PRODUCT MONOGRAPH

PrINVEGA®

paliperidone

Extended-release Tablets
3 mg, 6 mg, 9 mg and 12 mg‡

Antipsychotic Agent

Janssen Inc.
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‡ Not available in Canada

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Extended-release Tablets/3 mg, 6 mg, 9 mg and 12 mg‡	Butylated hydroxytoluene, carnauba wax, cellulose acetate, ferric oxide red, ferric oxide yellow, hydroxyethyl cellulose, hypromellose, iron oxide black, polyethylene oxides, polyethylene glycol, propylene glycol, povidone, sodium chloride, stearic acid, and titanium dioxide. The 3 mg tablets also contain lactose and triacetin. *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

‡ Not available in Canada

INDICATIONS AND CLINICAL USE

INVEGA® (paliperidone) is indicated for the treatment of schizophrenia and related psychotic disorders. In controlled clinical trials, INVEGA® was found to improve the symptoms of schizophrenia, including positive and negative symptoms.

Geriatrics (> 65 years of age):
See **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box** and **Special Populations**.

Pediatrics (< 18 years of age):
The safety and efficacy of INVEGA® in children under the age of 18 have not been established and its use is not recommended (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

INVEGA® is contraindicated in patients who are hypersensitive to paliperidone, risperidone, or to any ingredient in the formulation or component of the container. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. 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 (see WARNINGS AND PRECAUTIONS, Special Populations, Use in Geriatric Patients with Dementia).

General

QT Prolongation

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

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

QT Prolongation Study R076477-SCH-1009

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicentre QT study in adults with schizophrenia and schizoaffective disorder. Serial ECG assessments were scheduled at multiple days and multiple timepoints during the day. Least square mean changes from baseline in QTcLD were calculated at each scheduled ECG assessment timepoint and day.

In study R076477-SCH-1009 (n=141), the 8 mg dose of immediate-release oral paliperidone (n=44) showed a maximal (least square) mean change from baseline in QTcLD of 10.9 msec (90%

CI: 8.24; 13.62) and was noted on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA® ($C_{max\ ss}$ = 113 and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone ($C_{max\ ss}$ = 35 ng/mL) showed a maximal (least square) mean change from baseline in QTcLD of 9.3 msec (90% CI: 6.56; 11.98) and was noted on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.

Also, in this study, a 400 mg dose of moxifloxacin (n=58) showed a maximal least square mean change from baseline in QTcLD of 6.1 msec (90% CI: 3.64; 8.53) and was noted on day 8 at 3 hours post-dose. Placebo (n=58) showed a maximal least square mean change from baseline in QTcLD of 3.5 msec (90% CI: 1.05; 5.95) and was noted on day 2 at 30 minutes post-dose.

Concomitant Use of INVEGA® with Oral Risperidone
There are no systematically collected safety data to specifically address concomitant use of INVEGA® with risperidone, paliperidone palmitate or other antipsychotics. Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA® is co-administered with risperidone or paliperidone palmitate.

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.

Carcinogenesis and Mutagenesis
For animal data see ***Product Monograph Part II***: **TOXICOLOGY**.

Cardiovascular
Orthostatic Hypotension
Paliperidone may induce orthostatic hypotension and syncope in some patients based on its alpha-blocking activity. Based on pooled data from three placebo-controlled, 6-week, fixed-dose trials with INVEGA® (3, 6, 9 and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with INVEGA® compared with 0.8% of subjects treated with placebo. Syncope was reported in 0.8% of subjects treated with INVEGA® (3, 6, 9 and 12 mg) compared to 0.3% of subjects treated with placebo.

INVEGA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease or conditions that predispose the patient to hypotension such as dehydration and hypovolemia. Special care should be taken to avoid hypotension in patients with a history of cerebrovascular insufficiency or ischemic heart disease, and in patients taking medications to lower blood pressure.

Endocrine and Metabolism

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes, 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, and not in clinical trials. Diabetic ketoacidosis (DKA) has occurred in patients treated with antipsychotics with no reported history of hyperglycemia. Appropriate clinical monitoring of patients treated with antipsychotics is advisable in accordance with utilized antipsychotic guidelines.

In clinical trials, there have been few reports of glucose-related adverse events (e.g., hyperglycemia) in 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, which did not include INVEGA®, 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. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients should have baseline and periodic monitoring of blood glucose and body weight. Any patient treated with atypical antipsychotics, including INVEGA®, should be monitored for symptoms of hyperglycemia and diabetes mellitus 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. 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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Regular clinical monitoring of weight is recommended (see **ADVERSE REACTIONS**).

In the pooled data from three placebo-controlled, 6-week, fixed-dose studies in adult patients with schizophrenia, the proportions of patients meeting a weight gain criterion of ≥ 7% of body weight were compared, revealing a similar incidence of weight gain for INVEGA® 3 mg and 6 mg (7% and 6%, respectively) compared with placebo (5%), and a higher incidence of weight gain for INVEGA® 9 mg and 12 mg (9% and 9%, respectively). Increases in body weight were also observed in schizoaffective trials.

Hyperprolactinemia
As with other atypical antipsychotics that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone.

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. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects. As is common with dopamine D_2 antagonists, prolonged administration of risperidone in rodent carcinogenicity studies resulted in an increase in the incidence of pituitary gland, mammary gland, and endocrine pancreas hyperplasia and/or tumours (see **WARNINGS AND PRECAUTIONS: Carcinogenesis and Mutagenesis**). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. The carcinogenic potential of paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats.

In three placebo-controlled, 6-week, fixed-dose trials with INVEGA® (3, 6, 9, and 12 mg), the proportion of subjects who experienced potentially prolactin-related adverse events was similar for the placebo (1%) and INVEGA® (1–2%) groups.

Gastrointestinal
Potential for Gastrointestinal Obstruction
Because the INVEGA® tablet is nondeformable and does not appreciably change in shape in the GI tract, INVEGA® should 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 pseudo-obstruction, or Meckel's diverticulum) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Due to the controlled-release design of the tablet, INVEGA® should only be used in patients who are able to swallow the tablet whole (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

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.

Genitourinary
Priapism
Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during post-marketing surveillance (see **ADVERSE**

REACTIONS, Post-Market Adverse Drug Reactions). This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Leukopenia, Neutropenia, and Agranulocytosis Class Effect

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including paliperidone. Granulocytopenia and agranulocytosis have also been reported. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting INVEGA® and then periodically throughout treatment.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of INVEGA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 x 10^9/L) should discontinue INVEGA® and have their WBC counts followed until recovery (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Venous Thromboembolism

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs including INVEGA® in case reports and/or observational studies. When prescribing INVEGA® all possible risk factors for VTE should be identified and preventive measures undertaken.

Hepatic/Biliary/Pancreatic

Paliperidone is not extensively metabolized in the liver. In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of unbound paliperidone were similar to those of healthy subjects. No dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment is unknown.

Neurologic

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including paliperidone.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular blood pressure, tachycardia, cardiac arrhythmias, and diaphoresis). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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. 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 including INVEGA®, 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 requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

Tardive Dyskinesia (TD)
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD. It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. However, antipsychotic treatment itself may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown.

