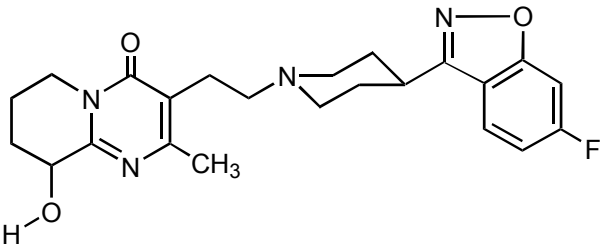
INVEGA™

PRODUCT INFORMATION

NAME OF THE MEDICINE

Paliperidone is chemically identified as (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.



CAS:144598-75-4 $C_{23}H_{27}FN_4O_3$ MW=426.49

DESCRIPTION

INVEGA™ (paliperidone) is a novel antipsychotic agent belonging to the benzisoxazole-derivatives class.

INVEGA™ utilizes osmotic drug-release technology, whereby osmotic pressure delivers paliperidone from the dosage form at a controlled rate. The system, which resembles a capsule-shaped tablet in appearance, comprises an osmotically active trilayer core surrounded by a subcoat and semipermeable membrane. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There are two precision laser-drilled orifices on the drug-layer dome of the tablet. Each strength is identified by a unique colour overcoat and print markings. In an aqueous environment, such as the gastrointestinal tract, the water-dispersible colour overcoat erodes quickly. Water is then imbibed through the semipermeable, rate-controlling membrane. The membrane controls the rate at which water enters the tablet core, which, in turn, controls drug delivery. The hydrophilic polymers of the core hydrate and swell, creating a gel containing paliperidone that is then pushed out through the tablet orifices. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethylcellulose, macrogol, polyethylene oxide, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

PHARMACOLOGY

Pharmacodynamics

Paliperidone is a centrally active dopamine D_2 antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)– and (-)- paliperidone enantiomers is qualitatively and quantitatively similar. Paliperidone is the major active metabolite of risperidone.

The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of paliperidone.

Polysomnography:

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

Pharmacokinetics

Following a single dose, the plasma concentrations of paliperidone steadily rise to reach peak plasma concentration (Cmax) in approximately 24 hours after dosing. The pharmacokinetics of paliperidone following INVEGA^{TM} administration are dose-proportional within the recommended clinical dose range (3 to 12 mg). The terminal elimination half-life of paliperidone is approximately 23 hours.

Steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects. In a study comparing the steady-state pharmacokinetics following once-daily administration of 12 mg paliperidone (administered as prolonged-release tablets) with 4 mg immediate-release risperidone in schizophrenic subjects, the fluctuation indexes were 38% for paliperidone prolonged-release compared to 125% for risperidone immediate-release (Figure 1).

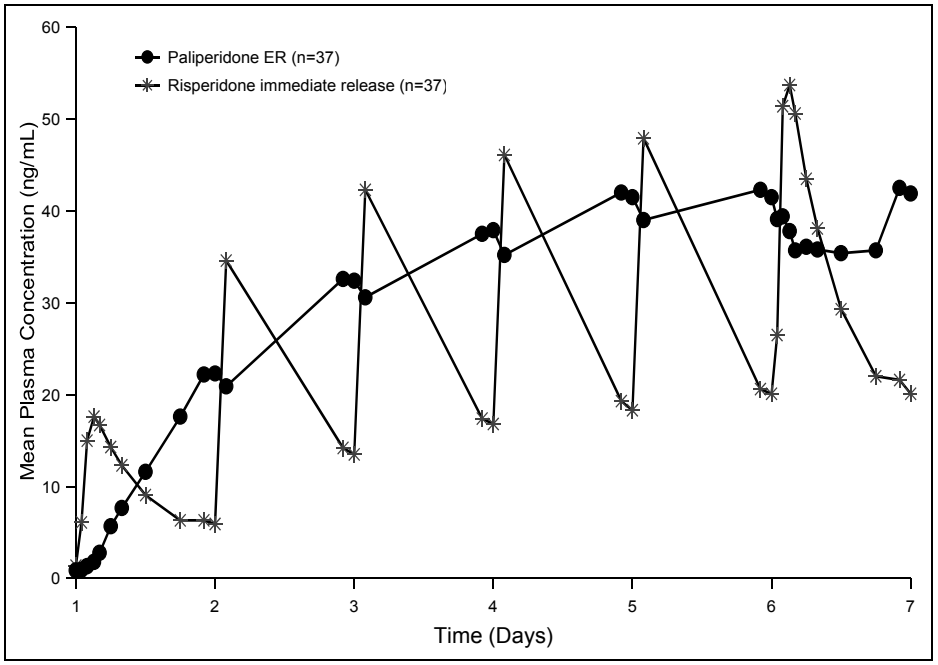


Figure 1. Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg prolonged-release tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release administered as 2 mg once daily on Day 1 and 4 mg once daily on Days 2 to 6 (paliperidone+risperidone concentrations are represented).

Following administration of INVEGA^{TM}, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6 at steady state.

