

## PRODUCT NAME

INVEGA® Extended-Release Tablets

## International Non-proprietary Name

Paliperidone

## DOSAGE FORMS AND STRENGTHS

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

For excipients, see List of Excipients.

- 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

### Therapeutic Indications

INVEGA® is indicated for the treatment of schizophrenia in adolescents 15 years and older, including acute treatment and recurrence prevention.

INVEGA® is indicated for the treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers (lithium and valproate).

### Dosage and Administration

#### *Treatment of schizophrenia, including acute treatment and recurrence prevention.*

##### *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. Although it has not been systematically established that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse effects. Thus, some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, small increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

In a longer-term study, INVEGA® has been shown to be effective in delaying time to relapse in patients with schizophrenia who were stabilized on INVEGA® for 6 weeks (see Pharmacodynamic Properties: Clinical Efficacy). INVEGA® should be prescribed at the lowest effective dose for maintaining clinical stability and the physician should periodically reevaluate the long-term usefulness of the drug in individual patients.

#### *Adolescents population*

*Schizophrenia:* The recommended starting dose of INVEGA® for the treatment of schizophrenia in adolescents 15 – 17 years old is 3 mg once daily, administered in the morning.

Adolescents weighing < 51 kg: the maximum recommended daily dose of INVEGA® is 6 mg.

Adolescents weighing ≥ 51 kg: the maximum recommended daily dose of INVEGA® is 12 mg.

Dosage adjustment, if indicated, should occur only after clinical reassessment based on the individual need of the patient. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of 5 days or more. The safety and efficacy of INVEGA® in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established.

Currently available data are described in section adverse reaction and Pharmacodynamic properties but no recommendation on a posology can be made. There is no relevant use of INVEGA® in children aged less than 12 years.

#### ***Treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers (lithium and valproate).***

##### 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.

This trend must be weighed against dose-related increase in adverse reactions. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increment of 3 mg/day are recommended and generally should occur at intervals on more than 4 days. The maximum recommended dose is 12 mg/day.

#### **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 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 and Administration above). 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  $\geq 50$  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  $\geq 10$  to  $< 50$  mL/min), the recommended dose of INVEGA<sup>®</sup> is 3 mg every other day, which may then be increased to 3 mg once daily after clinical reassessment. As INVEGA<sup>®</sup> 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<sup>®</sup> has not been studied in patients with severe hepatic impairment.

#### *Other populations*

No dose adjustment for INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> is for oral administration and can be administered with or without food.

INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>, 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, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. 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 antipsychotics use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

#### *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).

#### *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 10<sup>9</sup>/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 INVEGA® 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<sup>®</sup> to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

#### *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.

#### *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, including INVEGA<sup>®</sup> (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<sup>®</sup> with drugs known to prolong the QT interval.

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

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. *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<sup>®</sup> should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

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

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

Co-administration of INVEGA<sup>®</sup> 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<sup>®</sup>*

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate

that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. *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<sup>®</sup> was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Co-administration of INVEGA<sup>®</sup> 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<sup>®</sup> should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> should be considered when INVEGA<sup>®</sup> is co-administered with valproate after clinical assessment.

#### *Concomitant Use of INVEGA<sup>®</sup> with Risperidone*

Concomitant Use of INVEGA<sup>®</sup> 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<sup>®</sup>.

#### *Concomitant use of INVEGA<sup>®</sup> with psychostimulants*

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

### **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. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalizations.