In view of these considerations, INVEGA® should be prescribed in a manner that is most likely to minimize the risk of TD. As with any antipsychotic, INVEGA® should generally be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of TD develop during treatment with INVEGA®, withdrawal of the drug should be considered. However, some patients may require treatment with INVEGA® despite the presence of the syndrome.

Potential Effect on Cognitive and Motor Performance
Somnolence, sedation and blurred vision were reported in subjects treated with INVEGA® (see **ADVERSE REACTIONS**). Antipsychotics, including INVEGA®, have the potential to impair judgment, thinking, or motor skills and may have visual effects (e.g., blurred vision). 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.

Seizures
Antipsychotic drugs are known to lower the seizure threshold. During premarketing clinical trials (three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), the number of reports of seizures was similar between subjects treated with INVEGA® (3, 6, 9, 12 mg, 0.22%) and subjects treated with placebo (0.25%). 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.

Parkinson's Disease and Dementia with Lewy Bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotic drugs, including INVEGA®, to patients with Parkinson's disease or dementia with Lewy bodies (DLB) since both groups may be at increased risk of neuroleptic malignant syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Ophthalmologic
Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as INVEGA® ~~®~~ (see **ADVERSE REACTIONS — Post-Market Adverse Drug Reactions**).

This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Psychiatric
Suicide
The possibility of suicide or attempted suicide is inherent in psychosis, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Renal
The dose should be reduced in patients with moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION**). The disposition of paliperidone was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment corresponding to an average increase in exposure (AUC_{inf}) of 1.5-fold, 2.6-fold, and 4.8-fold, respectively, compared to healthy subjects. The mean terminal elimination half-life of paliperidone was 24, 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). INVEGA® has not been studied in subjects with CrCl < 10mL/min.

Special Populations

Pregnant Women:

Teratogenic Effects

The safety of INVEGA® during human pregnancy has not been established. No teratogenic effect was noted in any animal study. Laboratory animals treated with a high dose of paliperidone showed a slight increase in fetal deaths. This high dose was toxic to the mothers. The offspring were not affected at exposures 20- to 34-fold the maximum human exposure.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

INVEGA® should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus. The effect of INVEGA® on labour and delivery in humans is unknown.

Nursing Women: In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Patients should be advised not to breast-feed an infant if they are taking INVEGA®.

Pediatrics (< 18 years of age): The safety and efficacy of INVEGA® in children under the age of 18 years have not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

Although no head-to-head clinical trials designed to compare adolescents to adults were conducted, data from one 6-week, placebo-controlled study in adolescent (ages 12-17 years) patients with schizophrenia (n=201) were compared to those of the adult 6-week, placebo-controlled trials in schizophrenia (n=1205). The results suggested a qualitatively similar adverse event profile to that characterised in adult patients, with a higher incidence of treatment-emergent adverse events (TEAEs) related to somnolence, EPS-related events and weight increased in adolescents compared to adults (see **ADVERSE REACTIONS**, **Adverse Events in Adolescent Patients (ages 12-17 years)**).

Lactose
INVEGA® 3 mg tablets contain lactose. This should be considered when prescribing to patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

Geriatrics (> 65 years of age): The number of subjects 65 years of age or older exposed to INVEGA® during a placebo-controlled clinical trial in elderly subjects receiving flexible doses (3–12 mg/day) was limited (n=76). In general, the types and frequencies of adverse events reported in these subjects in this study were similar to those reported in the younger population of adult subjects studied in three placebo-controlled, 6-week, fixed-dose trials. Based on the limited data and consistent with general clinical practice, a greater sensitivity of older individuals to adverse events, including cardiac events, cannot be ruled out.

Because elderly subjects may have diminished renal function, dose adjustments may be required according to their renal function status (see **Renal** above and **DOSAGE AND ADMINISTRATION**).

Use in Geriatric Patients with Dementia
Overall Mortality
In a meta-analysis of 13 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotic drugs had an increased risk of mortality compared to placebo. INVEGA® is not indicated for the treatment of elderly patients with dementia.

Cerebrovascular Adverse Events (CVAEs) in Elderly Patients with Dementia
In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo. INVEGA® is not indicated for the treatment of elderly patients with dementia.

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Short-Term, Placebo-Controlled Studies
Five studies have been conducted in adult patients with schizophrenia and related psychotic disorders. The information presented in this section was derived from two sets of pooled data:

1. Three placebo-controlled, 6-week, fixed-dose studies conducted in non-elderly (mean age 38 years) patients with schizophrenia. The doses studied among these three trials included 3, 6, 9, 12, and 15 mg/day (see ***Product Monograph Part II*: CLINICAL TRIALS**).
2. Two placebo-controlled, 6-week studies, including one two-dose, parallel-group study and one flexible-dose study, in patients with related psychotic disorders (DSM-IV diagnosis of schizoaffective disorder). In one trial 206 subjects were assigned to one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg (n=108) or 12 mg with the option to reduce to 9 mg (n=98) once daily. In the other study, 214 subjects received flexible doses of INVEGA® (3–12 mg once daily) (see ***Product Monograph Part II*: CLINICAL TRIALS**).

Body systems and adverse event/adverse reaction terms are based on the MedDRA dictionary.

Adverse Events Associated with Discontinuation of Treatment
In the three fixed-dose short-term schizophrenia studies, overall, there was no difference in the incidence of discontinuation due to adverse events between patients who received INVEGA® (5%) and placebo-treated patients (5%). The types of adverse events that led to discontinuation were similar between patients treated with INVEGA® and placebo-treated patients, except for Nervous System Disorders (2% and 0%, respectively) and Gastrointestinal Disorders (1% and 0%, respectively) which were of greater incidence among patients treated with INVEGA® than placebo-treated patients, and Psychiatric Disorders which were of greater incidence among placebo-treated patients than patients treated with INVEGA® (3% and 1%, respectively). The pattern of adverse events observed in the schizoaffective trials were similar to those observed in schizophrenia trials.

Commonly Observed Adverse Drug Reactions
Table 1.1 enumerates all treatment-emergent adverse events, regardless of causality, reported at an incidence of ≥ 1% of adult patients treated with INVEGA® in the three fixed-dose short-term schizophrenia studies, and for which the incidence in patients treated with INVEGA® was greater than the incidence in patients treated with placebo.

The most common adverse events (incidence of ≥5% and paliperidone incidence at least twice the rate of placebo) in subjects treated with INVEGA® included: tachycardia (7%; placebo 3%), and extrapyramidal disorder (5%; placebo 2%).