Absorption:
The absolute oral bioavailability of paliperidone following INVEGA^{TM} administration is 28%. Following administration of a single 15 mg paliperidone prolonged-release tablet to healthy subjects, confined to bed for 36 hours, with a standard high-fat/high-caloric meal, the C_{max} and AUC values increased by 42% and 46%, respectively, compared with administration under fasting conditions. (See **DOSAGE AND ADMINISTRATION).**

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No in vivo data are available and the clinical relevance is unknown. (see **PRECAUTIONS** – Interactions with other medicines)

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

Metabolism and Elimination:
One week following administration of a single oral dose of 1 mg immediate-release 14C-paliperidone, 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 faeces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. *In vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, however, *in vivo* results indicate that these isozymes play a limited role in the metabolism of paliperidone. Despite the large variation in the general population with regard to the ability to metabolize CYP2D6 substrates, population pharmacokinetic analyses indicated no discernable difference on the exposure and apparent clearance of paliperidone after administration of INVEGA^{TM} between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies using microsomal preparations of heterologous systems indicate that CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5 are not involved in the metabolism of paliperidone.

Hepatic Impairment:
In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, 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. The effect of severe hepatic impairment is not known. (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

Renal Impairment:
The dose of INVEGA^{TM} should be reduced in patients with mild, moderate or severe renal impairment (see **DOSAGE AND ADMINISTRATION:** Dosing in Special Populations). The disposition of a single dose paliperidone 3 mg extended-release tablet was studied in 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 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects

with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 mL/min). (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

Gender:
The apparent clearance of paliperidone following INVEGA administration is approximately 19% lower in women than men. This difference is largely explained by differences in lean body mass and creatinine clearance between men and women.

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

Children and adolescents younger than 18 years of age:

No pharmacokinetics data on INVEGA^{TM} in patients < 18 years of age has been established.

Smoking Status:
Based on *in vitro* studies utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. A population pharmacokinetic analysis showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is unlikely to be of clinical relevance, though.

Clinical trials

The efficacy of INVEGA^{TM} (3 to 15 mg once daily) was established in three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose trials in subjects who met DSM-IV-TR criteria for schizophrenia. The active control was included for assay sensitivity purposes. 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 four domains of behaviour (socially useful activities including work and study, personal and social relationships, self care, and disturbing and aggressive behaviours).

In the first placebo-controlled 6-week trial (n=605) comparing fixed doses of paliperidone (3, 9, and 15 mg/day) with placebo, all doses were superior to placebo on the PANSS, all PANSS factors, and the PSP scale.

In the second placebo-controlled 6-week trial (n=628) comparing fixed doses of paliperidone (6, 9, and 12 mg/day) with placebo, all doses were superior to placebo on the PANSS, all PANSS factors, and the PSP scale.

In the third placebo-controlled 6-week trial (n=432) comparing fixed doses of paliperidone (6 and 12 mg/day) with placebo, both doses were superior to placebo on the PANSS, with the 6 mg/day dose of paliperidone superior to placebo on the PSP scale.

Additionally, in a pooled analysis of the three trials, the superiority of INVEGA^{TM} versus placebo at each dose (3 to 15 mg once daily) was established on total PANSS (including all PANSS factors) and in the response measure of ≥ 30% reduction in PANSS total score. Each dose of INVEGA^{TM} also showed superiority to placebo on the PSP scale demonstrating an improvement in social functioning.

An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of age, race, or gender.

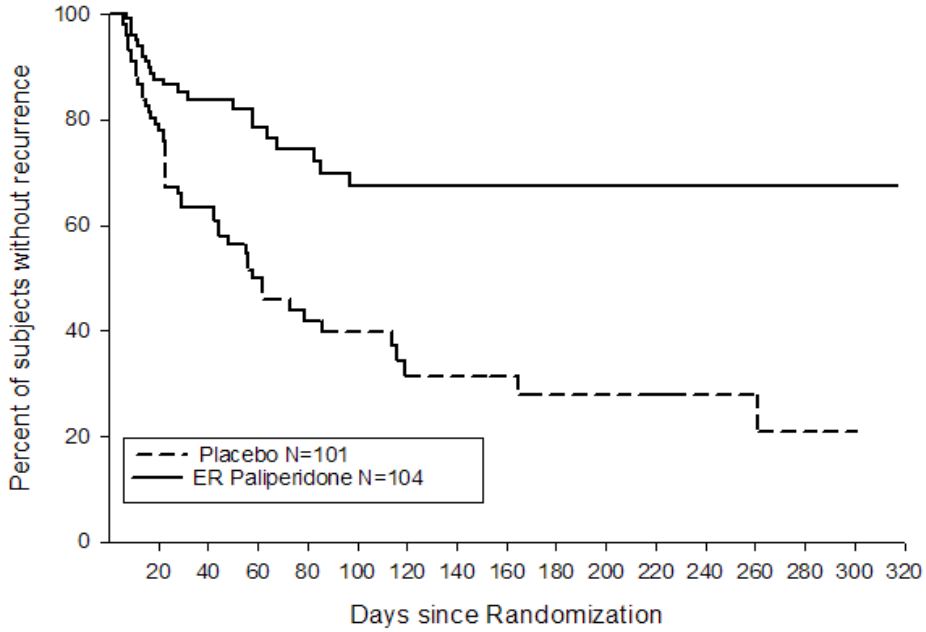
Table 1: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point- LOCF for Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set

