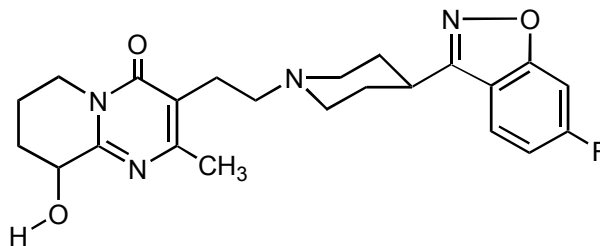


INVEGA[®]

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

C₂₃H₂₇FN₄O₃

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 D₂ antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α₁ and α₂ adrenergic receptors and H₁ histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β₁- and β₂-

adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar. 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 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism. Antagonism at receptors other than D₂ and 5HT_{2A} may explain some of the other effects of paliperidone.

Polysomnography:

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

Pharmacokinetics

Following a single dose, the plasma concentrations of paliperidone steadily rise to reach peak plasma concentration (C_{max}) in approximately 24 hours after dosing. The pharmacokinetics of paliperidone following INVEGA[®] 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).

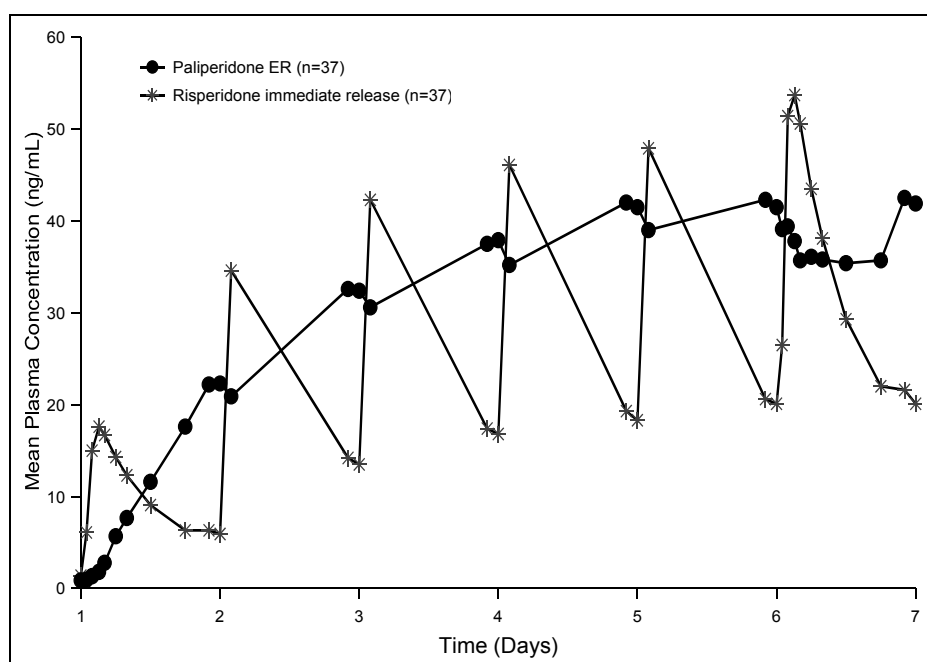


Figure 1. Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg prolonged-release tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release administered as 2 mg once daily on Day 1 and 4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

Following administration of INVEGA[®], 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[®] 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. (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[®] 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. Paliperidone has not been studied in patients with severe hepatic impairment. (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

Renal Impairment:

The dose of INVEGA[®] 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® 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

Schizophrenia:

The efficacy of INVEGA® (3 to 15 mg once daily) in the treatment of schizophrenia 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[®] 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 $\geq 30\%$ reduction in PANSS total score. Each dose of INVEGA[®] 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.

