INVEGA® (paliperidone) Extended-Release Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INVEGA® safely and effectively. See full prescribing information for INVEGA®.

INVEGA® (paliperidone) Extended-Release Tablets
Initial U.S. Approval: 2006

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

INDICATIONS AND USAGE
INVEGA® is an atypical antipsychotic agent indicated for Treatment of schizophrenia (1.1)
- Adults: Efficacy was established in three 6-week trials and one maintenance trial. (14.1)
- Adolescents (ages 12-17): Efficacy was established in one 6-week trial. (14.1)
- Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants. (1.2)
- Efficacy was established in two 6-week trials in adult patients. (14.2)

DOSE AND ADMINISTRATION
Initial Dose Recommended Dose Maximum Dose
Schizophrenia - adults (2.1) 6 mg/day 3 - 12 mg/day 12 mg/day
Schizophrenia-adolescents (2.1) Weight < 51kg 3 mg/day 3 - 6 mg/day 6 mg/day
Weight ≥ 51kg 3 mg/day 3 - 12 mg/day 12 mg/day
Schizoaffective disorder - adults (2.2) 6 mg/day 3 - 12 mg/day 12 mg/day

- Tablet should be swallowed whole and should not be chewed, divided, or crushed. (2.3)

DOSE FORMS AND STRENGTHS
Tablets: 1.5 mg, 3 mg, 6 mg, and 9 mg (3)

WARNINGS AND PRECAUTIONS
- Cerebrovascular Adverse Reactions: An increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotics. (5.2)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation of drug and close monitoring. (5.3)
- QT Prolongation: Increase in QT interval, avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. (5.4)
- Tardive Dyskinesia: Discontinue drug if clinically appropriate. (5.5)
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.6)
  o Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  o Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.6)
  o Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.6)

ADVERSE REACTIONS
Commonly observed adverse reactions (incidence ≥ 5% and at least twice that for placebo) were (6)
- Adults with schizophrenia: extrapyramidal symptoms, tachycardia, and akathisia.
- Adolescents with schizophrenia: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia.
- Adults with schizoaffective disorder: extrapyramidal symptoms, somnolence, dyspnea, constipation, weight increased, and nasopharyngitis.

SIDE EFFECTS ON LABORATORY TESTS
- Prolactin elevations occur and persist during chronic administration. (5.7)
- Gastrointestinal Narrowing: Obstructive symptoms may result in patients with gastrointestinal disease. (5.8)
- Orthostatic Hypotension and Syncope: Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension. (5.9)
- Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotics, including INVEGA®. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.11)
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery. (5.12)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.13)
- Suicide: Closely supervise high-risk patients. (5.15)

DRUG INTERACTIONS
- Centrally-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol. (7.1)
- Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with INVEGA®. (7.1)
- Strong CYP3A4/P-glycoprotein (P-gp) inducers: It may be necessary to increase the dose of INVEGA® when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA®. (7.2)
- Co-administration of divalproex sodium increased Cmax and AUC of paliperidone by approximately 50%. Adjust dose of INVEGA® if necessary based on clinical assessment. (7.2)

USE IN SPECIFIC POPULATIONS
- Renal impairment: Dosing must be individualized according to renal function status. (2.5)
- Elderly: Same as for younger adults (adjust dose according to renal function status). (2.4)
- Nursing Mothers: The benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone. (8.3)
- Pediatric Use: Safety and effectiveness in the treatment of schizophrenia not established in patients less than 12 years of age. Safety and effectiveness in the treatment of schizoaffective disorder not established in patients less than 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2018
**INVEGA® (paliperidone) Extended-Release Tablets**

### FULL PRESCRIBING INFORMATION:

**CONTENTS**

1 INDICATIONS AND USAGE
   1.1 Schizophrenia
   1.2 Schizoaffective Disorder

2 DOSAGE AND ADMINISTRATION
   2.1 Schizophrenia
   2.2 Schizoaffective Disorder
   2.3 Administration Instructions
   2.4 Use with Risperidone
   2.5 Dosage in Special Populations

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
   5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
   5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients With Dementia-Related Psychosis
   5.3 Neuroleptic Malignant Syndrome
   5.4 QT Prolongation
   5.5 Tardive Dyskinesia
   5.6 Metabolic Changes
   5.7 Hyperprolactinemia
   5.8 Potential for Gastrointestinal Obstruction
   5.9 Orthostatic Hypotension and Syncope
   5.10 Falls
   5.11 Leukopenia, Neutropenia, and Agranulocytosis
   5.12 Potential for Cognitive and Motor Impairment
   5.13 Seizures
   5.14 Dysphagia
   5.15 Suicide
   5.16 Priapism
   5.17 Thrombotic Thrombocytopenic Purpura (TTP)
   5.18 Body Temperature Regulation
   5.19 Antiemetic Effect
   5.20 Use in Patients with Concomitant Illness
   5.21 Monitoring: Laboratory Tests

6 ADVERSE REACTIONS
   6.1 Overall Adverse Reaction Profile
   6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo- Controlled Clinical Trials – Schizophrenia in Adults and Adolescents
   6.3 Commonly-Observed Adverse Reactions in Double-Blind, Placebo- Controlled Clinical Trials – Schizoaffective Disorder in Adults
   6.4 Discontinuations Due to Adverse Reactions
   6.5 Dose-Related Adverse Reactions
   6.6 Demographic Differences

---

**WARNING – INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® (paliperidone) Extended-Release Tablets is not approved for the treatment of patients with dementia-related psychosis. [see Warnings and Precautions (5.1)]

---

**INDICATIONS AND USAGE**

1.1 Schizophrenia

INVEGA® (paliperidone) Extended-Release Tablets are indicated for the treatment of schizophrenia [see Clinical Studies (14.1)].

