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)

RECENT MAJOR CHANGES
02/2017

INDICATIONS AND USAGE
INVEGA® is an atypical antipsychotic agent indicated for the 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)

- Efficacy was established in two 6-week trials in adult patients. (14.2)

DOSE AND ADMINISTRATION

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia - adults (2.1)</td>
<td>6 mg/day</td>
<td>3 - 12 mg/day</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>Schizophrenia-adolescents (2.1)</td>
<td>Weight &lt; 51kg</td>
<td>3 mg/day</td>
<td>6 mg/day</td>
</tr>
<tr>
<td>Schizophrenia-adolescents (2.1)</td>
<td>Weight ≥ 51kg</td>
<td>3 mg/day</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>Schizoaffective disorder - adults (2.2)</td>
<td>6 mg/day</td>
<td>3 - 12 mg/day</td>
<td>12 mg/day</td>
</tr>
</tbody>
</table>

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

DOSAGE FORMS AND STRENGTHS

Tablets: 1.5 mg, 3 mg, 6 mg, and 9 mg (3)

CONTRAINDICATIONS
Known hypersensitivity to paliperidone, risperidone, or to any excipients in INVEGA®. (4)

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)
  - 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)
  - Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.6)
  - Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.6)

- 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. (5.9)

- 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: 07/2017
FULL PRESCRIBING INFORMATION:

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FULL PRESCRIBING INFORMATION

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)]
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 schizophrenia 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 schizophrenia 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 Schizophrenic 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 increase 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 risperidone 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 subjects 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 symptom 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 signs and 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 increase 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.
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 ketoacidosis 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 trial 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.

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

<table>
<thead>
<tr>
<th>INVEGA®</th>
<th>Placebo 3 mg/day</th>
<th>6 mg/day</th>
<th>9 mg/day</th>
<th>12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean change from baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>n=322</td>
<td>n=122</td>
<td>n=212</td>
<td>n=234</td>
</tr>
<tr>
<td>Normal to High</td>
<td>5.1%</td>
<td>3.2%</td>
<td>4.5%</td>
<td>4.8%</td>
</tr>
<tr>
<td>(&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>(12/236)</td>
<td>(3/93)</td>
<td>(7/156)</td>
<td>(9/187)</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

<table>
<thead>
<tr>
<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>
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</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean change from baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>n=41</td>
<td>n=44</td>
<td>n=28</td>
<td>n=32</td>
</tr>
<tr>
<td>Normal to High</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>(&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>(1/32)</td>
<td>(0/34)</td>
<td>(0/9)</td>
<td>(0/20)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>INVEGA®</th>
<th>Placebo 3 mg/day</th>
<th>6 mg/day</th>
<th>9 mg/day</th>
<th>12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>Mean change from baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>n=331</td>
<td>n=120</td>
<td>n=216</td>
<td>n=236</td>
</tr>
<tr>
<td>Normal to High</td>
<td>2.6%</td>
<td>2.8%</td>
<td>5.6%</td>
<td>4.1%</td>
</tr>
<tr>
<td>(&lt;200 mg/dL to ≤240 mg/dL)</td>
<td>(5/194)</td>
<td>(2/71)</td>
<td>(7/125)</td>
<td>(6/147)</td>
</tr>
<tr>
<td>LDL</td>
<td>Normal to High</td>
<td>1.9%</td>
<td>0.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>(&lt;100 mg/dL to ≥160 mg/dL)</td>
<td>(2/105)</td>
<td>(0/44)</td>
<td>(3/60)</td>
<td>(3/81)</td>
</tr>
<tr>
<td>HDL</td>
<td>Normal to Low</td>
<td>22.0%</td>
<td>16.3%</td>
<td>29.1%</td>
</tr>
<tr>
<td>(&lt;40 mg/dL to ≤40 mg/dL)</td>
<td>(44/200)</td>
<td>(13/80)</td>
<td>(39/134)</td>
<td>(32/137)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Normal to High</td>
<td>5.3%</td>
<td>11.0%</td>
<td>8.8%</td>
</tr>
<tr>
<td>(&lt;150 mg/dL to ≤200 mg/dL)</td>
<td>(11/208)</td>
<td>(9/82)</td>
<td>(12/136)</td>
<td>(13/150)</td>
</tr>
</tbody>
</table>
INVEGA® (paliperidone) Extended-Release Tablets