Table 1.1: Treatment-Emergent Adverse Events Reported by ≥ 1% of INVEGA® –treated Adult Subjects with Schizophrenia in Three Short-term, Fixed Dose Placebo-Controlled Clinical Trials[a]. (Safety Analysis Set)

		INVEGA®			
	Placebo	3 mg	6 mg	9 mg	12 mg
Body System or Organ Class	(N=355)	(N=127)	(N=235)	(N=246)	(N=242)
Dictionary-derived Term	%	%	%	%	%
Total percentage of subjects with adverse events	66	72	66	70	76

Table 1.1: Treatment-Emergent Adverse Events Reported by ≥ 1% of INVEGA® –treated Adult Subjects with Schizophrenia in Three Short-term, Fixed Dose Placebo-Controlled Clinical Trials[a]. (Safety Analysis Set)

		INVEGA®			
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)
Dictionary-derived Term	%	%	%	%	%
Cardiac disorders					
Atrioventricular block first degree	1	2	0	2	1
Bradycardia	1	0	1	1	2
Bundle branch block	2	3	1	3	<1
Palpitations	0	2	1	0	1
Sinus arrhythmia	0	2	1	1	<1
Sinus tachycardia	4	9	4	4	7
Tachycardia	3	2	7	7	7
Eye disorders					
Dry eye	0	2	0	<1	<1
Oculogyration	0	0	0	2	0
Vision blurred	1	1	<1	0	2
Gastrointestinal disorders					
Abdominal pain	1	0	2	1	1
Abdominal pain upper	1	1	3	2	2
Diarrhea	2	1	1	1	2
Dry mouth	1	2	3	1	3
Dyspepsia	4	2	3	2	5
Nausea	5	6	4	4	4
Salivary hypersecretion	<1	0	<1	1	4
Stomach discomfort	<1	2	1	<1	1
Toothache	1	2	2	2	2
Vomiting	5	2	3	4	5
General disorders and administration site conditions					
Asthenia	1	2	<1	2	2
Fatigue	1	2	1	2	2
Pyrexia	1	1	<1	2	2
Infections and infestations					
Bronchitis	<1	0	1	<1	1
Nasopharyngitis	3	3	2	2	2
Rhinitis	<1	0	1	0	<1
Upper respiratory tract infection	1	1	1	1	1
Viral infection	<1	0	<1	1	1
Injury, poisoning and procedural complications					
Fall	<1	0	1	0	0
Investigations					

Table 1.1: Treatment-Emergent Adverse Events Reported by ≥ 1% of INVEGA® –treated Adult Subjects with Schizophrenia in Three Short-term, Fixed Dose Placebo-Controlled Clinical Trials[a]. (Safety Analysis Set)

		INVEGA®			
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)
Dictionary-derived Term	%	%	%	%	%
Alanine aminotransferase increased	1	1	2	1	1
Blood creatine phosphokinase increased	1	1	2	0	<1
Blood insulin increased	1	2	1	1	<1
Blood pressure increased	1	2	<1	<1	1
Blood triglycerides increased	<1	2	<1	0	0
Electrocardiogram QT corrected interval prolonged	3	3	4	3	5
Electrocardiogram T wave abnormal	1	2	1	2	1
Electrocardiogram T wave inversion	1	0	<1	1	1
Electrocardiogram abnormal	0	0	0	2	1
Heart rate increased	1	3	1	<1	1
Insulin C-peptide increased	1	2	1	1	0
Weight decreased	1	2	0	0	0
Weight increased	1	1	0	2	2
Metabolism and nutrition disorders					
Decreased appetite	0	2	<1	<1	1
Increased appetite	<1	2	0	1	1
Musculoskeletal and connective tissue disorders					
Arthralgia	1	0	2	1	0
Back pain	1	1	1	1	2
Muscle rigidity	0	1	0	1	<1
Neck pain	<1	0	0	0	1
Pain in extremity	1	0	1	0	2
Shoulder pain	0	1	1	1	1
Nervous system disorders					
Akathisia	4	4	3	8	10
Dizziness	4	6	5	4	5
Dyskinesia	1	0	<1	<1	2
Dystonia	1	1	1	4	4
Extrapyramidal disorder	2	5	2	7	7
Headache	12	11	12	14	14
Hypertonia	1	2	1	4	3
Parkinsonism	0	0	<1	2	1
Sedation	4	1	5	3	6
Somnolence	3	5	3	7	5
Syncope	<1	1	1	1	<1
Tremor	3	3	3	4	3
Psychiatric disorders					
Aggression	1	2	<1	1	1
Anxiety	8	9	7	6	5

Table 1.1: Treatment-Emergent Adverse Events Reported by ≥ 1% of INVEGA® –treated Adult Subjects with Schizophrenia in Three Short-term, Fixed Dose Placebo-Controlled Clinical Trials[a]. (Safety Analysis Set)

		INVEGA®			
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)
Dictionary-derived Term	%	%	%	%	%
Depression	<1	0	1	<1	<1
Nightmare	0	0	<1	1	<1
Suicidal ideation	1	2	1	<1	<1
Respiratory, thoracic and mediastinal disorders					
Cough	1	3	2	3	2
Nasal congestion	1	1	1	1	1
Skin and subcutaneous tissue disorders					
Pruritus	1	0	1	1	0
Vascular disorders					
Hypotension	<1	2	<1	1	1
Orthostatic hypotension	1	2	1	2	4

[a] Table includes adverse events reported in 1% or more of subjects in any of the INVEGA® dose groups and which occurred at a greater incidence than in the placebo group; cut-off criteria (incidence ≥ 1% and ≥ placebo) are based on percentages after rounding.

The adverse reactions, where a causal relationship is suspected between the drug and the reported event, that occurred in 2% or more of subjects treated with INVEGA® and for which the incidence in INVEGA®-treated subjects was greater than the incidence in subjects treated with placebo specific to schizoaffective trials were constipation, myalgia, bradykinesia, drooling, dysarthria, restlessness, sleep disorder, and pharyngolaryngeal pain.

Dose-Related Adverse Reactions

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, Parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose. The pattern of adverse reactions observed in schizoaffective trials were similar to those observed in the schizophrenia trial. In schizoaffective trials dysarthria, myalgia, nasopharyngitis, rhinitis, cough, and pharyngolaryngeal pain were seen in subjects who received higher doses of INVEGA® compared with subjects who received lower doses.

Elderly

The number of subjects 65 years of age or older exposed to INVEGA® during a placebo-controlled clinical trial in elderly subjects receiving flexible doses (3–12 mg/day) was limited (n=76). In general, the types and frequencies of adverse events reported in these subjects in this study were similar to those reported in the younger population of adult subjects studied in three placebo-controlled, 6-week, fixed-dose trials. Based on the limited data and consistent with general clinical

practice, a greater sensitivity of older individuals to adverse events, including cardiac events, cannot be ruled out.

Extrapyramidal Symptoms (EPS)

Pooled data from three placebo-controlled, 6-week, fixed-dose schizophrenia studies in adult subjects provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score, (2) the Barnes Akathisia Rating Scale global clinical rating score, (3) use of anticholinergic medications to treat emergent EPS, and (4) incidence of spontaneous reports of EPS. For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA® 3 mg and 6 mg doses for any of these EPS measures.

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

	Percentage of Adult Patients				
		INVEGA®			
Scale	Placebo (N=355)	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 at endpoint (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 at endpoint

c: Percent of patients who received anticholinergic medications to treat emergent EPS at any time during the double-blind phase

Similar findings on these parameters were seen in the schizoaffective disorder trials.

Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA EPS Group Term – Schizophrenia Studies

	Percentage of Adult Patients				
		INVEGA®			
EPS Group	Placebo (N=355)	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

Similar findings of EPS-related AEs were observed in schizoaffective disorder trials, with the exception of Parkinsonism (placebo-adjusted rate of 5.6%) and tremor (placebo-adjusted rate of 4.6%) in the overall schizoaffective disorder clinical trial population.