INVEGA® should only be used during pregnancy only if the potential benefit justifies the potential risks to the foetus. 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<sup>®</sup> (3-12 mg once daily). Both studies included subjects who received INVEGA<sup>®</sup> 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  $\geq 2\%$  of INVEGA<sup>®</sup>-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  $\geq 2\%$  of INVEGA<sup>®</sup>-Treated Subjects with Schizophrenia in Three 6-Week Double-Blind, Placebo-Controlled, Fixed-Dose Clinical Trials in Adults

| System/Organ Class<br>Adverse Reaction | Percentage of Patients                                      |                                                             |                                                             |                                                              |                           |
|----------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------|---------------------------|
|                                        | INVEGA <sup>®</sup><br>3 mg<br>once daily<br>(N = 127)<br>% | INVEGA <sup>®</sup><br>6 mg<br>once daily<br>(N = 235)<br>% | INVEGA <sup>®</sup><br>9 mg<br>once daily<br>(N = 246)<br>% | INVEGA <sup>®</sup><br>12 mg<br>once daily<br>(N = 242)<br>% | Placebo<br>(N = 355)<br>% |
| <b>Nervous System Disorders</b>        |                                                             |                                                             |                                                             |                                                              |                           |
| 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                         |
| <b>Eye Disorders</b>                   |                                                             |                                                             |                                                             |                                                              |                           |
| Oculogyric crisis                      | 0                                                           | 0                                                           | 2                                                           | 0                                                            | 0                         |
| <b>Cardiac Disorders</b>               |                                                             |                                                             |                                                             |                                                              |                           |
| 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                         |
| <b>Vascular Disorders</b>              |                                                             |                                                             |                                                             |                                                              |                           |
| Orthostatic hypotension                | 2                                                           | 1                                                           | 2                                                           | 4                                                            | 1                         |
| <b>Gastrointestinal Disorders</b>      |                                                             |                                                             |                                                             |                                                              |                           |
| 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                       |
| <b>General Disorders</b>               |                                                             |                                                             |                                                             |                                                              |                           |
| Asthenia                               | 2                                                           | < 1                                                         | 2                                                           | 2                                                            | 1                         |
| Fatigue                                | 2                                                           | 1                                                           | 2                                                           | 2                                                            | 1                         |

*Double-Blind, Placebo-Controlled Data - Schizophrenia - Adolescents*

Adverse reactions reported by  $\geq 2\%$  of INVEGA<sup>®</sup>-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  $\geq 2\%$  of INVEGA<sup>™</sup>-Treated Subjects with Schizophrenia in a Fixed-Dose, Placebo-Controlled Clinical Trial in Adolescents

|                                                 |                         | Percentage of Patients                                |                                                    |                                                     |                                                      |                   |
|-------------------------------------------------|-------------------------|-------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------|------------------------------------------------------|-------------------|
| Body Class                                      | System/Organ            | INVEGA <sup>®</sup><br>1.5 mg<br>once daily<br>(N=54) | INVEGA <sup>®</sup><br>3mg<br>once daily<br>(N=16) | INVEGA <sup>®</sup><br>6 mg<br>once daily<br>(N=45) | INVEGA <sup>®</sup><br>12 mg<br>once daily<br>(N=35) | Placebo<br>(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     | 0                                                     | 0                                                  | 0                                                   | 3                                                    | 0                 |
|                                                 | involuntary             |                                                       |                                                    |                                                     |                                                      |                   |
|                                                 | 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                 |

| Body Class                                             | System/Organ            | Percentage of Patients                       |                                           |                                            |                                             | Placebo (N=51) |
|--------------------------------------------------------|-------------------------|----------------------------------------------|-------------------------------------------|--------------------------------------------|---------------------------------------------|----------------|
|                                                        |                         | INVEGA <sup>®</sup> 1.5 mg once daily (N=54) | INVEGA <sup>®</sup> 3mg once daily (N=16) | INVEGA <sup>®</sup> 6 mg once daily (N=45) | INVEGA <sup>®</sup> 12 mg once daily (N=35) |                |
| Adverse Reaction                                       |                         |                                              |                                           |                                            |                                             |                |
| <b>Gastrointestinal disorders</b>                      |                         |                                              |                                           |                                            |                                             |                |
|                                                        | 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              |
| <b>Musculoskeletal and connective tissue disorders</b> |                         |                                              |                                           |                                            |                                             |                |
|                                                        | Muscle rigidity         | 0                                            | 0                                         | 2                                          | 3                                           | 0              |
|                                                        | Muscle contracture      | 0                                            | 0                                         | 0                                          | 3                                           | 0              |
|                                                        | Torticollis             | 0                                            | 0                                         | 2                                          | 0                                           | 0              |
| <b>Reproductive system and breast disorders</b>        |                         |                                              |                                           |                                            |                                             |                |
|                                                        | Galactorrhea            | 0                                            | 0                                         | 4                                          | 0                                           | 0              |
|                                                        | Amenorrhea              | 0                                            | 6                                         | 0                                          | 0                                           | 0              |
|                                                        | Breast swelling         | 0                                            | 0                                         | 0                                          | 3                                           | 0              |
| <b>General disorders</b>                               |                         |                                              |                                           |                                            |                                             |                |
|                                                        | Fatigue                 | 4                                            | 0                                         | 2                                          | 3                                           | 0              |
|                                                        | Asthenia                | 0                                            | 0                                         | 2                                          | 3                                           | 0              |
| <b>Investigations</b>                                  |                         |                                              |                                           |                                            |                                             |                |
|                                                        | Weight increased        | 7                                            | 6                                         | 2                                          | 3                                           | 0              |