In the uncontrolled, longer-term open-label extension studies, INVEGA® was associated with a mean change in (a) total cholesterol of -1.5 mg/dL at Week 24 (n=573) and -1.5 mg/dL at Week 52 (n=317); (b) triglycerides of -6.4 mg/dL at Week 24 (n=573) and -10.5 mg/dL at Week 52 (n=317); (c) LDL of -1.9 mg/dL at Week 24 (n=557) and -2.7 mg/dL at Week 52 (n=297); and (d) HDL of +2.2 mg/dL at Week 24 (n=568) and +3.6 mg/dL at Week 52 (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>INVEGA®</th>
<th>Placebo</th>
<th>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></td>
<td>Mean change from baseline (mg/dL)</td>
<td>n=39</td>
<td>n=45</td>
<td>n=11</td>
<td>n=28</td>
</tr>
<tr>
<td>Cholesterol</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>n=37</td>
<td>n=40</td>
<td>n=9</td>
<td>n=27</td>
<td>n=31</td>
</tr>
<tr>
<td>Change from baseline</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>n=37</td>
<td>n=41</td>
<td>n=9</td>
<td>n=27</td>
<td>n=31</td>
</tr>
<tr>
<td>Change from baseline</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>n=39</td>
<td>n=44</td>
<td>n=11</td>
<td>n=28</td>
<td>n=32</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-8.9</td>
<td>3.2</td>
<td>17.6</td>
<td>-5.4</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Proportion of Patients with Shifts

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Normal to High (&lt;170 mg/dL to ≥200 mg/dL)</th>
<th>7%</th>
<th>4%</th>
<th>0%</th>
<th>6%</th>
<th>11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>Normal to High (&lt;110 mg/dL to ≥130 mg/dL)</td>
<td>3%</td>
<td>4%</td>
<td>14%</td>
<td>0%</td>
<td>9%</td>
</tr>
<tr>
<td>Normal to Low (≥40 mg/dL to &lt;100 mg/dL)</td>
<td>14%</td>
<td>7%</td>
<td>29%</td>
<td>13%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Normal to High (&lt;150 mg/dL to ≥200 mg/dL)</td>
<td>3%</td>
<td>5%</td>
<td>13%</td>
<td>8%</td>
<td>7%</td>
</tr>
</tbody>
</table>

### Weight Gain

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

#### Schizophrenia Trials

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥ 7% of body weight from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects are presented in Table 2a.

#### Table 3a. Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥ 7% Gain in Body Weight from Three Placebo-Controlled, 6-Week, Fixed-Dose Studies in Adult Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>INVEGA®</th>
<th>Placebo</th>
<th>3 mg/day</th>
<th>6 mg/day</th>
<th>9 mg/day</th>
<th>12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change from baseline</td>
<td>n=323</td>
<td>n=344</td>
<td>n=215</td>
<td>n=235</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.4</td>
<td>0.6</td>
<td>0.6</td>
<td>1.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Weight Gain ≥ 7% increase from baseline

5% 7% 6% 9% 9%

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 52 (n=302). 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>INVEGA®</th>
<th>Placebo</th>
<th>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></td>
<td>Weight (kg)</td>
<td>n=12</td>
<td>n=64</td>
<td>n=51</td>
<td>n=31</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.0</td>
<td>0.3</td>
<td>0.8</td>
<td>1.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Weight Gain ≥ 7% increase from baseline

2% 6% 9% 19% 7% 18%
5.12 Potential for Cognitive and Motor Impairment

Priapism has been reported with INVEGA® during postmarketing drug use. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with INVEGA® during postmarketing drug use. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism 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. 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.

5.13 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 who 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.
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

Adolescent Patients with Schizophrenia

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.

Table 5. Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Adolescent Subjects with Schizophrenia in a Fixed-Dose, Placebo-Controlled Clinical Trial *

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=355)</th>
<th>INVEGA®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of Patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INVEGA®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (N=51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 mg once daily (N=54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mg once daily (N=16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mg once daily (N=45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 mg once daily (N=35)</td>
<td></td>
</tr>
<tr>
<td>Total percentage of subjects</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>with adverse reactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiac disorders

- Tachycardia

Gastrointestinal disorders

- Salivary hypersecretion
- Swollen tongue
- Vomiting

General disorders

- Asthenia
- Fatigue

Infections and infestations

- Nasopharyngitis

Investigations

- Weight increased

Nervous system disorders

- Akathisia
- Dizziness
- Extrapyramidal symptoms
- Headache
- Lethargy
- Somnolence
- Tongue paralysis

Psychiatric disorders

- Anxiety

Reproductive system and breast disorders

- Amenorrhea
- Galactorrhea
- Gynecomastia

Respiratory, thoracic and mediastinal disorders

- Epistaxis

* Table includes adverse reactions that were reported in ≥ 2% of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Extrapyramidal symptoms includes the terms oculogyric crisis, muscle rigidity, musculoskeletal stiffness, nuchal rigidity, torticollis, trismus, Bradykinesia, cogwheel rigidity, dyskinesia, dystonia, extrapyramidal disorder, hypertonia, hypokinesia, muscle contractions involuntary, parkinsonian gait, parkinsonism, tremor, and restlessness. Somnolence includes the terms somnolence, sedation, and hypersomnia. Insomnia includes the terms insomnia and initial insomnia. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Hypertension includes the terms hypertension and blood pressure increased. Gynecomastia includes the terms gynecomastia and breast swelling.