The efficacy of INVEGA® in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents, as well as one maintenance trial in adults.

1.2 Schizoaffective Disorder

INVEGA® (paliperidone) Extended-Release Tablets are indicated for the treatment of schizoaffective disorder as monotherapy and an adjunct to mood stabilizers and/or antidepressant therapy [see Clinical Studies (14.2)].

The efficacy of INVEGA® in schizoaffective disorder was established in two 6-week trials in adults.

---

**DOSAGE AND ADMINISTRATION**

2.1 Schizophrenia

Adults

The recommended dose of INVEGA® (paliperidone) Extended-Release Tablets for the treatment of schizophrenia in adults is 6 mg administered once daily. Initial dose titration is not required. Although it has not been systematically established...
that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse reactions. Thus, some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

In a longer-term study, INVEGA® has been shown to be effective in delaying time to relapse in patients with schizophrenia who were stabilized on INVEGA® for 6 weeks [see Clinical Studies (14)]. INVEGA® should be prescribed at the lowest effective dose for maintaining clinical stability and the physician should periodically reevaluate the long-term usefulness of the drug in individual patients.

Adolescents (12-17 years of age)

The recommended starting dose of INVEGA® (paliperidone) Extended-Release Tablets for the treatment of schizoaffective disorder in adolescents 12-17 years of age is 3 mg administered once daily. Initial dose titration is not required. Dose increases, if considered necessary, should be made only after clinical reassessment and should occur at increments of 3 mg/day at intervals of more than 5 days. Prescribers should be mindful that, in the adolescent schizoaffective study, there was no clear enhancement to efficacy at the higher doses, i.e., 6 mg for subjects weighing less than 51 kg and 12 mg for subjects weighing 51 kg or greater, while adverse events were dose-related.

2.2 Schizoaffective Disorder

The recommended dose of INVEGA® (paliperidone) Extended-Release Tablets for the treatment of schizoaffective disorder in adults is 6 mg administered once daily. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended dose range of 3 to 12 mg once daily. A general trend for greater effects was seen with higher doses. This trend must be weighed against dose-related increases in adverse reactions. Dosage adjustment, if indicated, should be made only after clinical reassessment. Dose increments, if indicated, generally should occur at intervals of more than 4 days. When dose increases are indicated, increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

2.3 Administration Instructions

INVEGA® can be taken with or without food.

INVEGA® must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

2.4 Use with Risperidone

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

2.5 Dosage in Special Populations

Renal Impairment

Dosing must be individualized according to the patient’s renal function status. For patients with mild renal impairment (creatinine clearance ≥50 mL/min to < 80 mL/min), the recommended initial dose of INVEGA® is 3 mg once daily. The dose may then be increased to a maximum of 6 mg once daily based on clinical response and tolerability. For patients with moderate to severe renal impairment (creatinine clearance ≥10 mL/min to < 50 mL/min), the recommended initial dose of INVEGA® is 1.5 mg once daily, which may be increased to a maximum of 3 mg once daily after clinical reassessment. As INVEGA® has not been studied in patients with creatinine clearance below 10 mL/min, use is not recommended in such patients. [See Clinical Pharmacology (12.3)].

Hepatic Impairment

For patients with mild to moderate hepatic impairment, (Child-Pugh Classification A and B), no dose adjustment is recommended [see Clinical Pharmacology (12.3)]. INVEGA® has not been studied in patients with severe hepatic impairment.

Elderly

Because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status. In general, recommended dosing for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. For patients with moderate to severe renal impairment (creatinine clearance 10 mL/min to < 50 mL/min), the maximum recommended dose of INVEGA® is 3 mg once daily [see Renal Impairment above].

3 DOSAGE FORMS AND STRENGTHS

INVEGA® Extended-Release Tablets are available in the following strengths and colors: 1.5 mg (orange-brown), 3 mg (white), 6 mg (beige), and 9 mg (pink). All tablets are capsule shaped and are imprinted with either “PAL 1.5”, “PAL 3”, “PAL 6”, or “PAL 9”.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA® (paliperidone) is not approved for the treatment of dementia-related psychosis [see Boxed Warning].

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

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA® was not marketed at the time these studies were performed. INVEGA® is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions (5.1)].

5.3 Neuroleptic Malignant Syndrome

A potentially fatal syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

5.4 QT Prolongation

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

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

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

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted decrease from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA® (Cmax ss = 113 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.
For the three fixed-dose efficacy studies in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA® 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA® had a QTcL exceeding 500 msec at any time in any of these three studies.