		INVEGA™			
	Placebo	3 mg	6 mg	9 mg	12 mg
R076477-SCH-303	(N=126)		(N=123)	(N=122)	(N=129)
Mean baseline (SD)	94.1 (10.74)		94.3 (10.48)	93.2 (11.90)	94.6 (10.98)
Mean change (SD)	-4.1 (23.16)		-17.9 (22.23)	-17.2 (20.23)	-23.3 (20.12)
P-value (vs. Placebo)			<0.001	<0.001	<0.001
Diff. of LS Means (SE)			-13.7 (2.63)	-13.5 (2.63)	-18.9 (2.60)
95% CI			(-19.91;-7.53)	(-19.65;-7.25)	(-25.07;-12.82)
R076477-SCH-304	(N=105)		(N=111)		(N=111)
Mean baseline (SD)	93.6 (11.71)		92.3 (11.96)		94.1 (11.42)
Mean change (SD)	-8.0 (21.48)		-15.7 (18.89)		-17.5 (19.83)
P-value (vs. Placebo)			0.006		<0.001
Diff. of LS Means (SE)			-7.0 (2.36)		-8.5 (2.35)
95% CI			(-12.27;-1.81)		(-13.75;-3.32)
R076477-SCH-305	(N=120)	(N=123)		(N=123)	
Mean baseline (SD)	93.9 (12.66)	91.6 (12.19)		93.9 (13.20)	
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)		-16.3 (21.81)	
P-value (vs. Placebo)		< 0.001		<0.001	
Diff. of LS Means (SE)		-11.6 (2.35)		-12.9 (2.34)	
95% CI		(-17.17;-6.09)		(-18.42;-7.38)	

Note: Negative change in score indicates improvement. For all 3 studies, an active control (olanzapine at a dose of 10 mg) was included. LOCF = last observation carried forward. The 1-7 version of the PANSS was used. A 15 mg dose was also included in Study R076477-SCH-305, but results are not presented since this is above the maximum recommended daily dose of 12 mg.

In a long-term trial designed to assess the maintenance of effect, INVEGA™ was significantly more effective than placebo in maintaining symptom control and preventing recurrence of schizophrenia symptoms. After having been treated for an acute episode for 6 weeks and stabilized for an additional 8 weeks with INVEGA™ (doses ranging from 3 to 15 mg, flexible dosage regimen), patients were then randomised in a double-blind manner to either continue on INVEGA™ or placebo until they experienced a recurrence of schizophrenia symptoms. Relapse was pre-defined as significant increase in PANSS (or pre-defined PANSS subscales), hospitalization, clinically significant suicidal or homicidal ideation, or deliberate injury to self or others. The trial was stopped early for efficacy reasons by showing a significantly longer time to recurrence in patients treated with INVEGA™ compared to placebo ($p<0.001$) (Figure 2). INVEGA™ was also significantly more effective than placebo in maintaining personal and social performance.

Figure 2. Kaplan-Meier Plot of Time to Recurrence



INDICATIONS

INVEGA^{TM} (paliperidone) prolonged release tablet is indicated for the treatment of schizophrenia, including acute treatment and recurrence prevention.

CONTRAINDICATIONS

INVEGA^{TM} (paliperidone) is contraindicated in patients with a known hypersensitivity to paliperidone, risperidone, or to any components in the INVEGA^{TM} formulation.

PRECAUTIONS

Use in the elderly

The safety, tolerability, and efficacy of INVEGA^{TM} 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, 76 subjects received flexible doses of INVEGA^{TM} (3 to 12 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^{TM} (3 to 15 mg once daily, see **PHARMACOLOGY**: Clinical Trials).

Overall, of the total number of subjects in clinical studies of INVEGA^{TM} (n = 1796), including those who received INVEGA^{TM} or placebo, 125 (7.0%) were 65 years of age and older, of whom 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 responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (also see Orthostatic Hypotension in this section).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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**).

Use in elderly patients with dementia

INVEGA^{TM} has not been studied in elderly patients with dementia.

Overall Mortality

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects 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. INVEGA^{TM} is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Events

In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo.

In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient ischaemic attacks in patients (mean age 85 years, range 73-97) treated with risperidone compared to patients treated with placebo. The pooled data from six placebo-controlled trials in mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular adverse events (serious and non-serious combined) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96(1.33, 7.45).

QT Prolongation

INVEGA^{TM} was not shown to result in any clinically significant increase in QTc intervals from baseline compared to placebo. However, as with other antipsychotics, caution should be exercised when INVEGA^{TM} is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other drugs known to increase the QTc interval particularly in elderly patients.

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 (olanzapine 10 mg), 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n = 141), a supratherapeutic dose of an immediate-release oral formulation (8 mg) resulted in a mean steady-state peak plasma concentration greater than twice the exposure observed with the maximum recommended INVEGA^{TM} dose of 12 mg ($C_{max\,ss}$ = 113 and 45 ng/mL, respectively). In the model-adjusted day-averaged linear-derived QT correction (QTcLD), there was a mean increase of 5.5 msec (90% CI: 3.66; 7.25) in the INVEGA^{TM} treatment group (n = 44). 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, extensive electrocardiography (ECG) measurements were taken at 15 time points on specified days (including the times of expected C_{max}) using a standardized methodology. Mean QTcLD increase did not exceed 5 msec in any treatment group at any time point, based on pooled data from 836 subjects treated with INVEGA^{TM}, 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the INVEGA^{TM} 12 mg and olanzapine groups had a change exceeding 60 msec at one time-point during these studies (changes of 62 and 110 msec,

respectively). No subject receiving INVEGA^{TM} had a QTcLD exceeding 500 msec at any time in any of these three studies.