6.3 Commonly-observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizoaffective Disorder in Adults

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.

Table 6. Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Adult Subjects with Schizoaffective Disorder in a Fixed-Dose, Placebo-Controlled Clinical Trial *

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=355)</th>
<th>INVEGA®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of Patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INVEGA®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (N=51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 mg once daily (N=54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mg once daily (N=16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mg once daily (N=45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 mg once daily (N=35)</td>
<td></td>
</tr>
<tr>
<td>Total percentage of subjects</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>with adverse reactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiac disorders

- Tachycardia

Gastrointestinal disorders

- Salivary hypersecretion
- Swollen tongue
- Vomiting

General disorders

- Asthenia
- Fatigue

Infections and infestations

- Nasopharyngitis

Investigations

- Weight increased

Nervous system disorders

- Akathisia
- Dizziness
- Extrapyramidal symptoms
- Headache
- Lethargy
- Somnolence
- Tongue paralysis

Psychiatric disorders

- Anxiety

Reproductive system and breast disorders

- Amenorrhea
- Galactorrhea
- Gynecomastia

Respiratory, thoracic and mediastinal disorders

- Epistaxis

* 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. Extrapyramidal symptoms includes the terms oculogyric crisis, muscle rigidity, musculoskeletal stiffness, nuchal rigidity, torticollis, trismus, Bradykinesia, cogwheel rigidity, dyskinesia, dystonia, extrapyramidal disorder, hypertonia, hypokinesia, muscle contractions involuntary, parkinsonian gait, parkinsonism, tremor, and restlessness. Somnolence includes the terms somnolence, sedation, and hypersomnia. Insomnia includes the terms insomnia and initial insomnia. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Hypertension includes the terms hypertension and blood pressure increased. Gynecomastia includes the terms gynecomastia and breast swelling.
230 (55%) subjects received INVEGA® as monotherapy and 190 (45%) subjects (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers 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). Among the adverse reactions in the 6-week, fixed-dose, placebo-controlled study in adolescents with schizophrenia, only dystonia led to discontinuation (<1% of INVEGA®-treated subjects).

### Cardiac disorders
- Tachycardia

### Gastrointestinal disorders
- Abdominal discomfort
  - Abdominal pain upper
- Constipation
- Dyspepsia
- Nausea
- Stomach discomfort

### General disorders
- Asthenia

### Infections and Infestations
- Nasopharyngitis
- Rhinitis
- Upper respiratory tract infection

### Investigations
- Weight increased

### Metabolism and nutrition disorders
- Decreased appetite
- Increased appetite

### Musculoskeletal and connective tissue disorders
- Back pain
- Myalgia

### Nervous system disorders
- Akathisia
- Dysarthria
- Extrapyramidal symptoms
- Somnolence

### Psychiatric disorders
- Sleep disorder

### Respiratory, thoracic and mediastinal disorders
- Cough
- Pharyngolaryngeal pain

### 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>Dictionary-Derived Term</th>
<th>Placebo (N=202)</th>
<th>INVEGA® 9-12 mg</th>
<th>INVEGA® 3-12 mg</th>
<th>INVEGA® 3-6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>one-time daily</td>
<td>one-time daily</td>
<td>one-time daily</td>
<td>one-time daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range (N=108)</td>
<td>range (N=98)</td>
<td>range (N=214)</td>
<td>range (N=18)</td>
</tr>
<tr>
<td>Total percentage of subjects with adverse reactions</td>
<td></td>
<td>32</td>
<td>48</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Tachycardia</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal discomfort</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Stomach discomfort</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>General disorders</td>
<td>Asthenia</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Nasopharyngitis</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>&lt;1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Increased appetite</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>&lt;1</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Akathisia</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
<td>8</td>
<td>20</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>5</td>
<td>12</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disorder</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pharyngolaryngeal pain</td>
<td>&lt;1</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Percentage of Patients

**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).

**6.5 Dose-Related Adverse Reactions**
In the 6-week, fixed-dose, placebo-controlled study in adolescents 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**
Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizoaffective disorder, 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: 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 schizoaffective disorder, 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.

**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, and (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.

**Extrapyramidal Symptoms (EPS)**
Pooled data from 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, and (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.