### 5.5 Tardive Dyskinesia

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

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

### 5.6 Metabolic Changes

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

#### Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoadosis or hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trials subjects treated with INVEGA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA® was not marketed at the time these studies were performed, it is not known if INVEGA® is associated with this increased risk.

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

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia are presented in Table 1a.

#### Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia are presented in Table 2a.

### Table 1a. Change in Fasting Glucose from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>INVEGA® (paliperidone) Extended-Release Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in Fasting Glucose from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
</tr>
<tr>
<td>Serum Glucose</td>
</tr>
<tr>
<td>(&lt;100 mg/dL to ≥126 mg/dL)</td>
</tr>
</tbody>
</table>
| In the uncontrolled, longer-term open-label extension studies, INVEGA® was associated with a mean change in glucose of +3.3 mg/dL at Week 24 (n=570) and +4.8 mg/dL at Week 52 (n=314).

Data from the placebo-controlled 6-week study in adolescent subjects (12-17 years of age) with schizophrenia are presented in Table 1b.

#### Table 1b. Change in Fasting Glucose from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia

| **Change in Fasting Glucose from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia** | **Proportion of Patients with Shifts** |
| | **Mean change from baseline (mg/dL)** | **Placebo** | **1.5 mg/day** | **3 mg/day** | **6 mg/day** | **12 mg/day** |
| | | **n=41** | **n=44** | **n=11** | **n=28** | **n=32** |
| Serum Glucose | Change from baseline | 0.8 | -1.4 | -1.8 | -0.1 | 5.2 |
| Serum Glucose | Normal to High | 3% | 0% | 0% | 0% | 11% |
| (<100 mg/dL to ≥126 mg/dL) | (1/32) | (0/34) | (0/9) | (0/20) | (3/27) |

#### Table 2a. Change in Fasting Lipids from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

| **Change in Fasting Lipids from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia** | **Proportion of Patients with Shifts** |
| | **Mean change from baseline (mg/dL)** | **Placebo** | **3 mg/day** | **6 mg/day** | **9 mg/day** | **12 mg/day** |
| | | **Cholesterol** | **n=331** | **n=120** | **n=216** | **n=236** | **n=231** |
| | | **Change from baseline** | 6.3 | -4.4 | -2.4 | -5.3 | -4.0 |
| | | **LDL** | **n=322** | **n=116** | **n=210** | **n=231** | **n=225** |
| | | **Change from baseline** | -3.2 | 0.5 | -0.8 | -3.9 | -2.0 |
| | | **HDL** | **n=331** | **n=119** | **n=216** | **n=234** | **n=230** |
| | | **Change from baseline** | 0.3 | -0.4 | 0.5 | 0.8 | 1.2 |
| | | **Triglycerides** | **n=331** | **n=120** | **n=216** | **n=236** | **n=231** |
| | | **Change from baseline** | -22.3 | -18.3 | -12.6 | -10.6 | -15.4 |

### Table 2b. Change in Fasting Lipids from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

| **Change in Fasting Lipids from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia** | **Proportion of Patients with Shifts** |
| | **Mean change from baseline (mg/dL)** | **Placebo** | **3 mg/day** | **6 mg/day** | **9 mg/day** | **12 mg/day** |
| | | **Cholesterol** | **n=331** | **n=120** | **n=216** | **n=236** | **n=231** |
| | | **Change from baseline** | 6.3 | -4.4 | -2.4 | -5.3 | -4.0 |
| | | **LDL** | **n=322** | **n=116** | **n=210** | **n=231** | **n=225** |
| | | **Change from baseline** | -3.2 | 0.5 | -0.8 | -3.9 | -2.0 |
| | | **HDL** | **n=331** | **n=119** | **n=216** | **n=234** | **n=230** |
| | | **Change from baseline** | 0.3 | -0.4 | 0.5 | 0.8 | 1.2 |
| | | **Triglycerides** | **n=331** | **n=120** | **n=216** | **n=236** | **n=231** |
| | | **Change from baseline** | -22.3 | -18.3 | -12.6 | -10.6 | -15.4 |
In the uncontrolled, longer-term open-label extension studies, INVEGA® was associated with a mean change in weight of -1.5 mg/dL at Week 24 (n=573) and 0.6 mg/dL at Week 24 (n=573) and -1.0 mg/dL at Week 25 (n=317); (c) LDL of -1.9 mg/dL at Week 24 (n=557) and -2.7 mg/dL at Week 25 (n=297); and (d) HDL of +2.2 mg/dL at Week 24 (n=556) and +3.6 mg/dL at Week 25 (n=302).

Data from the placebo-controlled 6-week study in adolescent subjects (12-17 years of age) with schizophrenia are presented in Table 2b.