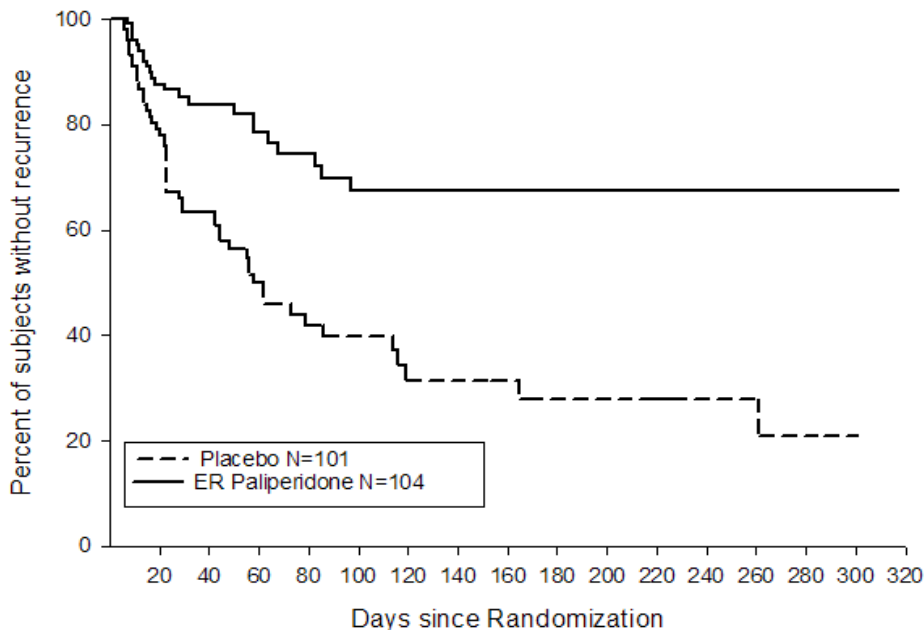
Table 1: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point- LOCF for Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set.

	Placebo	INVEGA [®]			
		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



Schizoaffective Disorder

Efficacy of INVEGA[®] in the treatment of acute exacerbation of schizoaffective disorder was established in two placebo-controlled, 6-week trials conducted in adult subjects. Enrolled subjects 1) met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders, 2) had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 3) had prominent mood symptoms as confirmed by a score of at least 16 on the Young Mania Rating Scale and/or Hamilton Rating Scale for Depression. The population included subjects with schizoaffective bipolar and depressive types.

Both studies included subjects who received INVEGA[®] either as monotherapy [no mood stabilizers and/or antidepressants (55%)] or in combination with mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. INVEGA[®] was taken 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. The primary efficacy end point was the change in the PANSS total score from baseline to week 6 last observation carried forward (LOCF) end point. Efficacy analyses were performed using the ITT analysis sets, which included subjects who received at least 1 dose of study medication, and both baseline and at least 1 post baseline PANSS assessment.

The safety and efficacy of INVEGA[®] in the prevention of relapse or recurrence of acute exacerbation of schizoaffective disorder has not been assessed.

In one of these trials subjects were permitted to have doses of INVEGA adjusted in the range of 3-12 mg once daily during the first 2 weeks, with doses fixed thereafter. The intent-to-treat (ITT) analysis set included 304 subjects (mean age: 37.6 years; range: 19-61 years), 186 subjects

completed the double blind treatment. Efficacy was assessed in 211 subjects who were assigned to at least 1 dose of active study medication, and had both baseline and at least 1 post baseline PANSS assessment.

In the other trial subjects received one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg or 12 mg with the option to reduce to 9 mg, once daily. The intent-to-treat (ITT) analysis set included 310 subjects (mean age: 37.3 years; range:18-61 years), 212 subjects completed the double blind treatment. Efficacy was assessed in 203 subjects who were assigned to at least 1 dose of study medication, and had both baseline and at least 1 post baseline PANSS assessment (n=105 INVEGA® 6 mg, with option to reduce to 3mg daily and n=98 INVEGA® 12 mg, with option to reduce to 9 mg daily).

Table 2: Change in Positive and Negative Syndrome Scale (PANSS) Total Score From Baseline to Week 6 Last Observation Carried Forward (LOCF) ITT Population