In the pooled double-blind safety analysis set, the largest mean increase in QTcLD interval, observed 22 hours after dose administration on Day 8, ranged between 1.6 to 4.4 msec across INVEGA^{TM} treatment groups.

In the overall phase 3 safety database (n=2054), which included both the double–blind and open-label extension studies, there were two patients with QTcLD prolongation > 500 msec.

Extrapyramidal symptoms

As with other antipsychotics, EPS has been reported (see **ADVERSE EFFECTS**).

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.

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.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with 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 is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. 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.

Orthostatic Hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA™ (3, 6, 9, 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 (dehydration, hypovolemia, and treatment with antihypertensive medications).

As expected based on its pharmacologic profile, treatment with INVEGA™ is associated with modest mean increases in heart rate at therapeutic doses.

Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Seizures

During premarketing clinical trials (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, 6, 9, 12 mg) and 0.25% of subjects treated with placebo. As with other antipsychotic drugs, INVEGA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinaemia

As with other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. 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. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumourigenesis in humans; the available evidence is considered too limited to be conclusive at this time. (see **PRECAUTIONS**: Carcinogenicity, Genotoxicity, Effects on fertility)

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA™ and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Weight gain

As with other atypical antipsychotics, weight gain has been reported (see **ADVERSE EFFECTS**).

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.

Potential for Cognitive and Motor Impairment

Somnolence and sedation were reported in subjects treated with INVEGA™ (see **ADVERSE EFFECTS**). 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.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA™, paliperidone shares this pharmacologic activity and, therefore, may be associated with this risk. Severe priapism may require surgical intervention.

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.

Gastrointestinal

Because the INVEGA^{TM} tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA^{TM} should ordinarily not be administered to 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 pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA^{TM} should only be used in patients who are able to swallow the tablet whole.

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.

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 tumour.

Use in patients with renal impairment

The plasma concentrations of paliperidone are increased in patients with renal impairment and, therefore, dosage adjustment may be required in patients with mild (creatinine clearance ≥ 50 to < 80 mL/min) and moderate to severe (creatinine clearance 10 to < 50 mL/min) renal impairment (see **PHARMACOLOGY –** Pharmacokinetics and **DOSAGE AND ADMINISTRATION**). No data are available in patients with a creatinine clearance below 10 mL/min. Paliperidone should not be used in patients with creatinine clearance below 10 mL/min.

Use in patients with hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if INVEGA^{TM} is used in such patients. In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. (see **DOSAGE AND ADMINISTRATION**)

Use in Children and adolescents younger than 18 years

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

Use in Patients with Concomitant Illness

Clinical experience with INVEGA^{TM} in patients with certain concomitant illnesses is limited.

Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including INVEGA^{TM}, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medication. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

The safety of use of INVEGA™ has not been evaluated in patients with relevant history of a significant or unstable cardiovascular or neurologic (including cerebrovascular) disease 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 **PRECAUTIONS**: Orthostatic Hypotension).

Effects on fertility

Mating and fertility of male and female rats was not affected at oral paliperidone doses up to 2.5 mg/kg/day (twice the maximum recommended clinical dose based on body surface area (mg/m^2)). The 2.5 mg/kg/day dose produced slight maternal toxicity, increased pre-implantation loss and slightly reduced the number of live embryos; the no-effect dose was 0.63 mg/kg/day.

In rat fertility studies with risperidone, which is extensively converted to paliperidone in rats and humans, mating (but not fertility) was impaired at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis, by an effect on females. In repeat dose toxicity studies in beagle dogs, risperidone at doses of 1 to 17 times the maximum human dose on a mg/m^2 basis was associated with adverse effects on the male reproductive system (inhibited ejaculation, incomplete spermatogenesis, reduced sperm motility and concentration, reduced gonadal and prostatic weight, prostatic immaturity, decreased serum testosterone). Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No-effect doses were not determined in either rat or dog.

Use in pregnancy - Category B3

The safety of INVEGA™ during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate have been observed following the use of risperidone during the last trimester of pregnancy. Risperidone is extensively converted to paliperidone in humans. It is not known whether neonatal extrapyramidal effects will occur following the use of paliperidone near the end of pregnancy.

No teratogenic effect was noted in rats and rabbits following oral administration of paliperidone during the period of organogenesis at respective exposures up to 28- and 17-fold the maximal anticipated clinical exposure, based on plasma AUC. Maternotoxic doses in rabbits were associated with increased fetal mortality. Studies with risperidone also found no teratogenic effects in rats and rabbits following oral administration of risperidone during the period of organogenesis at doses up to nine times the human dose on a mg/m^2 basis. INVEGA™ should only be used during pregnancy if the benefits outweigh the risks.

Use in lactation

In animal studies with paliperidone and human studies with risperidone, paliperidone is excreted in milk. Women receiving INVEGA™ should not breast feed.

Oral administration of paliperidone to rats from early gestation to lactation was associated with adverse effects in pups (clinical signs, reduced body weight gain and survival, impaired righting reflex) during lactation at doses similar to the maximal recommended clinical dose on mg/m^2 basis; the no-effect dose was less than the clinical dose. In risperidone studies in rats, oral administration of risperidone during late gestation and lactation was associated with increased pup deaths during early lactation at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis (a no effect dose was not determined) and with reduced pup weight gain at doses fivefold or greater than the maximal recommended human dose on a mg/m^2 basis. There were also increases in stillborn rat pups at an oral risperidone dose 2.5 to 5 times the maximum human dose on a mg/m^2 basis. It is not known whether these effects of risperidone and paliperidone resulted from a direct effect on the fetuses and pups and/or to an effect on the dams.