### Table 2b. Change in Fasting Lipids from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>INVEGA®</th>
<th>Placebo 1.5 mg/day</th>
<th>3 mg/day</th>
<th>6 mg/day</th>
<th>12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to High</td>
<td>(≥40 mg/dL to &lt;40 mg/dL)</td>
<td>7%</td>
<td>4%</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>LDL</td>
<td>(≥110 mg/dL to &lt;130 mg/dL)</td>
<td>3%</td>
<td>4%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>HDL</td>
<td>(≥40 mg/dL to &lt;60 mg/dL)</td>
<td>14%</td>
<td>7%</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>(≥150 mg/dL to ≥200 mg/dL)</td>
<td>3%</td>
<td>5%</td>
<td>13%</td>
<td>8%</td>
</tr>
</tbody>
</table>

#### Proportion of Patients with Shifts

- **Cholesterol**
  - Normal to High: 7% to 4% to 0% to 6% to 11%
  - LDL: 3% to 4% to 14% to 0% to 9%
  - HDL: 14% to 7% to 29% to 13% to 23%
  - Triglycerides: 3% to 5% to 13% to 8% to 7%

#### Mean Change from Baseline (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>INVEGA®</th>
<th>Placebo 1.5 mg/day</th>
<th>3 mg/day</th>
<th>6 mg/day</th>
<th>12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight Gain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-7.8</td>
<td>-3.3</td>
<td>12.7</td>
<td>3.0</td>
<td>-1.5</td>
</tr>
<tr>
<td>LDL</td>
<td>-4.1</td>
<td>-3.1</td>
<td>7.2</td>
<td>2.4</td>
<td>0.6</td>
</tr>
<tr>
<td>HDL</td>
<td>-1.9</td>
<td>0.0</td>
<td>1.3</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-8.9</td>
<td>3.2</td>
<td>17.6</td>
<td>-5.4</td>
<td>3.9</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term open-label extension studies, INVEGA® was associated with a mean change in weight of +1.4 kg at Week 24 (n=63) and +2.6 kg at Week 25 (n=317). Weight gain in adolescent subjects with schizophrenia was assessed in a 6-week, double-blind, placebo-controlled study and an open-label extension with a median duration of exposure to INVEGA® of 182 days. Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥ 7% of body weight (see Clinical Studies [14.1]) from the placebo-controlled 6-week study in adolescent subjects (12-17 years of age) are presented in Table 3b.

### Table 3b. Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥ 7% Gain in Body Weight from a Placebo-Controlled 6-Week Study in Adolescent Subjects (12-17 years of age) with Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>INVEGA®</th>
<th>Placebo 1.5 mg/day</th>
<th>3 mg/day</th>
<th>6 mg/day</th>
<th>12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight Gain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.4</td>
<td>0.6</td>
<td>0.6</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>LDL</td>
<td>-5%</td>
<td>7%</td>
<td>6%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>HDL</td>
<td>5%</td>
<td>7%</td>
<td>6%</td>
<td>9%</td>
<td>9%</td>
</tr>
</tbody>
</table>

In the pooled data from the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder, a higher percentage of INVEGA®-treated subjects (5%) had an increase in body weight of ≥ 7% compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of ≥ 7% was in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

### 5.7 Hyperprolactinemia

Like other drugs that antagonize dopamine D₂ receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies in animals, with no evidence to support an association with breast cancer. An increase in the incidence of pituitary, mammary, and pancreatic tumors is seen in rats [see Nonclinical Toxicology (13.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumors in humans, but the available evidence is too limited to be conclusive.

### 5.8 Potential for Gastrointestinal Obstruction

Because the INVEGA® tablet is non-coated and does not appreciably change in shape in the gastrointestinal tract, INVEGA® should be readily absorbed in patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo obstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known stricture in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA® should only be used in patients who are able to swallow the tablet whole [see Dosage and Administration (2.3) and Patient Counseling Information (17.8)].

A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract.
5.9 Orthostatic Hypotension and Syncope
Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

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

5.11 Leukopenia, Neutropenia, and Agranulocytosis
Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including INVEGA®. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. 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 <1000/mm³) should discontinue INVEGA® and have their WBC followed until recovery.

5.12 Potential for Cognitive and Motor Impairment
Somnolence, postural hypotension, motor and sensory instability have been reported in subjects treated with INVEGA® (see Adverse Reactions (6.1, 6.2)). Antipsychotics, including INVEGA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.13 Seizures
During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. Like other antipsychotic drugs, INVEGA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.14 Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer’s dementia. INVEGA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.15 Suicide
The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for INVEGA® should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.16 Priapism
Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with INVEGA® during postmarketing surveillance. Severe priapism may require surgical intervention.

5.17 Thrombotic Thrombocytopenic Purpura (TTP)
No cases of TTP were observed during clinical studies with paliperidone. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

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

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

5.20 Use in Patients with Concomitant Illness
Clinical experience with INVEGA® in patients with certain concomitant illnesses is limited (see Clinical Pharmacology (12.3)). Patients with Parkinson’s Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA®, caution should be observed in patients with known cardiovascular disease (see Warnings and Precautions (5.9)).