	Placebo	INVEGA®		
		6 mg, option to reduce to 3 mg	12 mg, option to reduce to 9 mg	3 mg to 12 mg
R076477-SCA-3001	(N=107)	(N=105)	(N=98)	
Mean baseline (SD)	91.6 (12.5)	95.9 (13.0)	92.7 (12.6)	
Mean change (SD)	-21.7 (21.4)	-27.4 (22.1)	-30.6 (19.1)	
P-value (vs. Placebo)		0.187	0.003	
Diff. of LS Means (SE)		-3.6 (2.7)	-8.3 (2.8)	
95% CI		(-9.0;1.8)	(-13.8;-2.9)	
R076477-SCA-3002	(N=93)			(N=211)
Mean baseline (SD)	91.7 (12.1)			92.3 (13.5)
Mean change (SD)	-10.8 (18.7)			-20.0 (18.9)
P-value (vs. Placebo)				<0.001
Diff. of LS Means (SE)				-9.4 (2.3)
95% CI				(-13.8;-4.9)
MONOTHERAPY				
R076477-SCA-3001	(N=67)	(N=67)	(N=59)	
Mean baseline (SD)	89.6 (10.9)	96.6 (12.3)	90.1 (12.1)	
Mean change (SD)	-20.6 (20.8)	-28.9 (20.8)	-31.0 (19.9)	
P-value (vs. Placebo)		0.166	0.003	
Diff. of LS Means (SE)		-4.7 (3.4)	-10.1 (3.4)	
95% CI		(-11.3;2.0)	(-16.8;-3.5)	
R076477-SCA-3002	(N=44)			(N=102)
Mean baseline (SD)	92.9 (11.7)			92.7 (13.5)
Mean change (SD)	-11.6 (20.1)			-22.4 (19.4)
P-value (vs. Placebo)				0.003
Diff. of LS Means (SE)				-10.7 (3.5)
95% CI				(-17.7;-3.8)
COMBINATION THERAPY				
R076477-SCA-3001	(N=40)	(N=38)	(N=39)	
Mean baseline (SD)	95.0 (14.3)	94.8 (14.2)	96.6 (12.4)	
Mean change (SD)	-23.5 (22.5)	-24.7 (24.2)	-30.0 (17.9)	
P-value (vs. Placebo)		0.828	0.222	
Diff. of LS Means (SE)		-1.0 (4.7)	-5.7 (4.6)	
95% CI		(-10.3;8.2)	(-14.9;3.5)	

R076477-SCA-3002	(N=49)	(N=109)
Mean baseline (SD)	90.7 (12.5)	91.9 (13.6)
Mean change (SD)	-10.1 (17.5)	-17.7 (18.2)
P-value (vs. Placebo)		0.007
Diff. of LS Means (SE)		-8.1 (3.0)
95% CI		(-14.0;-2.2)

Note: Negative change in score indicates improvement.

The INVEGA[®] group in the study permitting dose adjustment for the first two weeks, followed by fixed dosing (in a range of 3-12 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 with option to reduce to 9 mg daily), were each superior to placebo in the PANSS. In the lower dose group of the 2 dose-level study (6 mg with option to reduce to 3 mg daily), INVEGA[®] was not significantly different from placebo as measured by the PANSS.

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

INDICATIONS

INVEGA[®] is indicated for the treatment of schizophrenia, including acute treatment and recurrence prevention.

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

CONTRAINDICATIONS

INVEGA[®] (paliperidone) is contraindicated in patients with a known hypersensitivity to paliperidone, risperidone, or to any components in the INVEGA[®] formulation.

PRECAUTIONS

Use in the elderly

The safety, tolerability, and efficacy of INVEGA[®] were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, 76 subjects received flexible doses of INVEGA[®] (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[®] (3 to 15 mg once daily, see **PHARMACOLOGY**: Clinical Trials).

Overall, of the total number of subjects in clinical studies of INVEGA[®] (n = 1796), including those who received INVEGA[®] 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[®] 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[®] 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[®] 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[®] 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 suprathreshold 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[®] dose of 12 mg ($C_{max\ ss} = 113$ and 45 ng/mL, respectively). In the model-adjusted day-averaged linear-derived QT correction (QTcLD), there was a mean increase of 5.5 msec (90% CI: 3.66; 7.25) in the INVEGA[®] treatment group (n = 44). 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[®], 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the INVEGA[®] 12 mg and olanzapine groups had a change exceeding 60 msec

at one time-point during these studies (changes of 62 and 110 msec, respectively). No subject receiving INVEGA[®] 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[®] 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 in subjects with schizophrenia, 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 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, 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 D₂ 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)

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. Severe priapism may require surgical intervention. Priapism has been reported with INVEGA[®] during postmarketing surveillance (see **ADVERSE EFFECTS**).

Body Temperature Regulation

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

Gastrointestinal

Because the INVEGA[®] tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA[®] 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[®] 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 overdose 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[®] 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[®] in patients < 18 years of age have not been studied.

Use in Patients with Concomitant Illness

Clinical experience with INVEGA[®] in patients with certain concomitant illnesses is limited.

Patients with Parkinson’s Disease or Dementia with Lewy Bodies who receive antipsychotics, including INVEGA[®], 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/m²)). 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/m² 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/m² 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 C**

The safety of INVEGA[®] during human pregnancy has not been established. 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/m² basis.

**Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including INVEGA[®]) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases neonates have required additional medical treatment or monitoring.*

INVEGA[®] should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

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/m² 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/m² 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/m² 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/m² 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[®], 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/m² 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[®] 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[®] in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of INVEGA[®], 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[®] 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[®] 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).