ECG Changes

In the pooled data from three placebo-controlled, 6-week, fixed-dose studies in adult subjects, between-group comparisons revealed no clinically important differences between INVEGA® and placebo in the incidence of ECG parameters outside clinically important limits, with the exception of heart rate. Compared with placebo (23%), a higher percentage of adult subjects treated with INVEGA® (36%, 3, 6, 9, 12 mg) had heart rate values ≥ 100 bpm.

Abnormal Hematologic and Clinical Chemistry Findings

In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects, and in the pooled data from the two additional placebo-controlled, 6-week studies in adult subjects, between-group comparisons revealed no medically important differences between INVEGA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® and placebo in the incidence of discontinuations due to changes in hematology, 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 **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**). In the three fixed-dose, placebo-controlled schizophrenia studies, maximum mean increases of serum prolactin concentrations were generally observed on Day 15 of treatment (first post-baseline measurement), and remained above baseline

levels at study endpoint. The incidence of potentially prolactin-related adverse events was small and similar to that for placebo.

Constipation:
Patients should be advised of the risk of severe constipation during INVEGA® treatment, and they should tell their doctor if constipation occurs or worsens, since they may need medical intervention.

Clinical Trial Adverse Reactions in Adult Short-Term, Placebo-Controlled, Fixed-Dose Studies

The following adverse reactions, where a causal relationship is suspected between the drug and the reported event, were reported in patients treated with INVEGA® (n=1270) in the five placebo-controlled, 6-week, double-blind, fixed-dose clinical trials in patients with schizophrenia and schizoaffective disorder. The following terms and frequencies were applied: *very common* (≥ 10%), *common (frequent)* (≥ 1% to < 10%), *uncommon (infrequent)* (≥ 0.1% to < 1%), *rare* (≥ 0.01% to < 0.1%), and *very rare* (< 0.01%). The majority of adverse reactions were mild to moderate in severity.

Cardiac disorders: *common:* atrioventricular block first degree, bradycardia, sinus tachycardia, tachycardia, bundle branch block; *uncommon:* palpitations, sinus arrhythmia

Eye disorders: *uncommon:* oculogyration, vision blurred

Gastrointestinal disorders: *common:* abdominal pain upper, constipation, dry mouth, dyspepsia, nausea, salivary hypersecretion, stomach discomfort, vomiting; *uncommon:* abdominal discomfort; *rare:* small intestine obstruction

General disorders: *common:* asthenia, fatigue; *rare:* edema

Immune system disorders: *rare:* anaphylactic reaction

Investigations: *common*: weight increased; *uncommon:* electrocardiogram abnormal

Infections and infestations: *common:* nasopharyngitis, upper respiratory tract infection; *uncommon:* rhinitis

Musculoskeletal and connective tissue disorders: *common:* back pain; *uncommon:* muscle rigidity, myalgia; *rare:* muscle twitching

Nervous system disorders: *very common:* headache; *common:* akathisia, dizziness, dystonia, extrapyramidal disorder, hypertonia, sedation, somnolence, tremor; *uncommon:* bradykinesia, dizziness postural, drooling, dysarthria, dyskinesia, grand mal convulsion, lethargy, Parkinsonism, syncope; *rare:* Parkinsonism gait

Psychiatric disorders: *uncommon:* nightmare, restlessness, sleep disorder

Reproductive system and breast disorders: *uncommon:* amenorrhea, breast discharge, erectile dysfunction, galactorrhea; *rare:* breast engorgement, breast pain, gynecomastia, menstruation irregular

Respiratory, thoracic and mediastinal disorders: *common:* cough; *uncommon:* pharyngolaryngeal pain

Vascular disorders: *common:* orthostatic hypotension; *uncommon:* hypotension; *rare:* ischemia

Adverse Events in a Long-Term, Placebo-Controlled Study

The safety of INVEGA® was also evaluated in a longer-term trial in adults with schizophrenia (see ***Product Monograph Part II***: **CLINICAL TRIALS**). In general, the types, frequencies, and severities of adverse events reported during the initial 14-week open-label phase of this study were comparable to those reported in the 6-week, placebo-controlled, fixed-dose studies. The adverse events reported during the longer-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase, but occurred at generally lower frequencies.

Adverse Events in Adolescent Patients (ages 12-17 years)

The safety and efficacy of INVEGA® in children under the age of 18 have not been established and its use is not recommended (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

The same adverse events described above for adults should be considered for children and adolescents, including those described in the **WARNINGS AND PRECAUTIONS** section (e.g., hyperprolactinemia, hyperglycemia, etc).

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Although no head-to-head clinical trials designed to compare adolescents to adults were conducted, data from one 6-week, placebo-controlled study in adolescent (ages 12-17 years) patients with schizophrenia (n=201) were compared to those of the pooled adult 6-week, placebo-controlled trials in schizophrenia (n=1205).

The results of the trial in adolescents suggested a qualitatively similar adverse event profile to that characterised in adult patients, with a higher incidence of treatment-emergent adverse events (TEAEs) related to somnolence, EPS-related events and weight increased in adolescents compared to adults.

Somnolence: Somnolence was a dose-related event during INVEGA treatment in adolescents as observed also in adults. The incidence of somnolence-related TEAEs (somnolence, sedation, hypersomnia and lethargy) in the INVEGA combined groups was 16.7% (versus 3.9% in placebo) in adolescents compared to 9% (versus 7% in placebo) in adults.

EPS-Related Events:

EPS-related adverse events in the adolescent schizophrenia studies showed a dose-related pattern as observed also in the adult studies. There were notably higher incidences of dystonia, hyperkinesia, tremor, dyskinesia and parkinsonism in the adolescent population as compared to the adult studies.

Weight Gain:

In a 6-week, double-blind, placebo-controlled study in adolescent (ages 12-17 years) patients with schizophrenia, a higher percentage of INVEGA®-treated patients in the dose range of 1.5-12

mg/day (10%) had an increase in body weight of ≥ 7% from baseline compared with placebo-treated subjects (2%).

In an open-label long-term study in adolescent (ages 12-18 years) patients with schizophrenia (n=282, median duration of INVEGA® treatment of 182 days, 53% with treatment duration of 182 days or more) the proportion of total patients treated with INVEGA® with an increase in body weight of ≥ 7% from baseline was 33%. Weight gain in the open-label longer-term study was also assessed against that expected with normal growth in this population based on age and gender. An increase from baseline of at least 0.5 standard deviation in BMI was used as a clinically relevant measure of changes in weight relative to normative data; 17.4% of the patients in the study met this criterion.

There are limited data from one placebo-controlled trial in adolescents and the majority of patients had received treatment with other antipsychotic medications prior to inclusion in this study. Therefore, these data cannot be considered entirely predictive of the effects of paliperidone ER on metabolic parameters during use in adolescents with schizophrenia. Published studies have demonstrated that adverse effects of atypical antipsychotic drugs on weight, glucose and lipid metabolism can be greater in antipsychotic-naïve pediatric and adolescent patients than in patients who have been treated previously with antipsychotic drugs.

Other Clinical Trial Adverse Drug Reactions Reported with Paliperidone and Risperidone

Paliperidone is the active metabolite of risperidone. Therefore, the adverse reaction profiles of both the oral and injectable formulations of paliperidone are relevant to one another and, also, to risperidone. In addition to the above adverse reactions, the following adverse reactions have been noted with the use of paliperidone and/or risperidone products and can be expected to occur with both the oral and injectable formulations of paliperidone.