5.21 Monitoring: Laboratory Tests
No specific laboratory tests are recommended.

6 ADVERSE REACTIONS
6.1 Overall Adverse Reaction Profile
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.5)]
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis [see Warnings and Precautions (5.2)]
- Neuroleptic malignant syndrome [see Warnings and Precautions (5.3)]
- QT prolongation [see Warnings and Precautions (5.4)]
- Tardive dyskinesia [see Warnings and Precautions (5.5)]
- Metabolic changes [see Warnings and Precautions (5.6)]
- Hyperprolactinemia [see Warnings and Precautions (5.7)]
- Potential for gastrointestinal obstruction [see Warnings and Precautions (5.8)]
- Orthostatic hypotension and syncope [see Warnings and Precautions (5.9)]
- Falls [see Warnings and Precautions (5.10)]
- Leukopenia, neutropenia, and agranulocytosis [see Warnings and Precautions (5.11)]
- Potential for cognitive and motor impairment [see Warnings and Precautions (5.12)]
- Seizures [see Warnings and Precautions (5.13)]
- Dysphagia [see Warnings and Precautions (5.14)]
- Suicide [see Warnings and Precautions (5.15)]
- Priapism [see Warnings and Precautions (5.16)]
- Thrombotic thrombocytopenic purpura (TTP) [see Warnings and Precautions (5.17)]
- Disruption of body temperature regulation [see Warnings and Precautions (5.18)]
- Antiemetic effect [see Warnings and Precautions (5.19)]
- Increased sensitivity in patients with Parkinson’s disease or those with dementia with Lewy bodies [see Warnings and Precautions (5.20)]
- Diseases or conditions that could affect metabolism or hemodynamic responses [see Warnings and Precautions (5.20)]

The most common adverse reactions in clinical trials in adult subjects with schizophrenia (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate in any of the dose groups) were extrapyramidal symptoms, tachycardia, and akathisia. The most common adverse reactions in clinical trials in adult patients with schizoaffective disorder (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate) were extrapyramidal symptoms, somnolence, dysphagia, constipation, weight increase, and nasopharyngitis. The most common adverse reactions that were associated with discontinuation from clinical trials in adult subjects with schizophrenia (causing discontinuation in 2% of INVEGA®-treated subjects) were nervous system disorders. The most common adverse reactions that were associated with discontinuation from clinical trials in adult subjects with schizoaffective disorder were gastrointestinal disorders, which resulted from the placebo-controlled phase of the long-term maintenance study, in which subjects received INVEGA® at daily doses within the range of 3 mg to 15 mg (n=104), is also included.
The safety of INVEGA® was evaluated in 150 adolescent subjects 12-17 years of age with schizophrenia who received INVEGA® in the dose range of 1.5 mg to 12 mg/day in a 6-week, double-blind, placebo-controlled trial. The safety of INVEGA® was also evaluated in 622 adult subjects with schizoaffective disorder who participated in two placebo-controlled, 6-week, double-blind trials. In one of these trials, 206 subjects were assigned to one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg (N=108) or 12 mg with the option to reduce to 9 mg (N=98) once daily. In the other study, 214 subjects received flexible doses of INVEGA® (3-12 mg once daily). Both studies included subjects who received INVEGA® either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

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

6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia in Adults and Adolescents

Adult Patients with Schizophrenia

Table 4 enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies in adults, listing those that occurred in 2% or more of subjects treated with INVEGA® in any of the dose groups, and for which the incidence in INVEGA®-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

Table 5 lists the adverse reactions reported in a fixed-dose, placebo-controlled study in adolescent subjects 12-17 years of age with schizophrenia, listing those that occurred in 2% or more of subjects treated with INVEGA® in any of the dose groups, and for which the incidence in INVEGA®-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

INVEGA® (paliperidone) Extended-Release Tablets

Table 6 enumerates the pooled incidences of adverse reactions reported in the two placebo-controlled 6-week studies in adult subjects, listing those that occurred in 2% or more of subjects treated with INVEGA® and for which the incidence in INVEGA®-treated subjects was greater than the incidence in subjects treated with placebo.
INVEGA® (paliperidone) Extended-Release Tablets

Table 6. Adverse Drug Reactions Reported by ≥ 2% of INVEGA®-Treated Adult Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials *

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=202)</td>
</tr>
<tr>
<td>Total percentage of subjects with adverse reactions</td>
<td>32</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal discomfort/Abdominal pain upper</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Stomach discomfort</td>
</tr>
<tr>
<td>General disorders</td>
<td>Asthenia</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Increased appetite</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Akathisia</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorder</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Pharyngolaryngeal pain</td>
</tr>
</tbody>
</table>

*Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from two studies. One study included once-daily INVEGA® doses of 6 mg (with the option to reduce to 3 mg) and 12 mg (with the option to reduce to 9 mg). The second study included flexible once-daily doses of 3 to 12 mg. Among the 420 subjects treated with INVEGA®, 230 (55%) received INVEGA® as monotherapy and 190 (45%) received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. Extrapyramidal symptoms include the terms bradykinesia, drooling, dyskinesia, dystonia, hypertonia, muscle rigidity, muscle twitching, oculogyration, parkinsonian gait, parkinsonism, restlessness, and tremor. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased.

Monotherapy versus Adjunctive Therapy

The designs of the two placebo-controlled, 6-week, double-blind trials in adult subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received INVEGA® as monotherapy and 190 (45%) subjects received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥ 5% difference) in subjects receiving INVEGA® as monotherapy.