**Pharmacokinetic interaction between INVEGA® and lithium is unlikely.*

Co-administration of INVEGA® at steady-state (12 mg once daily) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

Potential for other 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.

Paliperidone is metabolised to a limited extent by CYP2D6 (see **PHARMACOLOGY**: Pharmacokinetics – Metabolism and Elimination). In an interaction study in healthy males who were CYP2D6 extensive metabolisers, single doses of INVEGA® 3 mg were administered alone or after treatment with the potent CYP2D6 inhibitor paroxetine, 20 mg daily for 13 days. The mean peak plasma concentration and systemic exposure of unbound paliperidone were increased by 12% and 19%, respectively. This effect is unlikely to be clinically significant.

Co-administration of INVEGA® once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. The decrease may be greater with higher carbamazepine doses. On initiation of carbamazepine or when increasing the dose of carbamazepine, the dose of INVEGA® should be re-evaluated and increased if necessary. Conversely, on discontinuation or dose reduction of carbamazepine, the dose of INVEGA® should be re-evaluated and decreased if necessary.

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

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

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

Pharmacokinetic interaction between lithium and INVEGA[®] is unlikely.

Effect on ability to drive or operate machinery

INVEGA[®] may interfere with activities requiring mental alertness and may have visual effects (see **ADVERSE EFFECTS**). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

ADVERSE EFFECTS

Clinical Trial Data

The safety of INVEGA[®] in the treatment of schizophrenia was evaluated in 1205 adult subjects with schizophrenia who participated in 3 double-blind, placebo-controlled 6-week trials, of whom 850 subjects received INVEGA[®] at fixed doses ranging from 3 mg to 12 mg once daily.

The safety of INVEGA[®] was also evaluated in 622 subjects with schizoaffective disorder who participated in two double-blind, placebo-controlled, 6-week trials. In one of these trials, 206 subjects were assigned to one of two dose levels of INVEGA[®]: 6 mg with the option to reduce to 3 mg (n = 108) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. In the other study, 214 subjects received doses of INVEGA[®] adjusted in the range of 3-12 mg once daily during the first 2 weeks (Mean Dose= 8.9 mg/day), with doses fixed thereafter. Both studies included subjects who received INVEGA[®] either as monotherapy or in combination with antidepressants and/or mood stabilizers.

The information in this section was derived from pooled data.

The majority of Adverse Drug Reactions (ADRs) were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data – Schizophrenia:

Adverse drug reactions reported by $\geq 2\%$ of INVEGA[®] -treated subjects in the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia trials are shown in Table 3.

Table 3. Adverse Drug Reactions Reported by $\geq 2\%$ of INVEGA[®] -Treated Subjects with Schizophrenia in Three 6-Week Double-Blind, Placebo-Controlled, Fixed-Dose Clinical Trials

System/Organ Class Adverse Reaction	INVEGA [®]				
	3 mg (N=127) %	6 mg (N=235) %	9 mg (N=246) %	12 mg (N=242) %	Placebo (N=355) %
Nervous System Disorders					
Headache	11	12	14	14	12
Dizziness	6	5	4	5	4
Extrapyramidal disorder	5	2	7	7	2
Somnolence	5	3	7	5	3
Akathisia	4	3	8	10	4
Tremor	3	3	4	3	3
Hypertonia	2	1	4	3	1
Dystonia	1	1	4	4	1
Sedation	1	5	3	6	4
Parkinsonism	0	<1	2	1	0
Eye Disorders					
Oculogyric crisis	0	0	2	0	0

Cardiac Disorders					
Sinus tachycardia	9	4	4	7	4
Tachycardia	2	7	7	7	3
Bundle branch block	3	1	3	<1	2
Sinus arrhythmia	2	1	1	<1	0
Atrioventricular block first degree	2	0	2	1	1
Vascular Disorders					
Orthostatic hypotension	2	1	2	4	1
Gastrointestinal Disorders					
Vomiting	2	3	4	5	5
Dry mouth	2	3	1	3	1
Abdominal pain upper	1	3	2	2	1
Salivary hypersecretion	0	<1	1	4	<1
General disorders					
Asthenia	2	<1	2	2	1
Fatigue	2	1	2	2	1

Double-Blind, Placebo-Controlled Data – Schizoaffective Disorder:

ADRs reported by $\geq 2\%$ of INVEGA[®]--treated subjects in the two placebo-controlled schizoaffective disorder trials are shown in Table 4.