*Double-Blind, Placebo-Controlled Data – Bipolar Disorder - Adults*

Adverse reactions reported by  $\geq 2\%$  of INVEGA<sup>®</sup>-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  $\geq 2\%$  of INVEGA<sup>®</sup>-Treated Subjects with Bipolar I Disorder in Three Double-Blind, Placebo-Controlled Clinical Trials in Adults

| System/Organ Class | Percentage of Patients                         |                 |
|--------------------|------------------------------------------------|-----------------|
|                    | INVEGA <sup>®</sup> 3-12 mg once daily (N=739) | Placebo (N=376) |
| Adverse Reaction   | %                                              | %               |

|                                           |    |    |
|-------------------------------------------|----|----|
| <b>Metabolism and Nutrition Disorders</b> |    |    |
| Increased appetite                        | 3  | 1  |
| <b>Psychiatric Disorders</b>              |    |    |
| Agitation                                 | 3  | 3  |
| <b>Nervous System Disorders</b>           |    |    |
| Headache                                  | 14 | 10 |
| Somnolence                                | 8  | 5  |
| Akathisia                                 | 7  | 2  |
| Sedation                                  | 7  | 3  |
| Dizziness                                 | 6  | 2  |
| Tremor                                    | 5  | 3  |
| Extrapyramidal disorder                   | 4  | 2  |
| Droling                                   | 4  | 1  |
| Hypertonia                                | 3  | 2  |
| Dystonia                                  | 2  | 0  |
| <b>Eye Disorders</b>                      |    |    |
| Vision blurred                            | 2  | <1 |
| <b>Cardiac Disorders</b>                  |    |    |
| Tachycardia                               | 2  | 1  |
| <b>Gastrointestinal Disorders</b>         |    |    |
| Constipation                              | 6  | 4  |
| Vomiting                                  | 4  | 3  |
| Nausea                                    | 4  | 6  |
| Dyspepsia                                 | 4  | 2  |
| <b>General Disorders</b>                  |    |    |
| Fatigue                                   | 3  | 1  |
| <b>Investigations</b>                     |    |    |
| Weight increased                          | 4  | 2  |

*Double-Blind, Placebo-Controlled Data – Schizoaffective Disorder - Adults*

Adverse reactions reported by  $\geq 2\%$  of INVEGA<sup>®</sup> -treated subjects in the two placebo-controlled schizoaffective disorder trials in adults are shown in Table 4.