Table 7. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>EPS Group</th>
<th>Placebo (N=202)</th>
<th>INVEGA® (paliperidone) Extended-Release Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients</td>
<td>3 mg once daily (N=127)</td>
<td>6 mg once daily (N=235)</td>
</tr>
<tr>
<td>Parkinsonism a</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Akathisia b</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Use of anticholinergic medications c</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

a For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items)

b For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2

c Percent of patients who received anticholinergic medications to treat emergent EPS

6.4 Discontinuations Due to Adverse Reactions

Schizophrenia Trials

The percentages of subjects who discontinued due to adverse reactions in the three schizophrenia placebo-controlled, 6-week, fixed-dose studies in adults were 3% and 1% in INVEGA® and placebo-treated subjects, respectively. The most common reasons for discontinuation were nervous system disorders (2% and 0% in INVEGA® and placebo-treated subjects, respectively).

Schizoaffective Disorder Trials

The percentages of subjects who discontinued due to adverse reactions in the two schizoaffective disorder placebo-controlled 6-week studies in adults were 1% and <1% in INVEGA® and placebo-treated subjects, respectively. The most common reasons for discontinuation were gastrointestinal disorders (1% and 0% in INVEGA® and placebo-treated subjects, respectively).

6.5 Dose-Related Adverse Reactions

Schizophrenia Trials

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

In the 6-week, fixed-dose, placebo-controlled study in adolescents with schizophrenia, among the adverse reactions that occurred with >2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: tachycardia, akathisia, extrapyramidal symptoms, somnolence, and headache.

Schizoaffective Disorder Trials

In a placebo-controlled, 6-week, high- and low-dose study in adult subjects with schizoaffective disorder, akathisia, dystonia, dysarthria, myalgia, nasopharyngitis, rhinitis, cough, and pharyngolaryngeal pain occurred more frequently (i.e., a difference of at least 2%) in subjects who received higher doses of INVEGA® compared with subjects who received lower doses.

6.6 Demographic Differences

An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS (Table 7), and (4) incidence of spontaneous reports of EPS (Table 8). For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA® 3 mg and 6 mg doses for any of these EPS measures.
The incidences of EPS-related adverse events in the adolescent schizophrenia studies showed a similar dose-related pattern to those in the adult studies. There were notably higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescent population as compared to the adult studies (Table 10).

### Table 8. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>EPS Group</th>
<th>Placebo (N=355)</th>
<th>3 mg once daily (N=127)</th>
<th>6 mg once daily (N=235)</th>
<th>9 mg once daily (N=246)</th>
<th>12 mg once daily (N=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall percentage of patients with EPS-related AE</td>
<td>11</td>
<td>13</td>
<td>25</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Dystonia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Dyskinesia group includes: Dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia
Dystonia group includes: Dystonia, muscle spasms, oculogyration, trismus
Hyperkinesia group includes: Akathisia, hyperkinesia
Parkinsonism group includes: Bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism
Tremor group includes: Tremor

### Table 9. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies in Adults

<table>
<thead>
<tr>
<th>EPS Group</th>
<th>Placebo (N=202)</th>
<th>3-6 mg once-daily fixed-dose range (N=108)</th>
<th>9-12 mg once-daily fixed-dose range (N=98)</th>
<th>3-12 mg once-daily flexible dose (N=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall percentage of patients with EPS-related AE</td>
<td>11</td>
<td>23</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dystonia</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>3</td>
<td>14</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>12</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Dyskinesia group includes: Dyskinesia, muscle twitching
Dystonia group includes: Dystonia, muscle spasms, oculogyration
Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness
Parkinsonism group includes: Bradykinesia, drooling, hypertonia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonian gait, parkinsonism
Tremor group includes: Tremor

In the adolescent population as compared to the adult studies (Table 10).
The safety of INVEGA® was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA® in adults with schizophrenia [see Clinical Studies (14)]. In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

6.10 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of INVEGA®; because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: angiodema, ileus, priapism, somnambulism, swollen tongue, tardive dyskinesia, urinary incontinence, urinary retention.

6.11 Adverse Reactions Reported With Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

7 DRUG INTERACTIONS

7.1 Potential for INVEGA® to Affect Other Drugs

Given the primary CNS effects of paliperidone [see Adverse Reactions (6.1, 6.2)], INVEGA® should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA® is administered with other therapeutic agents that have this potential [see Warnings and Precautions (5.9)].

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isoforms. In vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isoforms, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties. Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No in vivo data are available and the clinical relevance is unknown.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely. In a drug interaction study, co-administration of INVEGA® (12 mg once daily for 5 days) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics (AUC_{ss,lin} and C_{ss,lin}) of valproate in 13 patients stabilized on valproate. In a clinical study, subjects on stable doses of valproate who had comparable valproate average plasma concentrations when INVEGA® 3-15 mg/day was added to their existing valproate treatment.

7.2 Potential for Other Drugs to Affect INVEGA®

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isoforms is unlikely. While in vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, in vivo studies do not show decreased elimination by these isoforms and they contribute to only a small fraction of total body clearance. In vitro studies have shown that paliperidone is a P-gp substrate.