Table 4. Adverse Drug Reactions Reported by $\geq 2\%$ of INVEGA[®]--Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials

System/Organ Class Adverse Reaction	INVEGA [®] 3-12 mg once daily (N=420)*	Placebo (N=202)
	%	%
Infections and Infestations		
Nasopharyngitis	3	1
Metabolism and Nutrition Disorders		
Increased appetite	2	<1
Nervous System Disorders		
Tremor	8	3
Akathisia	5	4
Sedation	5	3
Somnolence	5	2
Hypertonia	5	2
Drooling	2	0
Dysarthria	2	0
Gastrointestinal Disorders		
Nausea	6	6
Dyspepsia	5	2
Constipation	4	2
Musculoskeletal and Connective Tissue Disorders		
Myalgia	2	<1

Investigations

Weight increased 4 1

* Among the 420 subjects treated with INVEGA[®], 230 (55%) received INVEGA[®] as monotherapy and 190 (45%) received INVEGA[®], in combination with antidepressants and/or mood stabilizers.

Additional ADRs reported by <2% of INVEGA-treated subjects in the Schizoaffective Disorder and schizophrenia clinical double blind, placebo-controlled trial datasets are shown below. Table 5 also includes ADRs reported at any frequency in other clinical trials:

Table 5: Adverse Drug Reactions Reported by <2% of INVEGA-Treated Subjects in a pooled dataset of the three double-blind, placebo-controlled schizophrenia trials, two placebo-controlled Schizoaffective Disorder trials, and at any frequency in other clinical trials

System/Organ Class

Adverse Reaction

Infections and infestations

Urinary tract Infection, Upper respiratory tract infection, Rhinitis

Immune System Disorders

Anaphylactic reaction

Endocrine Disorders

Hyperprolactinaemia

Metabolism and nutrition disorders

Decreased appetite

Psychiatric disorders

Agitation, Restlessness, Sleep disorder, Nightmare

Nervous system disorders

Cerebrovascular accident, Grand mal convulsion, convulsion, Transient ischaemic attack, Syncope, Dyskinesia, Bradykinesia, Parkinsonian gait, Lethargy, Cogwheel rigidity, Dizziness postural

Eye disorders

Vision blurred

Cardiac disorders

Palpitations, Bradycardia, Bundle branch block left

Vascular disorders

Ischaemia, Hypotension

Respiratory, thoracic and mediastinal disorders

Pneumonia aspiration, Cough, Pharyngolaryngeal pain, Nasal congestion

Gastrointestinal disorders

Abdominal discomfort Stomach discomfort, Small intestinal obstruction, Flatulence

Musculoskeletal and connective tissue disorders

Muscle spasms, Pain in extremity, Arthralgia, Trismus, Torticollis, Back pain, Muscle rigidity, Muscle twitching, Musculoskeletal pain

Reproductive system and breast disorders

Galactorrhoea, Amenorrhoea, Gynaecomastia, Erectile dysfunction, Menstruation irregular, Breast discharge, Breast engorgement, Retrograde ejaculation, Breast tenderness/Breast pain

General disorders and administration site conditions

Oedema, Oedema peripheral

Investigations

Electrocardiogram abnormal

Monotherapy versus Combination Therapy:

The designs of the two placebo-controlled, 6-week, double-blind trials in subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received INVEGA[®] as monotherapy and 190 (45%) subjects received INVEGA[®] in combination with antidepressants and/or mood stabilizers. When comparing these 2 subpopulations, only nausea occurred at a greater frequency ($\geq 3\%$ difference) in subjects receiving INVEGA[®] as monotherapy.

Discontinuations Due to Adverse Reactions

Schizophrenia Trials:

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

Schizoaffective Disorder Trials:

In a placebo-controlled, 6-week high- and low-dose study in subjects with schizoaffective disorder, dystonia, dysarthria, and nasopharyngitis occurred more frequently (i.e., a difference of at least 3%) in subjects who received higher doses of INVEGA[®] compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of INVEGA[®] compared with subjects who received higher doses.

Dose Related Adverse Events

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose schizophrenia studies, adverse events that occurred with 2% or more 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.

In the placebo-controlled, 6-week high- and low-dose study in subjects with schizoaffective disorder, dystonia, dysarthria, and nasopharyngitis occurred more frequently (i.e., a difference of at least 3%) in subjects who received higher doses of INVEGA[®] compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of INVEGA[®] compared with subjects who received higher doses.