The following ADRs were reported with paliperidone and /or risperidone by ≥2% of paliperidone-treated subjects in the pooled clinical trial database:

Psychiatric disorders: Insomnia (includes initial insomnia, middle insomnia)

Nervous system disorders: Akathisia (includes hyperkinesia, restless legs syndrome, restlessness), Dystonia (includes blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus), Parkinsonism (akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness)

Gastrointestinal disorders: Abdominal discomfort

Musculoskeletal and connective tissue disorders: Musculoskeletal pain

The following ADRs were reported with paliperidone and /or risperidone by <2% of paliperidone-treated subjects in the pooled clinical trial database:

Infections and infestations: Acarodermatitis, Cellulitis, Cystitis, Ear infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Tonsillitis, Urinary tract infection

Blood and lymphatic system disorders: Anemia, Eosinophil count increased , Hematocrit decreased, Neutropenia, White blood cell count decreased

Immune system disorders: Hypersensitivity

Endocrine disorders: Glucose urine present, Hyperprolactinemia

Metabolism and nutritional disorders: Polydipsia, Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycemia, Weight decreased, Hyperinsulinaemia

Psychiatric disorders: Agitation, Anorgasmia, Blunted effect, Confusional state, Libido decreased

Nervous system disorders: Balance disorder, Cerebrovascular accident, Cerebrovascular disorder, Convulsion (includes grand mal convulsion), Coordination abnormal, Depressed level of consciousness, Diabetic coma, Disturbance in attention, Dizziness postural, Dyskinesia (includes athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus), Head titubation, Hypoesthesia, Loss of consciousness, Neuroleptic malignant syndrome, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia, Unresponsive to stimuli

Eye disorders: Conjunctivitis, Dry eye, Lacrimation increased, Photophobia, Eye movement disorder, Eye infection, Eye rolling, Glaucoma, Ocular hyperaemia

Ear and labyrinth disorders: Ear pain, Tinnitus, Vertigo

Cardiac disorders: Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations, Postural orthostatic tachycardia syndrome

Vascular disorders: Flushing, Hypertension, Ischemia

Respiratory, thoracic and medistinal disorders: Cough, Dyspnea, Epistaxis, Hyperventilation, Nasal congestion, Pharyngolaryngeal pain, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory tract congestion, Wheezing, Dysphonia

Gastrointestinal disorders: Cheilitis, Dysphagia, Fecal incontinence, Fecaloma, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue, Toothache

Hepatobiliary disorders: Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased

Skin and subcutaneous tissue disorders: Acne, Dry skin, Drug eruption, Hyperkeratosis, Eczema, Erythema, Pruritus, Rash, Seborrheic dermatitis, Skin discolouration, Urticaria

Musculoskeletal and connective tissue disorders: Arthralgia, Back pain, Blood creatine phosphokinase increased, Joint stiffness, Joint swelling, Muscle spasms, Muscular weakness, Neck pain, Posture abnormal, Rhabdomyolysis

Renal and urinary disorders: Dysuria, Pollakiuria, Urinary incontinence

Reproductive system and breast disorders: Breast discharge, Breast discomfort, Breast enlargement, Breast engorgement, Breast swelling, Ejaculation disorder, Erectile dysfunction, Gynacomastia, Menstruation delayed, Menstrual disorder (includes menstruation irregular, oligomenorrhea), Sexual disfunction, Vaginal discharge

General disorders: Body temperature increased, Body temperature decreased, Chest discomfort, Chills, Drug withdrawal syndrome, Face edema, Gait abnormal, Edema (includes generalized edema, edema peripheral, pitting edema), Induration, Malaise, Pyrexia, Thirst

Injury, poisoning and procedural complications: Fall

Post-Market Adverse Drug Reactions

Adverse events first identified as ADRs during post-marketing experience with INVEGA® are included in Table 1.2. The frequencies are provided according to the following convention:

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

Table 1.2: Adverse Drug Reactions Identified During Post-Marketing Experience with INVEGA® by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia
Endocrine disorders	
Not known	Inappropriate antidiuretic hormone syndrome
Metabolism and nutrition disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia
Not known	Water intoxication
Psychiatric disorders	
Very rare	Mania
Nervous system disorders	
Very rare	Dysgeusia
Eye disorders	
Not known	Floppy iris syndrome
Cardiac disorders	
Very rare	Atrial fibrillation
Vascular disorders	
Very rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal disorders	
Very rare	Pancreatitis, ileus
Hepatobiliary disorders	
Not known	Jaundice
Skin and subcutaneous tissue disorders	
Rare	Angioedema
Very rare	Alopecia
Renal and urinary disorders	
Very rare	Urinary retention
Pregnancy, puerperium and perinatal conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	
Very rare	Priapism
General disorders	
Very rare	Hypothermia

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including paliperidone. Granulocytopenia and agranulocytosis have also been reported (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Safety Information Reported with Risperidone

Paliperidone is the major active metabolite of risperidone. The release profile and pharmacokinetic characteristics of INVEGA® are considerably different than those observed with oral immediate-release risperidone formulations (see **ACTION AND CLINICAL PHARMACOLOGY**); however, the receptor binding profile of paliperidone is very similar to that of the parent compound. Safety information reported with risperidone in clinical trials and post-marketing experience that may be relevant to INVEGA® can be found in local labelling for risperidone.

DRUG INTERACTIONS

Drug-Drug Interactions

Caution is advised when prescribing INVEGA® with drugs known to prolong the QT interval.

Potential for INVEGA® to Affect Other Drugs

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

A population pharmacokinetic analysis to evaluate the influence of predicted CYP2D6 phenotype on exposure indicated that no adjustment in the paliperidone dose on the basis of predicted phenotype is warranted.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No in vivo data are available and the clinical relevance of this with respect to P-gp mediated transport of other drugs is unknown.

Given the primary CNS effects of paliperidone (see **ADVERSE REACTIONS**), INVEGA® should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension (see **WARNINGS AND PRECAUTIONS, Cardiovascular**), an additive effect may be observed when INVEGA® is administered with other therapeutic agents that have this potential.

Pharmacokinetic interaction between INVEGA® and lithium is unlikely.

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

Potential for Other Drugs to Affect INVEGA®

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 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

In an interaction study in healthy subjects in which INVEGA® was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Carbamazepine and other potent CYP3A4 inducers:
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. As is typical of CYP3A4 inducers, carbamazepine is also a P-glycoprotein (P-gp) inducer. Although in-vitro studies have shown that paliperidone is a substrate of both P-gp and CYP3A4, the relative contributions of P-gp and CYP3A4 to changes in the pharmacokinetic parameters are unclear.

On initiation of carbamazepine, the dose of INVEGA® should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® should be re-evaluated and decreased if necessary. Until more data are available, these recommendations should be extended to other potent CYP3A4 inducers and/or P-glycoprotein upregulators.

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

Co-administration of a single dose of INVEGA® 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. If valproate is co-administered with INVEGA®, following initiation of treatment and clinical reassessment, a dosage reduction for INVEGA® may be considered.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

Concomitant Use of INVEGA® with Risperidone
There are no systematically collected safety data to specifically address concomitant use of INVEGA® with risperidone, paliperidone palmitate or other antipsychotics. Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA® is co-administered with risperidone or paliperidone palmitate.