Co-administration of INVEGA® 8 mg once daily with carbamazepine, a strong inducer of both CYP3A4 and P-glycoprotein (P-gp), at 200 mg twice daily caused a decrease of approximately 57% in the mean steady-state C_{max} and AUC of paliperidone. Therefore, paliperidone is not expected to substantially decrease renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA® should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 [see Clinical Pharmacology (12.3)]. In an interaction study in healthy subjects in which a single 3 mg dose of INVEGA® was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4; 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

Co-administration of a single dose of INVEGA® 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Dosage reduction for INVEGA® should be considered when INVEGA® is co-administered with valproate after clinical assessment.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well controlled studies of INVEGA® in pregnant women.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken close to the end of pregnancy, will lead to similar neonatal signs and symptoms. In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated during the period of organogenesis with up to 8 times the maximum recommended human dose of paliperidone (on a mg/m² basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, there were increases in pup deaths seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m² basis (see risperidone package insert).

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. 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 hospitalization.

INVEGA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Paliperidone is excreted in human breast milk. The known benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone.

8.4 Pediatric Use

Safety and effectiveness of INVEGA® in the treatment of schizophrenia were evaluated in 150 adolescent subjects 12-17 years of age with schizophrenia who received INVEGA® in the dose range of 1.5 mg to 12 mg/day in a 6-week, double-blind, placebo-controlled trial. Safety and effectiveness of INVEGA® for the treatment of schizophrenia in patients < 12 years of age have not been established. Safety and effectiveness of INVEGA® for the treatment of schizoaffective disorder in patients < 18 years of age have not been studied.

In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents. Safety and effectiveness of INVEGA® on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

The safety, tolerability, and efficacy of INVEGA® were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received INVEGA® in the dose range of 1.5 mg to 15 mg once daily. In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA® (3 mg to 15 mg once daily) [see Clinical Studies (14)]. There were no subjects > 65 years of age in the schizoaffective disorder studies.

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n=1798), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; practically insoluble in water, 0.1N NaOH, and hexane; and slightly soluble in N,N-dimethylformamide.

INVEGA® (paliperidone) Extended-Release Tablets are available in 1.5 mg (orange-brown), 3 mg (white), 6 mg (beige), and 9 mg (pink) strengths. INVEGA® utilizes OROS® omotic drug-release technology [see Description (11.1)]. Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

11.1 Delivery System Components and Performance

INVEGA® uses omotic pressure to deliver paliperidone at a controlled rate. The delivery system, which resembles a capsule-shaped tablet in appearance, consists of an osmotically active trilayer core surrounded by a subcoat and semi-permeable membrane. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There are two precision laser-drilled orifices on the drug-layer dome of the tablet. Each tablet strength has a different colored water-dispersible overcoat and print markings. In an aqueous environment, such as the gastrointestinal tract, the water-dispersible color overcoat erodes quickly. Water then enters the tablet through the semi-permeable membrane that controls the rate at which water enters the tablet core, which, in turn, determines the rate of drug delivery. The hydrophilic polymers of the core hydrate and swell, creating a gel that pushes paliperidone that is then pushed out through the tablet orifices. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug’s therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism.

12.2 Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D2) antagonist and with predominant serotonin Type 2 (5HT2A) activity. Paliperidone is also active as an antagonist at α1 and α2 adrenergic receptors and H2 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β1- and β2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers is qualitatively and quantitatively similar in vitro.

12.3 Pharmacokinetics

Following a single dose, the plasma concentrations of paliperidone gradually rise to reach peak plasma concentration (Cmax) approximately 24 hours after dosing. The pharmacokinetics of paliperidone following INVEGA® administration are dose-proportional within the available dose range. The terminal elimination half-life of paliperidone is approximately 23 hours. Steady-state concentrations of paliperidone are attained within 4-5 days of dosing with INVEGA® in most subjects. The mean steady-state peak/trough ratio for an INVEGA® dose of 9 mg was 1.7 with a range of 1.2-3.1.

Following administration of INVEGA®, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+)/(-) ratio of approximately 1.6 at steady state.

Absorption and Distribution

The absolute oral bioavailability of paliperidone following INVEGA® administration is 28%.

Administration of a 12 mg paliperidone extended-release tablet to healthy ambulatory subjects with a standard high-fat/high-caloric meal gave mean Cmax and AUC values of paliperidone that were increased by 80% and 54%, respectively, compared with administration under fasting conditions. Clinical trials establishing the safety and efficacy of INVEGA® were carried out in subjects without regard to the timing of meals. While INVEGA® can be taken without regard to food, the presence of food at the time of INVEGA® administration may increase exposure to paliperidone [see Dosage and Administration (2.3)].

Based on a population analysis, the apparent volume of distribution of paliperidone is 487 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, in vivo results indicate that these isozymes play a limited role in the overall elimination of paliperidone [see Drug Interactions (7)].

One week following administration of a single oral dose of 1 mg immediate-release 14C-paliperidone to 5 healthy volunteers, 59% (range 51% - 67%) of the dose was excreted unchanged into urine, 32% (26% - 41%) of the dose was recovered as...
metabolites, and 6% - 12% of the dose was not recovered. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four primary metabolic pathways have been identified in vivo, none of which could be shown to account for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission.

