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 ($\geq 3\%$ difference) in subjects receiving INVEGA™ as monotherapy.

Dose-Related Adverse Reactions

In the placebo-controlled, 6-week high- and low-dose study in 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 ADRs reported with paliperidone and/or risperidone in clinical trials.

ADRs reported with paliperidone and/or risperidone by $\geq 2\%$ 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 3a.

Table 3a ADRs Reported with Paliperidone and/or Risperidone by $\geq 2\%$ 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, Diarrhoea

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.

ADRs 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 3b.

Table 3b ADRs 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

Anaemia, Haematocrit decreased, Neutropenia, White blood cell count decreased

Immune System Disorders

Anaphylactic reaction, Hypersensitivity

Endocrine Disorders

Hyperprolactinaemia

Metabolism and Nutritional Disorders

Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycaemia, Weight decreased

Psychiatric Disorders

Anorgasmia, Depression, Libido decreased, Nightmare, Sleep disorder

Nervous System Disorders

Cerebrovascular accident, Convulsion, Disturbance in attention, Dizziness postural, Dyskinesia*, Hypoaesthesia, Loss of consciousness, Paraesthesia, 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, Ischaemia

Respiratory, Thoracic and Mediastinal Disorders

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

Gastrointestinal Disorders

System/Organ Class**Adverse Reaction**

Cheilitis, Dysphagia, Faecal 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, Seborrhoeic dermatitis, Skin discolouration

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, Gynaecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge

General Disorders

Body temperature increased, Chest discomfort, Chills, Face oedema, Gait abnormal, Oedema*, 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, oligomenorrhoea; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema.

ADRs 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 3c.

Table 3c. ADRs 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

System/Organ Class

Adverse Reaction

Metabolism and Nutritional Disorders

Hyperinsulinaemia, 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 hyperaemia

Cardiac Disorders

Postural orthostatic tachycardia syndrome

Respiratory, Thoracic and Mediastinal Disorders

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

Gastrointestinal Disorders

Faecaloma

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

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 ADRs cannot be ruled out.

Events of Particular Interest to the Class

Extrapyramidal Symptoms (EPS). Pooled data from the three placebo-controlled, 6-week, fixed-dose 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 studies (see Pharmacodynamic Properties), the proportions of subjects meeting a weight gain criterion of $\geq 7\%$ 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).

In the pooled data from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder (see: Pharmacodynamic Properties: Clinical Efficacy), a higher percentage of INVEGA™ -treated subjects (5%) had an increase in body weight of $\geq 7\%$ compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of $\geq 7\%$ 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 placebo-controlled, 6-week, fixed-dose studies (see Pharmacodynamic Properties: Clinical Efficacy), median 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: ADRs 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 ADRs 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 ADRs 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

Adverse events first identified as ADRs during postmarketing experience with paliperidone and/or risperidone are included in Table 4. In the table, the frequencies are provided according to the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1000$ to $< 1/100$
Rare	$\geq 1/10000$ to $< 1/1000$
Very rare	$< 1/10000$, including isolated reports

In Table 4 ADRs are presented by frequency category based on spontaneous reporting rates.

Table 4 Adverse Drug Reactions Identified During Postmarketing Experience with INVEGA™ 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, Hypoglycaemia
<i>Not known</i>	Water intoxication
Psychiatric Disorders	
<i>Very rare</i>	Mania
Nervous System Disorders	
<i>Very rare</i>	Dysgeusia
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 apnoea syndrome
Gastrointestinal Disorders	
<i>Very rare</i>	Pancreatitis
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	
<i>Very rare</i>	Hypothermia

Overdose

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 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. Gastric lavage (after intubation if the patient is unconscious) and 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

Paliperidone, the active ingredient in INVEGA™, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives (atypical neuroleptic antipsychotic, ATC Code: N05AX13). INVEGA™ contains a racemic mixture of (+)- and (-)-paliperidone.

Pharmacodynamic Properties

Mechanism of Action

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, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism. Antagonism at receptors other than D₂ 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.

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 any 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

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.

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

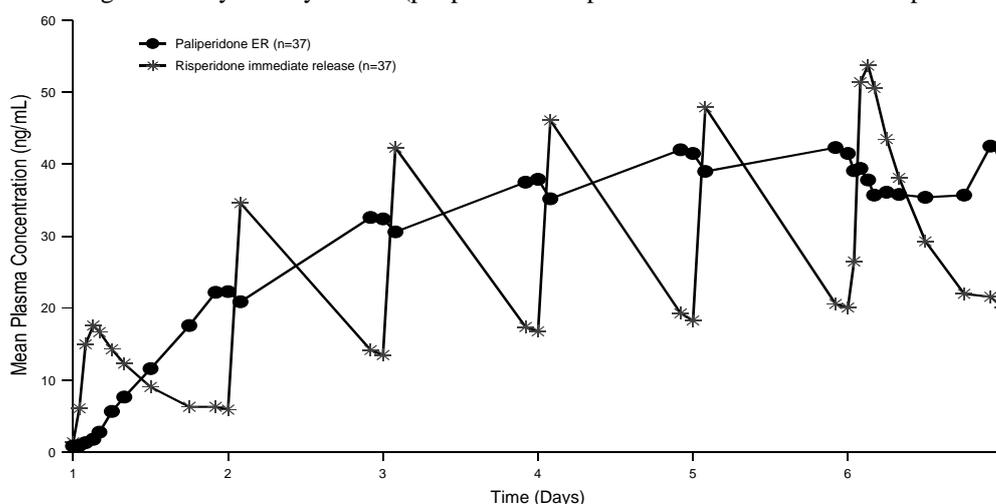
The pharmacokinetics of paliperidone following INVEGA™ administration are dose-proportional within the recommended clinical dose range (3 to 12 mg).

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 tablets) with 4 mg immediate-release risperidone in schizophrenic subjects, the fluctuation indexes were 38% for paliperidone extended-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 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 Posology and Method of Administration).

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 discernable 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

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.

Renal Impairment. The dose should be reduced in patients with moderate and severe renal impairment (see Posology and Method of 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 \geq 80 mL/min).

Elderly. Data from a pharmacokinetic study in elderly subjects (\geq 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.

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.

Preclinical Safety Data

Toxicology

As with other drugs that antagonize dopamine D₂ receptors, paliperidone elevated serum prolactin levels in repeat-dose toxicity studies.

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 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.

Impairment of 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 PARTICULARS

List of Excipients

Inactive ingredients of INVEGA™ are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene oxides, polyethylene glycol, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and glycerol triacetate.

Incompatibilities

None

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Do not store above 30°C. Protect from moisture.

Keep out of reach of children.

Nature and Contents of Container

Bottles:

White high-density polyethylene (HDPE) bottle with induction sealing and polypropylene child-resistant closure. Each bottle contains a desiccant pouch. 75-cc size bottle for 30 tablets, 160-cc size bottle for 350 tablets.

Blisters:

- Polyvinyl chloride (PVC) laminated with polychloro-trifluoroethylene (PCTFE)/aluminum push-through layer.
- Oriented polyamide (OPA)-aluminum-polyvinyl chloride (PVC)/ aluminum push-through layer.

Instructions for Use and Handling

No special requirements.

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

July 2011