Drug-Food Interactions

Following administration of a single 12 mg paliperidone extended-release tablet to healthy ambulatory subjects with a standard high-fat/high-caloric meal, the mean C_{max} and AUC values of paliperidone increased by 60% and 54%, respectively, compared with administration under fasting conditions. Although the presence or absence of food at the time of administration of INVEGA® may increase or decrease exposure to paliperidone, these changes are not considered clinically relevant. Clinical trials establishing the safety and efficacy of INVEGA® were carried out in subjects without regard to the timing of meals.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Smoking

No dosage adjustment is recommended based on smoking status. Based on in vitro studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Consistent with these in vitro results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- There are no systematically collected safety data to specifically address concomitant use of INVEGA® with risperidone, paliperidone palmitate or other antipsychotics. Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA® is co-administered with risperidone or paliperidone palmitate.
- INVEGA® should be administered orally once daily, preferably in the morning, without regard to meals. Clinical trials establishing the safety and efficacy of INVEGA® were carried out in patients without regard to food intake. INVEGA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool.

Recommended Dose and Dosage Adjustment

Adult

The recommended starting and target dose of INVEGA® is 6 mg once daily. No initial dose titration is required. However, in some cases a lower dose of 3 mg/day may be sufficient.

In clinical trials a dose range of 3 to 12 mg/day was studied and while efficacy was observed across all doses, there was a dose-related increase in adverse effects (see **ADVERSE REACTIONS** and ***Product Monograph Part II*: CLINICAL TRIALS**).

Dose adjustments should be made after clinical reassessment and generally should occur at intervals of more than 5 days. When dose adjustments are indicated, small increments/decrements of 3 mg/day are recommended, up to a maximum of 12 mg/day.

Patients with Hepatic Impairment

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

Patients with Renal Impairment

For patients with mild renal impairment (creatinine clearance = 50 to < 80 mL/min), the maximum recommended initial dose is 3 mg once daily. The dose may be increased to a maxiumum of 6 mg once daily based on clinical response and tolerability.

For patients with moderate to severe renal impairment (creatinine clearance = 10 to < 50 mL/min), the recommended initial dose of INVEGA® is 3 mg every other day, which may then be increased to 3 mg once daily after clinical reassessment.

As INVEGA® has not been studied in patients with creatinine clearance < 10 mL/min, use is not recommended in such patients.

Elderly
Dosing recommendations for elderly patients with normal renal function (≥ 80 mL/min) are the same as for adults with normal renal function. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see *Patients with Renal Impairment* above).

Pediatrics
Safety and effectiveness of INVEGA® in patients < 18 years of age have not been established and its use is not recommended.

Other Special Populations
No dose adjustment for INVEGA® is recommended based on gender, race, or smoking status.

OVERDOSAGE

Symptoms
In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsades de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose. In the case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment
Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. Gastric lavage (after intubation if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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.

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.

Pharmacodynamics

Formulation Characteristics

The controlled rate of release of paliperidone from the extended-release technology results in a pharmacokinetic profile with a slower rate of absorption than an immediate-release formulation, leading to an ascending plasma concentration profile over 24 hours on Day 1 of dosing. In studies with paliperidone and risperidone, an ascending profile paliperidone formulation concept demonstrated a differential effect on orthostatic hypotension compared to a flat or immediate-release profile. In one study (n=27), paliperidone administered to achieve an ascending profile with a total dose of 4 mg compared to a lower dose (2 mg) of immediate release risperidone resulted in lower incidences of orthostatic hypotension (32% vs. 46%). The extended-release profile showed a lower incidence of orthostatic hypotension and allows for initiation of treatment at an effective dose without titration, as is the typical practice with antipsychotic drugs to address initial orthostatic intolerance.

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 available dose range. The terminal elimination half-life of paliperidone, regardless of formulation, is approximately 23 hours.

Steady-state concentrations of paliperidone are attained within 4–5 days of dosing in most subjects. The release characteristics of INVEGA® result in minimal peak-trough fluctuations as compared to those observed with immediate-release risperidone. In a study comparing the steady-state pharmacokinetics following once-daily administration of 12 mg paliperidone (administered as extended-release tablets) with 4 mg immediate-release risperidone in schizophrenic subjects, the fluctuation indexes were 38% for paliperidone extended-release compared to 125% for risperidone immediate-release (Figure 1.1).

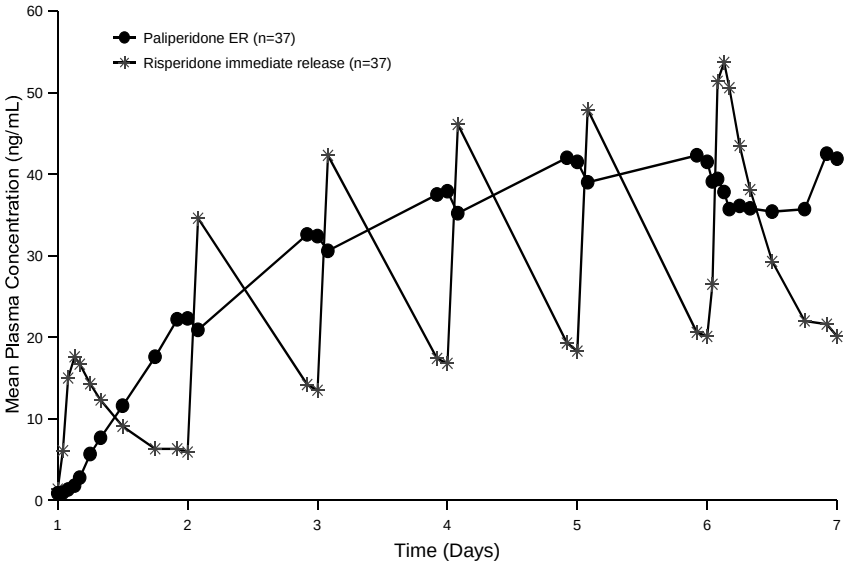


Figure 1.1 Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg extended-release tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release administered as 2 mg once daily on Day 1 and 4 mg once daily on Days 2 to 6 (paliperidone + risperidone concentrations are represented).

Following administration of INVEGA®, 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 from INVEGA® (i.e., the extended-release formulation) is 28%. It is thought that this is due to a higher fraction of paliperidone being released in the colon, where absorption is lower.

Following administration of a single 12 mg paliperidone extended-release tablet to healthy ambulatory subjects with a standard high-fat/high-caloric meal, the mean C_{max} and AUC values of paliperidone increased by 60% and 54%, respectively, compared with administration under fasting conditions. Although the presence or absence of food at the time of INVEGA® administration may increase or decrease exposure to paliperidone, these changes are not considered clinically relevant. Clinical trials establishing the safety and efficacy of INVEGA® were carried out in subjects without regard to the timing of meals (see **DOSAGE AND ADMINISTRATION**).

Distribution: Paliperidone is rapidly distributed. The apparent volume of distribution is 487 L. The plasma protein binding of paliperidone is 74%. It binds primarily to 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 Excretion: The following data are based on a human mass balance study using oral solution of ^{14}C-paliperidone, a dosage form which has approximately 100% bioavailability. One week following administration of a single 1 mg dose of oral solution ^{14}C-paliperidone, 59% of the administered dose was excreted unchanged into urine, indicating that paliperidone is not

extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces.