Alcohol

Given the primary CNS effects of INVEGA^{TM}, patients should be advised to avoid alcohol while taking this medicine.

Carcinogenicity

The carcinogenic potential of paliperidone has not been determined. Paliperidone is the major active metabolite of risperidone, which has been assessed for carcinogenic potential in rodents.

Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times (in mice) or 0.6, 2.5 and 10 times (in rats) the maximum human dose on a mg/m^2 basis.

There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies but measurements during repeat-dose toxicity studies showed that risperidone elevated serum prolactin levels by 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated.

The relevance for human risk of the findings of prolactin mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL® elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, RISPERDAL® and INVEGA^{TM} should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia (see **ADVERSE EFFECTS**).

Genotoxicity

No evidence of genotoxic potential for paliperidone was found in bacterial reverse mutation tests, forward mutation tests in mammalian cells (mouse lymphoma), or an *in vivo* chromosomal aberration assay (rat micronucleus test). Risperidone, which is metabolised to paliperidone in humans, was also negative in genotoxicity assays.

Interactions with other medicines

The risks of using INVEGA^{TM} in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of INVEGA^{TM}, it should be used with caution in combination with other centrally acting drugs.

Use with medicines known to cause QT prolongation:

Caution is advised when INVEGA^{TM} is used in combination with medicines known to cause QT prolongation e.g. class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine).

Use with medicines containing risperidone:

Concomitant use of INVEGA^{TM} with oral risperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive paliperidone exposure.

Potential for INVEGA™ to affect other medicines:

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Given the primary CNS effects of paliperidone (see **ADVERSE EFFECTS**), INVEGA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Caution is advised when paliperidone is combined with medicines known to lower the seizure threshold. (e.g. phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.)

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 **PRECAUTIONS**: Orthostatic Hypotension).

Potential for other medicines to affect INVEGA™:

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone.

In vitro studies have shown that paliperidone is a P-gp substrate. No *in vivo* data are available.

Paliperidone, a cation under physiological pH, is primarily excreted unchanged by the kidneys, approximately half via filtration and half via active secretion. Concomitant administration of trimethoprim, a drug known to inhibit active renal cation drug transport, did not influence the pharmacokinetics of paliperidone.

Medicinal products affecting gastrointestinal transit time may affect the absorption of paliperidone, e.g. metoclopramide.

Effect on ability to drive or operate machinery

INVEGA™ may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

ADVERSE EFFECTS

Adverse Events Observed in Short-Term, Placebo-Controlled Trials of Subjects with Schizophrenia

The information presented in this section were derived from pooled data from the three placebo-controlled, 6-week, fixed-dose studies based on subjects with schizophrenia who received INVEGA™ at daily doses within the recommended range of 3 to 12 mg (n = 1205).

Adverse Events Associated with Discontinuation of Treatment in Controlled Clinical Studies

Overall, there was no difference in the incidence of discontinuation due to adverse events between INVEGA™-treated (5%) and placebo-treated (5%) subjects. The types of adverse events that led to discontinuation were similar between INVEGA™- and placebo-treated subjects, except for Nervous System Disorders events (including dizziness, headache, sedation, akathisia, and tremor), which were of greater incidence among INVEGA™ treated subjects than placebo-treated subjects (2% and 0%, respectively), and Psychiatric Disorders events (including agitation and insomnia), which were of

greater incidence among placebo-treated subjects than INVEGA™ treated subjects (3% and 1%, respectively).

Commonly Observed Adverse Events in Controlled Clinical Studies

The most commonly observed adverse events associated with the use of INVEGA™ (incidence of ≥ 5% and that occurred at least twice the incidence observed with placebo) were tachycardia, akathisia, and extrapyramidal disorder (see Table 2). Electrocardiogram prolonged QT corrected interval was also reported. When an appropriate correction factor, QTc Linear Derived, was applied there were no cases of QTc prolongation.

Adverse Events Occurring at an Incidence of 1% or More in Controlled Clinical Studies

Table 2 enumerates the pooled incidences of treatment-emergent adverse events that were spontaneously reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those events that occurred in 1% 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 2. Treatment-Emergent Adverse Events, Regardless of Causality, Reported by ≥ 1% of Subjects with Schizophrenia in Any INVEGA™ Group and Which Occurred at Greater Incidence Than in the Placebo Group in the Three Placebo-Controlled, 6-Week, Double-Blind, Fixed-Dose Clinical Trials