**Table 4.** Adverse Reactions Reported by  $\geq 2\%$  of INVEGA<sup>®</sup> -Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials in Adults

| System/Organ Class<br>Adverse Reaction | Percentage of Patients                                        |                         |
|----------------------------------------|---------------------------------------------------------------|-------------------------|
|                                        | INVEGA <sup>®</sup><br>3-12 mg<br>once daily<br>(N=420)*<br>% | Placebo<br>(N=202)<br>% |

**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<sup>®</sup>, 230 (55%) received INVEGA<sup>®</sup> as monotherapy and 190 (45%) received INVEGA<sup>®</sup> 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<sup>®</sup> as monotherapy and 190 (45%) subjects received INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of INVEGA<sup>®</sup> 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  $\geq 2\%$  of INVEGA<sup>®</sup>-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  $\geq 2\%$  of INVEGA<sup>®</sup>-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                                       |
| <b>Infections and Infestations</b>                     |
| Upper respiratory tract infection                      |
| <b>Psychiatric Disorders</b>                           |
| Insomnia*                                              |
| <b>Nervous System Disorders</b>                        |
| Akathisia*, Dystonia*, Parkinsonism*                   |
| <b>Gastrointestinal Disorders</b>                      |
| Abdominal discomfort, Diarrhea                         |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |
| 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<sup>®</sup>-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.

| <b>System/Organ Class</b>                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Adverse Reaction</b>                                                                                                                                                                                    |
| <b>Infections and Infestations</b>                                                                                                                                                                         |
| Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Ear infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Tonsillitis, Urinary tract infection                        |
| <b>Blood and Lymphatic System Disorders</b>                                                                                                                                                                |
| Anemia, Hematocrit decreased, Neutropenia, White blood cell count decreased                                                                                                                                |
| <b>Immune System Disorders</b>                                                                                                                                                                             |
| Anaphylactic reaction, Hypersensitivity                                                                                                                                                                    |
| <b>Endocrine Disorders</b>                                                                                                                                                                                 |
| Hyperprolactinemia                                                                                                                                                                                         |
| <b>Metabolism and Nutritional Disorders</b>                                                                                                                                                                |
| Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycemia, Weight decreased                                                                                  |
| <b>Psychiatric Disorders</b>                                                                                                                                                                               |
| Anorgasmia, Depression, Libido decreased, Nightmare, Sleep disorder                                                                                                                                        |
| <b>Nervous System Disorders</b>                                                                                                                                                                            |
| Cerebrovascular accident, Convulsion*, Disturbance in attention, Dizziness postural, Dyskinesia*, Hypoesthesia, Loss of consciousness, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia |
| <b>Eye Disorders</b>                                                                                                                                                                                       |
| Conjunctivitis, Dry eye, Lacrimation increased, Photophobia                                                                                                                                                |
| <b>Ear and Labyrinth Disorders</b>                                                                                                                                                                         |
| Ear pain, Tinnitus, Vertigo                                                                                                                                                                                |
| <b>Cardiac Disorders</b>                                                                                                                                                                                   |
| Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations                                                                         |
| <b>Vascular Disorders</b>                                                                                                                                                                                  |
| Flushing, Hypertension, Hypotension, Ischemia                                                                                                                                                              |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>                                                                                                                                                     |
| Cough, Dyspnea, Hyperventilation, Nasal congestion, Pharyngolaryngeal pain, Wheezing                                                                                                                       |
| <b>Gastrointestinal Disorders</b>                                                                                                                                                                          |
| Cheilitis, Dysphagia, Fecal incontinence, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue, Toothache                                                                                   |

| System/Organ Class |
|--------------------|
| Adverse Reaction   |

#### **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<sup>®</sup> (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<sup>®</sup> (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                            |
| <b>Infections and Infestations</b>          |
| Eye infection                               |
| <b>Blood and Lymphatic System Disorders</b> |
| Eosinophil count increased                  |

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**System/Organ Class**

Adverse Reaction

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**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<sup>®</sup> 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<sup>®</sup> 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 Section 5.1: 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  $\geq 7\%$  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).