Four metabolic pathways have been identified in vivo, of which each accounted for no more than 6.5% of the administered 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 very 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 discernible 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. Paliperidone is not expected to have enzyme-inducing properties.

Special Populations and Conditions

Geriatrics: No dosage adjustment is recommended based on age alone. However, because elderly subjects may have diminished renal function, dose adjustments may be required according to their renal function status (see **Renal Insufficiency** below). 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 discernible effect of age in the population pharmacokinetic analysis involving schizophrenia subjects after correction for age-related decreases in CrCl.

Gender: No dosage adjustment is recommended based on 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, as a population pharmacokinetics evaluation revealed no evidence of clinically significant gender-related differences in the pharmacokinetics of paliperidone following INVEGA® administration after correction for lean body mass and creatinine clearance.

Race: No dosage adjustment is recommended based on race. Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA® administration. No differences were observed in a pharmacokinetics study conducted in Japanese and Caucasian subjects.

Hepatic Insufficiency: Paliperidone is not extensively metabolized in the liver. In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of unbound paliperidone were similar to those of healthy subjects. No dose adjustment is required in patients with mild to moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

Renal Insufficiency: The dose should be reduced in patients with mild and moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION**). The disposition of paliperidone was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (CrCl = 50 to < 80 mL/min), 64%

in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥80 mL/min). INVEGA® has not been studied in subjects with CrCl < 10 mL/min.

Smoking Status: No dosage adjustment is recommended based on smoking status. Based on in vitro studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Consistent with these in vitro results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

STORAGE AND STABILITY

INVEGA® should be stored at 15–30ºC. Protect from moisture.

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

INVEGA® Extended-release Tablets contain paliperidone as the medicinal ingredient and are available in 3 mg, 6 mg, 9 mg and 12 mg‡ dosage strengths as follows:

3 mg: A white capsule-shaped tablet printed with “PAL 3”. Orifices may or may not be visible. Bottles of 30 tablets.

6 mg: A beige capsule-shaped tablet printed with “PAL 6”. Orifices may or may not be visible. Bottles of 30 tablets.

9 mg: A pink capsule-shaped tablet printed with “PAL 9”. Orifices may or may not be visible. Bottles of 30 tablets.

12 mg‡: A dark-yellow capsule-shaped tabled printed with “PAL 12”. Orifices may or may not be visible.

‡ Not available in Canada

Composition

The following inactive ingredients are common to all tablet strengths: butylated hydroxytoluene, carnauba wax, cellulose acetate, ferric oxide red, ferric oxide yellow, hydroxyethyl cellulose, hypromellose, iron oxide black, polyethylene oxides, polyethylene glycol, propylene glycol, povidone, sodium chloride, stearic acid, and titanium dioxide.

The 3 mg tablets also contain lactose monohydrate and triacetin (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Lactose**).

System Components and Performance

INVEGA® tablets utilize osmotic pressure to deliver 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 semi-permeable, 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 drug release rate from the system is designed to increase with time over a period of approximately 16 to 22 hours due to the drug-concentration gradient incorporated into the two drug layers of INVEGA®. The ascending release rate of INVEGA® allows patients to receive a therapeutically effective dose of paliperidone without the need for dose titration. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool, along with insoluble core components.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

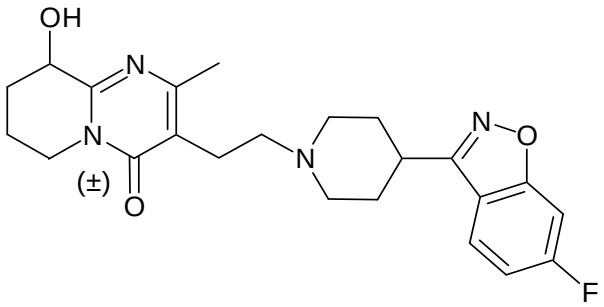
Drug Substance

Proper name: paliperidone

Chemical name: (±)-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

Molecular formula and molecular mass: $C_{23}H_{27}FN_4O_3$, 426.49

Structural formula:



Physicochemical properties: Paliperidone is a white to yellow powder.
Ionization Constant: $pKa_1 = 8.2$
$pKa_2 = 2.6$
Partition Coefficient: log P = 2.39
Melting Point: 172.0 – 190.0°C

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Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; practically insoluble in water, 0.1N NaOH, and hexane; and slightly soluble in N,N-dimethylformamide

CLINICAL TRIALS

Adults

Trials in Schizophrenia

The efficacy of INVEGA® was established in three placebo-controlled, double-blind, 6-week studies in non-elderly (mean age 37 years) patients.

The doses of INVEGA®, which varied across the three studies, ranged from 3 to 15 mg once daily; an active control (olanzapine) was included in the 6-week studies in adults 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. The primary endpoint was decrease in total PANSS scores from baseline to endpoint.

The Clinical Global Impression - Severity (CGI-S) scale was one of the secondary outcomes. The CGI-S is an independent investigator-rated assessment of overall severity of illness.

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

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

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

Table 2.1: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score – Change From Baseline to End Point – LOCF for Each Study and 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)
N	126		123	122	129
Mean baseline	94.1		94.3	93.2	94.6
Mean change	-4.1		-17.9	-17.2	-23.3
P-value (vs. Placebo) [a, b]			<0.001	<0.001	<0.001
R076477-SCH-304	(N=105)		(N=111)		(N=111)
N	105		110		111
Mean baseline	93.6		92.3		94.1
Mean change	-8.0		-15.7		-17.5
P-value (vs. Placebo) [a, b]			0.006		<0.001
R076477-SCH-305	(N=120)	(N=123)		(N=123)	
N	120	123		123	
Mean baseline	93.9	91.6		93.9	
Mean change	-2.8	-15.0		-16.3	
P-value (vs. Placebo) [a, b]		<0.001		<0.001	

[a] Based on ANCOVA model with treatment (placebo and ER OROS paliperidone arms in each protocol) and analysis center as factors, and baseline value as a covariate.

[b] Pairwise comparison: p-values associated with Dunnett's procedure.

In a longer-term, placebo-controlled trial, clinically stable patients with schizophrenia who were being maintained on INVEGA® for 8 weeks (doses ranging from 3 to 15 mg once daily) were then randomized in a double-blind manner to either continue on INVEGA® at their achieved stable dose or to placebo until they experienced a recurrence of schizophrenia symptoms. Patients treated with INVEGA® experienced a significantly longer time to relapse following randomization compared to placebo. An interim analysis performed when 43 recurrence events were reported, allowing for early termination of the study by predefined criteria, showed a significantly longer time to first recurrence in patients treated with INVEGA® compared to placebo (p=0.0053). At the final

analysis, twice as many patients in the placebo group (51.5%) experienced a recurrence event as in the INVEGA® group (22.1%).

Trials in Other Related Psychotic Disorders

Two placebo-controlled, 6-week trials were conducted in non-elderly adult subjects with a DSM-IV diagnosis of schizoaffective disorder. Enrolled subjects had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 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.