		INVEGA™			
Body System or Organ Class Dictionary-derived Term	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)
Cardiac disorders					
Atrioventricular block first degree	5 (1.4)	2 (1.6)	0	6 (2.4)	2 (0.8)
Bradycardia	3 (0.8)	0	3 (1.3)	3 (1.2)	4 (1.7)
Bundle branch block	6 (1.7)	4 (3.1)	3 (1.3)	7 (2.8)	1 (0.4)
Palpitations	0	2 (1.6)	2 (0.9)	0	3 (1.2)
Sinus arrhythmia	0	3 (2.4)	2 (0.9)	2 (0.8)	1 (0.4)
Sinus tachycardia	15 (4.2)	11 (8.7)	9 (3.8)	10 (4.1)	17 (7.0)
Tachycardia	10 (2.8)	3 (2.4)	17 (7.2)	18 (7.3)	18 (7.4)
Eye disorders					
Dry eye	0	2 (1.6)	0	1 (0.4)	1 (0.4)
Oculogyration	0	0	0	5 (2.0)	0
Vision blurred	4 (1.1)	1 (0.8)	1 (0.4)	0	5 (2.1)
Gastrointestinal disorders					
Abdominal pain	3 (0.8)	0	4 (1.7)	2 (0.8)	2 (0.8)
Abdominal pain upper	2 (0.6)	1 (0.8)	6 (2.6)	5 (2.0)	4 (1.7)
Diarrhea	8 (2.3)	1 (0.8)	2 (0.9)	3 (1.2)	6 (2.5)
Dry mouth	2 (0.6)	3 (2.4)	8 (3.4)	2 (0.8)	7 (2.9)
Dyspepsia	14 (3.9)	3 (2.4)	6 (2.6)	5 (2.0)	12 (5.0)
Nausea	19 (5.4)	8 (6.3)	9 (3.8)	10 (4.1)	10 (4.1)
Salivary hypersecretion	1 (0.3)	0	1 (0.4)	3 (1.2)	10 (4.1)
Stomach discomfort	1 (0.3)	2 (1.6)	3 (1.3)	1 (0.4)	2 (0.8)
Toothache	4 (1.1)	2 (1.6)	5 (2.1)	6 (2.4)	5 (2.1)
Vomiting	17 (4.8)	2 (1.6)	6 (2.6)	9 (3.7)	12 (5.0)
General disorders					
Asthenia	3 (0.8)	2 (1.6)	1 (0.4)	5 (2.0)	5 (2.1)
Fatigue	5 (1.4)	2 (1.6)	2 (0.9)	4 (1.6)	5 (2.1)
Pyrexia	4 (1.1)	1 (0.8)	1 (0.4)	5 (2.0)	4 (1.7)
Infections and infestations					
Bronchitis	1 (0.3)	0	3 (1.3)	1 (0.4)	2 (0.8)
Nasopharyngitis	10 (2.8)	4 (3.1)	5 (2.1)	4 (1.6)	6 (2.5)

Body System or Organ Class Dictionary-derived Term	Placebo (N=355) n (%)	INVEGA™ 3 mg (N=127) n (%)	 6 mg (N=235) n (%)	 9 mg (N=246) n (%)	 12 mg (N=242) n (%)
Rhinitis	1 (0.3)	0	3 (1.3)	0	1 (0.4)
Upper respiratory tract infection	2 (0.6)	1 (0.8)	2 (0.9)	3 (1.2)	2 (0.8)
Viral infection	1 (0.3)	0	1 (0.4)	2 (0.8)	3 (1.2)
Injury, poisoning and procedural complications					
Fall	1 (0.3)	0	3 (1.3)	0	0
Investigations					
Alanine aminotransferase increased	4 (1.1)	1 (0.8)	4 (1.7)	2 (0.8)	2 (0.8)
Blood creatine phosphokinase increased	5 (1.4)	1 (0.8)	4 (1.7)	0	1 (0.4)
Blood insulin increased	2 (0.6)	3 (2.4)	3 (1.3)	2 (0.8)	1 (0.4)
Blood pressure increased	2 (0.6)	3 (2.4)	1 (0.4)	1 (0.4)	3 (1.2)
Blood triglycerides increased	1 (0.3)	2 (1.6)	1 (0.4)	0	0
Electrocardiogram QT corrected interval prolonged *	9 (2.5)	4 (3.1)	9 (3.8)	7 (2.8)	12 (5.0)
Electrocardiogram T wave abnormal	4 (1.1)	3 (2.4)	2 (0.9)	4 (1.6)	2 (0.8)
Electrocardiogram T wave inversion	3 (0.8)	0	1 (0.4)	3 (1.2)	2 (0.8)
Electrocardiogram abnormal	0	0	0	4 (1.6)	2 (0.8)
Heart rate increased	2 (0.6)	4 (3.1)	2 (0.9)	1 (0.4)	3 (1.2)
Insulin C-peptide increased	3 (0.8)	2 (1.6)	3 (1.3)	2 (0.8)	0
Weight decreased	3 (0.8)	2 (1.6)	0	0	0
Weight increased	5 (1.4)	1 (0.8)	0	4 (1.6)	4 (1.7)
Metabolism and nutrition disorders					
Decreased appetite	0	2 (1.6)	1 (0.4)	1 (0.4)	2 (0.8)
Increased appetite	1 (0.3)	2 (1.6)	0	3 (1.2)	3 (1.2)
Musculoskeletal and connective tissue disorders					
Arthralgia	3 (0.8)	0	4 (1.7)	2 (0.8)	0
Back pain	3 (0.8)	1 (0.8)	2 (0.9)	3 (1.2)	5 (2.1)
Muscle rigidity	0	1 (0.8)	0	3 (1.2)	1 (0.4)
Neck pain	1 (0.3)	0	0	0	3 (1.2)
Pain in extremity	4 (1.1)	0	2 (0.9)	0	5 (2.1)
Shoulder pain	0	1 (0.8)	3 (1.3)	2 (0.8)	2 (0.8)
Nervous system disorders					
Akathisia	14 (3.9)	5 (3.9)	7 (3.0)	20 (8.1)	23 (9.5)
Dizziness	14 (3.9)	7 (5.5)	11 (4.7)	11 (4.5)	12 (5.0)
Dyskinesia	3 (0.8)	0	1 (0.4)	1 (0.4)	4 (1.7)
Dystonia	2 (0.6)	1 (0.8)	3 (1.3)	9 (3.7)	9 (3.7)
Extrapyramidal disorder	8 (2.3)	6 (4.7)	5 (2.1)	17 (6.9)	18 (7.4)
Headache	42 (11.8)	14 (11.0)	29 (12.3)	34 (13.8)	35 (14.5)
Hypertonia	4 (1.1)	3 (2.4)	3 (1.3)	10 (4.1)	8 (3.3)
Parkinsonism	0	0	1 (0.4)	5 (2.0)	3 (1.2)
Sedation	13 (3.7)	1 (0.8)	12 (5.1)	8 (3.3)	15 (6.2)
Somnolence	12 (3.4)	6 (4.7)	8 (3.4)	17 (6.9)	11 (4.5)
Syncope	1 (0.3)	1 (0.8)	2 (0.9)	3 (1.2)	1 (0.4)
Tremor	12 (3.4)	4 (3.1)	6 (2.6)	11 (4.5)	8 (3.3)
Psychiatric disorders					
Aggression	4 (1.1)	2 (1.6)	1 (0.4)	3 (1.2)	2 (0.8)
Anxiety	29 (8.2)	12 (9.4)	16 (6.8)	14 (5.7)	11 (4.5)
Depression	1 (0.3)	0	3 (1.3)	1 (0.4)	1 (0.4)
Nightmare	0	0	1 (0.4)	3 (1.2)	1 (0.4)
Suicidal ideation	4 (1.1)	2 (1.6)	2 (0.9)	1 (0.4)	1 (0.4)
Respiratory, thoracic and mediastinal disorders					
Cough	4 (1.1)	4 (3.1)	4 (1.7)	7 (2.8)	4 (1.7)
Nasal congestion	3 (0.8)	1 (0.8)	3 (1.3)	2 (0.8)	2 (0.8)