Population pharmacokinetic analyses found no difference in exposure or clearance of paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

**Special Populations**

**Renal Impairment**

The dose of INVEGA® should be reduced in patients with moderate or severe renal impairment. (see Dosage and Administration (2.5)). The disposition of a single dose paliperidone 3 mg extended-release tablet was studied in adult subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 mL/min to < 80 mL/min), 64% in moderate (CrCl = 30 mL/min to < 50 mL/min), and 71% in severe (CrCl = 10 mL/min to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC∞) of 1.5 fold, 2.6 fold, and 4.8 fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24 hours, 40 hours, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 mL/min).

**Hepatic Impairment**

In a study in adult subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Consequently, no dose adjustment is required in patients with mild or moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

**Adolescents (12-17 years of age)**

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

**Elderly**

No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see Renal Impairment above and Dosage and Administration (2.1, 2.5)).

**Race**

No dosage adjustment is recommended based on race. No differences in pharmacokinetics were observed in a pharmacokinetic study conducted in Japanese and Caucasians.

**Gender**

No dosage adjustment is recommended based on gender. No differences in pharmacokinetics were observed in a pharmacokinetic study conducted in men and women.

**Smoking**

No dosage adjustment is recommended based on smoking status. Based on in vitro studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**

Carcinogenicity studies of paliperidone have not been performed. Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in dogs and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63 mg/kg, 2.5 mg/kg, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone on a mg/m² basis (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see Warnings and Precautions (5.7)).

**Mutagenesis**

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

**Impairment of Fertility**

In a study of fertility, the percentage of treated female rats that became pregnant was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose on a mg/m² basis.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).
at the baseline visit were randomly assigned to receive placebo or 1.5 mg (Low dose), 3 mg (Medium dose), or 6 mg (High dose) of INVEGA® daily, and subjects weighing at least 51 kg at the baseline visit were randomly assigned to receive placebo or 1.5 mg (Low dose), 6 mg (Medium dose), or 12 mg (High dose) of INVEGA® daily. Dosing was in the morning without regard to meals.

Efficacy was evaluated using PANSS. Overall, this study demonstrated the efficacy of INVEGA® in adolescents with schizophrenia in the dose range of 3 to 12 mg/day. Doses within this broad range were shown to be effective, however, there was no clear enhancement to efficacy at the higher doses, i.e., 6 mg for subjects weighing less than 51 kg and 12 mg for subjects weighing 51 kg or greater. Although paliperidone was adequately tolerated within the dose range of 3 to 12 mg/day, adverse events were dose related.

### 14.2 Schizoaffective Disorder

**Adults**

The acute efficacy of INVEGA® (3 mg to 12 mg once daily) in the treatment of schizoaffective disorder was established in two placebo-controlled, 6-week trials in non-elderly adult subjects. Enrolled subjects 1) met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders, 2) had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 3) had prominent mood symptoms as confirmed by a score of at least 16 on the Young Mania Rating Scale and/or Hamilton Rating Scale for Depression. The population included subjects with schizoaffective bipolar and depressive types. In one of these trials, efficacy was assessed in 211 subjects who received flexible doses of INVEGA® (3-12 mg once daily). In the other study, efficacy was assessed in 202 subjects who were assigned to one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg (n=105) or 12 mg with the option to reduce to 9 mg (n=98) once daily. Both studies included subjects who received INVEGA® either as monotherapy [no mood stabilizers and/or antidepressants (55%) or as an adjunct to mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. INVEGA® was dosed in the morning without regard to meals. Studies were carried out in the United States, Eastern Europe, Russia, and Asia.

Efficacy was evaluated using the PANSS, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. As secondary outcomes, mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D-21) and the Young Mania Rating Scale (YMRS).

The INVEGA® group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) and the higher dose group of INVEGA® in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day) were each superior to placebo in the PANSS. Numerical improvements in mood symptoms were also observed, as measured by the HAM-D-21 and YMRS. In the lower dose group of the 2 dose-level study (6 mg/day with option to reduce to 3 mg/day), INVEGA® was not significantly different from placebo as measured by the PANSS.

Taking the results of both studies together, INVEGA® improved the symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age, or geographic region. There were insufficient data to explore differential effects based on race.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA® (paliperidone) Extended-Release Tablets are available in the following strengths and packages. All tablets are capsule-shaped.

1.5 mg tablets are orange-brown and imprinted with “PAL 1.5”, and are available in bottles of 30 (NDC 50458-554-01).

3 mg tablets are white and imprinted with “PAL 3”, and are available in bottles of 30 (NDC 50458-550-01) and hospital unit dose packs of 100 (NDC 50458-550-10).

6 mg tablets are beige and imprinted with “PAL 6”, and are available in bottles of 30 (NDC 50458-551-01) and hospital unit dose packs of 100 (NDC 50458-551-10).

9 mg tablets are pink and imprinted with “PAL 9”, and are available in bottles of 30 (NDC 50458-552-01) and hospital unit dose packs of 100 (NDC 50458-552-10).

**Storage and Handling**

Store up to 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep out of reach of children.