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  $\geq 7\%$  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  $\geq 7\%$  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  $\geq 7\%$  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 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 (Table 8). In the table, the frequencies are provided according to the following convention:

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

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

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

|                                                        |                                                        |
|--------------------------------------------------------|--------------------------------------------------------|
| <b>Blood and Lymphatic System Disorders</b>            |                                                        |
| <i>Very rare</i>                                       | Agranulocytosis, Thrombocytopenia                      |
| <b>Endocrine Disorders</b>                             |                                                        |
| <i>Not known</i>                                       | Inappropriate antidiuretic hormone secretion           |
| <b>Metabolism and Nutrition Disorders</b>              |                                                        |
| <i>Very rare</i>                                       | Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia |
| <i>Not known</i>                                       | Water intoxication                                     |
| <b>Psychiatric Disorders</b>                           |                                                        |
| <i>Very rare</i>                                       | Catatonia, Mania, Somnambulism                         |
| <i>Not known</i>                                       | Sleep-related eating disorder                          |
| <b>Nervous System Disorders</b>                        |                                                        |
| <i>Very rare</i>                                       | Dysgeusia, restless leg syndrome                       |
| <b>Eye Disorders</b>                                   |                                                        |
| <i>Not known</i>                                       | Floppy iris syndrome (intraoperative)                  |
| <b>Cardiac Disorders</b>                               |                                                        |
| <i>Very rare</i>                                       | Atrial fibrillation                                    |
| <b>Vascular Disorder</b>                               |                                                        |
| <i>Very rare</i>                                       | Deep vein thrombosis, Pulmonary embolism               |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b> |                                                        |
| <i>Very rare</i>                                       | Sleep apnea syndrome*                                  |
| <b>Gastrointestinal Disorders</b>                      |                                                        |
| <i>Very rare</i>                                       | Pancreatitis                                           |
| <i>Very rare</i>                                       | Ileus                                                  |
| <b>Hepatobiliary Disorders</b>                         |                                                        |
| <i>Not known</i>                                       | Jaundice                                               |
| <b>Skin and Subcutaneous Tissue Disorders</b>          |                                                        |
| <i>Rare</i>                                            | Angioedema                                             |
| <i>Very rare</i>                                       | Alopecia                                               |
| <i>Not known</i>                                       | Stevens-Johnson syndrome/Toxic epidermal necrolysis    |
| <b>Renal and Urinary Disorders</b>                     |                                                        |
| <i>Very rare</i>                                       | Urinary retention                                      |
| <b>Pregnancy, Puerperium and Perinatal Conditions</b>  |                                                        |
| <i>Very rare</i>                                       | Drug withdrawal syndrome neonatal                      |
| <b>Reproductive System and Breast Disorders</b>        |                                                        |
| <i>Very rare</i>                                       | Priapism                                               |
| <b>General Disorders</b>                               |                                                        |
| <i>Very rare</i>                                       | Hypothermia                                            |

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

## 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 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<sup>®</sup>, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives (atypical neuroleptic antipsychotic). INVEGA<sup>®</sup> contains a racemic mixture of (+)- and (-)-paliperidone.

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

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

#### *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<sup>®</sup> on sleep architecture and continuity, a placebo-controlled study was conducted in 36 subjects with schizophrenia in which INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> treatment group (n = 44).

In the second phase 1 study (n = 109), subjects were randomized to receive either placebo, the maximum recommended INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup>, 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> (doses ranging from 3 to 15 mg once daily) were then randomized in a double-blind manner to either continue on INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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  $\pm$  16.03] points), but after randomization to double-blind treatment, the patients receiving placebo deteriorated significantly more than those on INVEGA<sup>®</sup> ( $p < 0.001$ ). INVEGA<sup>®</sup> 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<sup>®</sup> remained clinically stable.

#### *Schizophrenia – adolescents*

The efficacy of INVEGA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup> daily. Dosing was in the morning without regard to meals.

Efficacy was evaluated using PANSS. This study demonstrated the efficacy of INVEGA<sup>®</sup> 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<sup>®</sup> in this population was 3 mg/day.

### *Schizoaffective Disorder*

The efficacy of INVEGA<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> (3-12 mg once daily). Both studies included subjects who received INVEGA<sup>®</sup> 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<sup>®</sup> in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day), and the INVEGA<sup>®</sup> 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<sup>®</sup> was not significantly different from placebo as measured by the PANSS.