		INVEGA™			
Body System or Organ Class Dictionary-derived Term	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)
Skin and subcutaneous tissue disorders					
Pruritus	4 (1.1)	0	3 (1.3)	2 (0.8)	0
Vascular disorders					
Hypotension	1 (0.3)	2 (1.6)	1 (0.4)	2 (0.8)	2 (0.8)
Orthostatic hypotension	3 (0.8)	3 (2.4)	3 (1.3)	6 (2.4)	9 (3.7)

*When an appropriate correction factor, QTc Linear Derived, was applied there were no cases of QTc prolongation.

Dose Dependency of Adverse Events

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, adverse events that occurred with a greater than 1% incidence in the subjects treated with INVEGA™, the incidences of the following adverse events increased with dose: somnolence, orthostatic hypotension, salivary hypersecretion, akathisia, dystonia, extrapyramidal disorder, hypertonia and Parkinsonism. For most of these, the increased incidence was seen primarily at the 12 mg, and in some cases the 9 mg dose.

Extrapyramidal Symptoms (EPS)

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies provided information regarding treatment-emergent EPS and dose-relatedness for EPS with the two higher doses of INVEGA™ (9 and 12 mg once daily). Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates EPS-related symptoms, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale total score (mean change from baseline) which evaluates dyskinesia, (4) incidence of spontaneous reports of EPS, and (5) use of anticholinergic medications to treat emergent EPS. For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 and 12 mg doses. There was no difference observed between placebo and INVEGA™ 3 and 6 mg doses for any of these EPS measures.

	Percentage of Patients				
		INVEGA™			
	Placebo	3 mg once daily	6 mg once daily	9 mg once daily	12 mg once daily
EPS Group	(N=355)	(N=127)	(N=235)	(N=246)	(N=242)
Parkinsonism [a]	9	11	3	15	14
Akathisia [b]	6	6	4	7	9
Use of anticholinergic medications [c]	10	10	9	22	22

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

	Percentage of Patients INVEGA™				
	Placebo	3 mg once daily	6 mg once daily	9 mg once daily	12 mg once daily
EPS Group	(N=355)	(N=127)	(N=235)	(N=246)	(N=242)
Overall percentage of patients with EPS-related AE	11.0	12.6	10.2	25.2	26.0
Dyskinesia	3.4	4.7	2.6	7.7	8.7
Dystonia	1.1	0.8	1.3	5.3	4.5
Hyperkinesia	3.9	3.9	3.0	8.1	9.9
Parkinsonism	2.3	3.1	2.6	7.3	6.2
Tremor	3.4	3.1	2.6	4.5	3.3

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

Laboratory Test Abnormalities

In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, a between-group comparison revealed no medically important differences between INVEGA™ and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, haematology, or urinalysis parameters. Similarly, there were no differences between INVEGA™ and placebo in the incidence of discontinuations due to changes in haematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA™ was associated with increases in serum prolactin (see **PRECAUTIONS**: Hyperprolactinaemia).

Weight Gain

In the pooled data from the three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose studies, the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were compared. Weight gain incidence for INVEGA™ 3 mg, 6 mg, 9 mg and 12 mg was 7%, 6%, 9% and 9% respectively. In comparison the incidence for placebo was 5%.