**Schizophrenia Studies in Adults**

**6.7 Extrapyramidal Symptoms (EPS)**
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.

**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=204)</th>
<th>3 mg once daily (N=174)</th>
<th>6 mg once daily (N=235)</th>
<th>9 mg once daily (N=246)</th>
<th>12 mg once daily (N=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism a</td>
<td>9</td>
<td>11</td>
<td>3</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia b</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Use of anticholinergic medications c</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>22</td>
<td>22</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
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>10</td>
<td>25</td>
<td>26</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>2</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</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

Compared to data from the studies in adults subjects with schizophrenia, pooled data from the two placebo-controlled 6-week studies in adult subjects with schizoaffective disorder showed similar types and frequencies of EPS as measured by rating scales, anticholinergic medication use, and spontaneous reports of EPS-related adverse events. For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

Table 9 shows the EPS data from the pooled schizoaffective disorder trials.

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

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).
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: angioedema, ileus, priapism, 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 concomitantly with dopaminergic agents. 

Paliperidone is metabolized to a limited extent by CYP2D6, and 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.

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, CYP2C9, CYP2C19, 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 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 (AUCCmax and Cmax/con) 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 isozymes is unlikely. While in vivo 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. Paliperidone is also not expected to have enzyme inducing properties.

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INVEGA® (paliperidone) Extended-Release Tablets

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment [see Clinical Pharmacology (12.3)], who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Dosage and Administration (2.5)].

8.6 Renal Impairment

Dosing must be individualized according to the patient’s renal function status [see Dosage and Administration (2.5)].

8.7 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA® (paliperidone) is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of INVEGA® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of 10 OVERDOSAGE potential for tolerance or physical dependence. Paliperidone has not been systematically studied in animals or humans for its theoretical hazard of additive QT-prolonging effects when administered in patients with concomitant use of class 1A or 1C antiarrhythmics, and potentially with patients who have an increased risk for QT prolongation. Torsade de pointes and ventricular fibrillation have been reported in case of acute overdose, establish and maintain an airway and ensure adequate ventilation. Administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of the trilayer core 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 semipermeable 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 structure. 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 H1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or ß 1- and ß 2-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 (+) to (-) 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 (AU{sub}C{sub}last) 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 rats, mice, 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).

14 CLINICAL STUDIES
14.1 Schizophrenia
Adults
The acute efficacy of INVEGA® (3 mg to 15 mg once daily) was established in three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose trials in non-elderly adult subjects (mean age of 37) who met DSM-IV criteria for schizophrenia. Studies were carried out in North America, Eastern Europe, Western Europe, and Asia. The doses studied among these three trials included 3 mg/day, 6 mg/day, 9 mg/day, 12 mg/day, and 15 mg/day. Dosing was in the morning, without regard to meals.

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. Efficacy was also evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in the domains of socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors.

In all 3 studies (n=1665), INVEGA® was superior to placebo on the PANSS at all doses. Mean effects at all doses were fairly similar, although the higher doses in all studies were numerically superior. INVEGA® was also superior to placebo on the PSP in these trials.

An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age (there were few patients over 65), or geographic region. There were insufficient data to explore differential effects based on race.

In a longer-term trial, adult outpatients meeting DSM-IV criteria for schizophrenia who had clinically responded (defined as PANSS score ≤ 70 or ≤ 4 on pre-defined PANSS subscales, as well as having been on a stable fixed dose of INVEGA® for the last two weeks of an 8-week run-in phase) were entered into a 6-week open-label stabilization phase where they received INVEGA® (doses ranging from 3 mg to 15 mg once daily). After the stabilization phase, patients were randomized in a double-blind manner to either continue on INVEGA® at their achieved stable dose, or to placebo, until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as a significant increase in PANSS (or pre-defined PANSS subscales), hospitalization, clinically significant suicidal or homicidal ideation, or deliberate injury to self or others. An interim analysis of the data showed a significantly longer time to relapse in patients treated with INVEGA® compared to placebo, and the trial was stopped early because maintenance of efficacy was demonstrated.

Adolescents
The efficacy of INVEGA® in adolescent subjects with schizophrenia was established in a randomized, double-blind, parallel-group, placebo-controlled, 6-week study using a fixed-dose weight-based treatment group design over the dose range of 1.5 to 12 mg/day. The study was carried out in the US, India, Romania, Russia, and Ukraine, and involved subjects 12-17 years of age meeting DSM-IV criteria for schizophrenia, with diagnosis confirmation using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL).

Eligible subjects were randomly assigned to 1 of 4 treatment groups: a placebo group or INVEGA® Low, Medium, or High dose groups. Doses were administered based on body weight to minimize the risk of exposing lower-weight adolescents to high doses of INVEGA®. Subjects weighing between 29 kg and less than 51 kg subjects.
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®, 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 less than 80, 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 203 subjects who were assigned to one of two dose levels of INVEGA®, 6 mg with the option to reduce to 3 mg (n=105) or 12 mg with the option to reduce to 9 mg (n=98) once daily. Both studies included subjects who received INVEGA® either as monotherapy and/or antidepressants and/or antipsychotics (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 antipsychotics 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.