Taking the results of both studies together, INVEGA<sup>®</sup> 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**

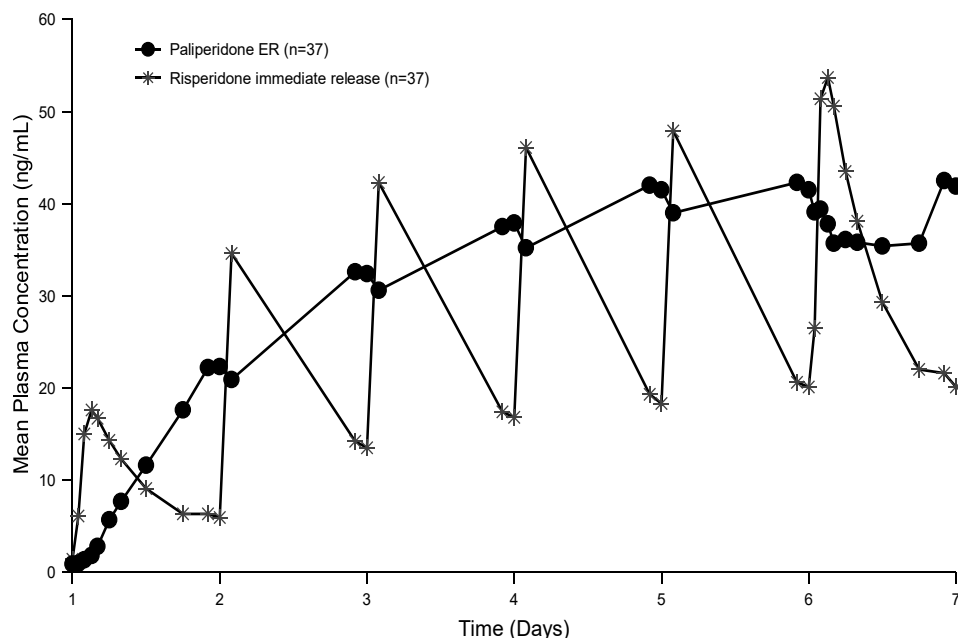
Unless where otherwise stated, the pharmacokinetic information presented in this section are based on data from studies in adults.

The pharmacokinetics of paliperidone following INVEGA<sup>®</sup> administration are dose-proportional within the recommended clinical dose range (3 to 12 mg).

### *Absorption*

Following a single dose of INVEGA<sup>®</sup>, 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<sup>®</sup>, steady-state concentrations of paliperidone are attained within 4 - 5 days of dosing in most subjects.

The release characteristics of INVEGA<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> 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 extended-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<sup>®</sup> administration may increase or decrease exposure to paliperidone, these changes are not considered clinically relevant. Clinical trials establishing the safety and efficacy of INVEGA<sup>®</sup> were carried out in subjects without regard to the timing of meals. (See Dosage and 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  $\alpha_1$ -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 <sup>14</sup>C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized

in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sub>2</sub> 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<sup>2</sup> 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<sub>2</sub> 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<sup>®</sup> are acetone, butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxyethyl cellulose, ink water-based black, iron oxides, polyethylene glycol, polyethylene oxides, purified water, sodium chloride and stearic acid. The 9 mg tablets also contain color overcoating material pink and povidone. The 6 mg tablets also contain color overcoating material beige and povidone. The 3 mg tablets also contain color overcoating material white.

**Incompatibilities**

None.

**Shelf Life**

24 months

See expiry date on the outer pack.

**Storage Conditions**

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

Keep out of the sight and reach of children.

**Nature and Contents of Container**

Bottles:

White high-density polyethylene (HDPE) 75 mL bottle with induction sealing, 33 mm polypropylene (PP) child-resistant (CR) closure and two 1 g desiccant silica gel pouches for 30 tablets.

Blisters:

Pack size of 28 tablets in:

- Oriented polyamide (OPA)-aluminum-PVC/aluminum push-through child-resistant (CR) blister.

**Instructions for Use and Handling <and Disposal>**

No special requirements.

**PRODUCT REGISTRATION HOLDER**

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