Other Findings Observed During Clinical Studies

An examination of population subgroups did not reveal any evidence of differences in safety on the basis of gender or race; there was also no difference on the basis of age (see **PRECAUTIONS**: Use in the elderly).

The following list contains all treatment-emergent adverse events reported at anytime by individuals taking INVEGA™ in the pooled clinical studies, except (1) those listed in Table 1 above or elsewhere in the Product Information, (2) those for which a causal relationship to INVEGA™ use was considered remote, and (3) those occurring in only one subject treated with INVEGA™ and which did not have a substantial probability of being acutely life-threatening. Events are classified within body system categories using the following definitions: *frequent* adverse events are defined as those occurring on one or more occasions in at least 1/100 subjects, *infrequent* adverse events are those occurring in 1/100 to 1/1000 subjects, and *rare* events are those occurring in < 1/1000 subjects.

Cardiac Disorders: *infrequent:* arrhythmia, myocardial ischemia, palpitations

Ear and Labyrinth Disorders: *infrequent:* tinnitus

Eye Disorders: *infrequent:* dry eye, eye irritation

Gastrointestinal Disorders: *infrequent:* gastritis, stomach discomfort, tongue disorder

General Disorders: *infrequent:* chest pain, hunger, oedema

Immune System Disorders: *infrequent:* anaphylactic reaction, hypersensitivity

Infections and Infestations: *infrequent:* bronchitis, respiratory tract infection, rhinitis, upper respiratory tract infection

Injury, Poisoning, and Procedural Complications: *infrequent:* fall

Investigations: *frequent:* increased weight; *infrequent:* increased blood glucose, increased insulin C peptide, increased blood lactate dehydrogenase, increased blood triglycerides, increased hepatic transaminases, increased neutrophil count

Metabolism and Nutrition Disorders: *infrequent:* decreased appetite, diabetes mellitus, hyperglycaemia, hypoglycaemia, hypokalemia, increased appetite, water intoxication

Musculoskeletal and Connective Tissue Disorders: *Infrequent:* chest wall pain, costochondritis, shoulder pain

Nervous System Disorders: *infrequent:* paresthesia

Psychiatric Disorders: *infrequent:* aggression, nervousness, irritability, nightmares, anorgasmia, sleep disorder

Renal and Urinary Disorders: *infrequent:* acute renal failure

Reproductive System and Breast Disorders: *infrequent:* amenorrhea, galactorrhea

Respiratory, Thoracic, and Mediastinal Disorders: *infrequent:* dyspnea, nasal congestion, rhinorrhea

Adverse Events Reported With Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse events reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone Product Information.

DOSAGE AND ADMINISTRATION

The recommended dose of INVEGA^{TM} (paliperidone) Prolonged-Release Tablets is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the usual range of 3 to 9 mg once daily. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, small increments of 3 mg/day are recommended. If required the dose may be increased to the maximum recommended dose of 12 mg once daily.

The administration of INVEGA should be standardised in relation to food intake (see **PHARMACOLOGY** – Pharmacokinetics). The patient should be instructed to always take INVEGA in the fasting state or always take it together with breakfast and not to alternate between administration in the fasting state or in the fed state.

INVEGA^{TM} 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.

Concomitant use of INVEGA^{TM} 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^{TM}. Concomitant use of INVEGA^{TM} with oral risperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive paliperidone exposure.

Dosing in Special Populations

Hepatic Impairment:
For patients with hepatic impairment, no dose adjustment is required. As INVEGA^{TM} has not been studied in patients with severe hepatic impairment, caution is recommended when using the medicine in such patients.

Renal Impairment:
Dosing must be individualized according to the patient's renal function status. For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), the recommended initial dose is 3 mg once daily. The dose may be increased based on clinical response and tolerability.

For patients with moderate renal impairment (creatinine clearance ≥ 30 to < 50 ml/min), the recommended dose of INVEGA^{TM} is 3 mg once daily. For patients with severe renal impairment (creatinine clearance ≥ 10 to < 30 ml/min), the recommended initial dose of INVEGA is 3 mg every other day, which may be increased to 3 mg once daily after clinical reassessment. As INVEGA^{TM} has not been studied in patients with creatinine clearance below 10 ml/min, use is not recommended in such patients.

Elderly:
In general, the same dosing recommendations apply for elderly patients with normal renal function as for adult patients with normal renal function (creatinine clearance ≥ 80 mL/min). However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal Impairment above).

Children and adolescents younger than 18 years of age:
INVEGA^{TM} has not been studied in this patient group and should not be used in this age group.

OVERDOSAGE

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 INVEGA^{TM} was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation.

Management of Overdosage

There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the prolonged-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation if patient is unconscious) and 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, disopyride, 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 bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (adrenaline and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

PRESENTATION AND STORAGE CONDITIONS

3 mg White, capsule shaped tablets imprinted with “PAL 3”.
Pack size: Blister pack of 28 tablets.

6 mg Beige, capsule shaped tablets imprinted with “PAL 6”.
Pack size: Blister pack of 28 tablets.

9 mg Pink, capsule shaped tablets imprinted with “PAL 9”.
Pack size: Blister pack of 28 tablets.

12 mg Dark yellow, capsule shaped tablets imprinted with “PAL 12”.
Pack size: Blister pack of 28 tablets.

Store below 25^{o}C.

POISON SCHEDULE

S4 - Prescription Only Medicine

SPONSOR

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