Extrapyramidal Symptoms (EPS)

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia 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.

Table 6. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies

EPS Group	Percentage of Patients				
	Placebo (N=355)	INVEGA [®] 3 mg once daily (N=127)	6 mg once daily (N=235)	9 mg once daily (N=246)	12 mg once daily (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

Table 7. Treatment-Emergent Extrapyramidal Symptoms (EPS)- Related Adverse Events by MedDRA Preferred Term– Schizophrenia Studies

EPS Group	Percentage of Patients				
	Placebo (N=355)	INVEGA [®] 3 mg once daily (N=127)	6 mg once daily (N=235)	9 mg once daily (N=246)	12 mg once daily (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

Table 8 shows the EPS data from the pooled schizoaffective disorder trials.

Table 8. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies

EPS Group	Percentage of Patients			
	Placebo (N=202)	INVEGA [®] 3-6 mg once-daily fixed- dose range (N=108)	9-12 mg once-daily fixed-dose range (N=98)	3-12 mg once-daily flexible dose (N=214)

Overall percentage of patients with EPS-related AE	11	23	22	17
Dyskinesia	1	3	1	1
Dystonia	1	2	3	2
Hyperkinesia	5	5	8	7
Parkinsonism	3	14	7	7
Tremor	3	12	11	5

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

Compared to data from the studies in schizophrenia, pooled data from the two placebo-controlled 6-week studies in 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.

Laboratory Test Abnormalities

In the pooled data from the three placebo-controlled, 6-week, fixed-dose schizophrenia 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 schizophrenia studies, the proportions of subjects meeting a weight gain criterion of $\geq 7\%$ 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%.

In the pooled data from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, a higher percentage of INVEGA[®]-treated subjects (5%) had an increase in body weight of $\geq 7\%$ compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of $\geq 7\%$ was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

Other Findings Observed During Clinical Studies

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 **PHARMACOLOGY** Clinical Trials). 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.

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with INVEGA® are included in Table 9.

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports
Unknown	cannot be estimated from the available clinical trial data

Table 9. Adverse Drug Reactions Identified During Postmarketing Experience with INVEGA® by Frequency Category estimated from Spontaneous Reporting Rates	
Immune System Disorders	
<i>Rare</i>	Angioedema
Nervous System Disorders	
<i>Very rare</i>	Tardive dyskinesia
Gastrointestinal Disorders	
<i>Very rare</i>	Swollen tongue
Renal and Urinary Disorders	
<i>Very rare</i>	Urinary incontinence
<i>Very rare</i>	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
<i>Very rare</i>	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
<i>Unknown</i>	Priapism

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 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® 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.

Schizophrenia

The recommended dose of INVEGA® for the treatment of schizophrenia 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.

Acute exacerbation of Schizoaffective Disorder

The recommended dose of INVEGA[®] for the treatment of schizoaffective disorder is 6 mg once daily, administered in the morning. While initial dose titration is not required, the patients would require dosage adjustment to lower or higher doses within the dose range of 3 to 12 mg once daily.

**There was a trend towards significant improvement compared to placebo, from low dose (3mg) to high dose (12mg) paliperidone. This trend must be weighed against dose-related increase in adverse reactions.*

Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days.

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[®]. Concomitant use of INVEGA[®] 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:

No dose adjustment is required in patients with mild to moderate hepatic impairment. As INVEGA[®] 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[®] 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[®] 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[®] has not been studied in this patient group and should not be used in this age group.

OVERDOSAGE

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA[®] 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.

Contact the POISONS INFORMATION CENTRE on telephone no. 13 11 26 regarding overdose management.

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 7, 28 or 56[^] tablets.
- 6 mg Beige, capsule shaped tablets imprinted with "PAL 6".
Pack size: Blister pack of 7, 28 or 56[^] tablets.
- 9 mg Pink, capsule shaped tablets imprinted with "PAL 9".
Pack size: Blister pack of 7, 28 or 56[^] tablets.
- 12 mg[^] Dark yellow, capsule shaped tablets imprinted with "PAL 12".
Pack size: Blister packs of 7, 28 or 56 tablets.

[^] indicates not marketed presentations.

Store below 25°C.

POISON SCHEDULE

S4 - Prescription Only Medicine

SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road, Macquarie Park, NSW, 2113, Australia
NZ Office: Auckland, New Zealand.

Date of TGA approval: 23 December 2010

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Please note changes (presented as *italicised text*) in Product Information.