In one of these trials, efficacy was assessed in 211 subjects who received flexible doses of INVEGA® (3-12 mg once daily). In the other study, efficacy was assessed in 203 subjects who were assigned to one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg (n=105) or 12 mg with the option to reduce to 9 mg (n=98) once daily. Both studies included subjects who received INVEGA® either as monotherapy [no mood stabilizers and/or antidepressants (55%)] or as an adjunct to mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. INVEGA® was dosed in the morning without regard to meals. Studies were carried out in the United States, Eastern Europe, Russia, and Asia.

Primary efficacy outcome was evaluated using the PANSS. As secondary outcomes, mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D-21) and the Young Mania Rating Scale (YMRS).

The INVEGA® group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) and the higher dose group of INVEGA® in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day) were each superior to placebo in the PANSS. Mean changes from baseline to endpoint were -20.0 and -10.8 for the INVEGA® and placebo groups, respectively, ($p<0.001$) in the flexible dose study and -30.6 and -21.7, for the INVEGA® higher dose group and placebo group, respectively, ($p=0.003$) in the 2 dose-level study. Numerical improvements in the HAM-D-21 and YMRS were also observed. In the lower dose group of the 2 dose-level study (6 mg/day with option to reduce to 3 mg/day), INVEGA® was not significantly different from placebo as measured by the PANSS.

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.

DETAILED PHARMACOLOGY

Preclinical Pharmacodynamics

Paliperidone is the major active metabolite of risperidone and is pharmacologically very similar to the parent compound. In a series of standard in vivo pharmacology tests, paliperidone, its enantiomers and risperidone showed similar effects at closely related doses. In vitro, paliperidone and risperidone (1) shared nearly the same binding affinity for 5-HT_{2A}, D_2, α_1, and α_2 receptors, (2) reversed dopamine-induced suppression of PRL release from anterior pituitary cells, and (3) reduced 5-HT-induced human platelet aggregation.

Paliperidone displays approximately 15 times higher affinity towards 5-HT_{2A} receptors when compared with clozapine and approximately 120 times higher affinity compared with haloperidol. The affinity to D_2 receptors was about 20 times higher compared to clozapine and only 2 to 3 times lower compared with haloperidol. Paliperidone differed from clozapine and haloperidol by the remarkably shallow slope of its D_2 receptor dose occupancy curve.

Similar to risperidone, paliperidone does not interact with cholinergic muscarinic receptors.

Cardiovascular Pharmacology

Paliperidone was devoid of major effects on several electrophysiological parameters in isolated cells and cardiac tissues in vitro, at concentrations matching and slightly exceeding therapeutically achieved plasma levels in man. Paliperidone and risperidone produced similar effects on cardio-hemodynamic parameters. Following administration of paliperidone in awake rats (i.v., s.c.) and dogs (p.o.), and in anesthetized dogs, guinea pigs and rabbits (i.v.) at higher tested dose levels, paliperidone produced cardiovascular effects consisting mainly of increased heart rate, decreased blood pressure, and changes in QT- and PQ-intervals. However, the results from these in vivo studies indicated an absence of cardiac electrophysiological effects, including QTc changes, with paliperidone at doses yielding plasma concentrations slightly in excess of the therapeutic ones in humans.

Preclinical Pharmacokinetics

Paliperidone exhibited species-dependent stereoselectivity in disposition and plasma protein binding. (-)-Paliperidone was more abundant than (+)-paliperidone in plasma of laboratory animals but not in humans. In mice and rats, (+)-paliperidone showed a higher free fraction, while in dogs and humans, the free fraction of (-)-paliperidone was higher than that of (+)-paliperidone.

Paliperidone was shown to distribute to specific brain regions with high density of 5-HT_{2A}- and D_2-receptors and to achieve exposure that was in excess of that in plasma. There was no undue tissue retention of paliperidone except in melanin-containing tissues of pigmented rats. The melanin binding of paliperidone was shown to be reversible.

The major biotransformation routes of paliperidone were similar in laboratory animals and in humans. All metabolites identified in the human mass balance study were also observed in at least one laboratory animal species. All the metabolites that were identified following paliperidone administration in humans were also observed following risperidone administration in humans.

Drug Interactions

Paliperidone at relevant clinical concentrations had no or only marginal inhibitory effect on the major CYP450s including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Paliperidone was shown to be a P-glycoprotein substrate but the influence of any drug-drug interaction with P-glycoprotein at the level of the blood-brain barrier is likely to be modest.

TOXICOLOGY

Paliperidone was tested in an extensive series of toxicity studies. At equal dose levels, the toxicity profile of paliperidone was similar to risperidone in comparative repeat-dose toxicity studies in

mice, rats and dogs. The toxicity profile mainly consisted of findings related to exaggerated pharmacodynamic effects of CNS- and PRL-mediated actions.

In the repeat-dose toxicity studies, NOELs could not be established because signs of exaggerated pharmacology were evident at the lowest dose tested; however, NOAELS were established. Exposure-based safety margins generally were low compared to the systemic exposure at the maximum recommended human dose. However, the main toxicity findings are either species-specific or can be easily assessed in the clinic.

Paliperidone ER tablets containing 15 mg of paliperidone were shown to be well tolerated in the GI tract of dogs in a 3-month repeat-dose toxicity study.

Genotoxicity studies were negative.

Slight pre-implantation loss was noted at the highest dose level (2.5 mg/kg/day for 21 days) in the female fertility study. The estimated exposure at the embryo-fetal NOEL in this study is similar to that attained in humans and the maximum recommended human dose. Since the increase in pre-implantation loss only occurred in the presence of maternal toxicity, this effect is of little relevance in terms of human risk.

The embryo-fetal developmental toxicity study with paliperidone in rabbits showed slight post-implantation loss at the highest dose level (5 mg/kg/day). The embryo-fetal NOAEL in this study yielded systemic exposure 22- to 34-fold higher than in humans at the maximum recommended human dose. These findings are considered to be of little relevance in terms of human risk.

In a 7-week juvenile toxicity study in rats with oral doses of paliperidone of 0.16, 0.63, and 2.5 mg/kg/day, which are 0.12, 0.5, and 1.8 times the maximum human oral exposure of 12 mg/day in adolescents on a mg/m^2 basis, CNS clinical signs and increased serum prolactin levels in both sexes and pseudopregnancy in females were evident at all dose levels, however no effects on growth, sexual maturation, and reproductive performance were observed after cessation of treatment. Oral doses up to 2.5 mg/kg/day did not generally affect neurobehavioral development in males and females, except for an impairment of learning and memory in female rats treated at 2.5 mg/kg/day and thus there was no safety margin. This effect was not observed on repeated daily testing after discontinuation of treatment.

In a 40-week study in juvenile dogs treated with oral risperidone (which is extensively converted to paliperidone) at doses of 0, 0.31, 1.25, and 5 mg/kg/day, sexual maturation was arrested/delayed at all dose levels, but showed evidence of recovery after discontinuation of treatment in both sexes at 0.31 and 1.25 mg/kg/day and males at 5 mg/kg/day. Effects seen include increased serum prolactin levels in both sexes, presumably due to dopamine receptor antagonist activity of risperidone; decreased plasma testosterone levels and sperm counts in males; plasma progesterone undetectable, absence of estrus cycling, low ovary and uterus/cervix weights, absence of active mammary gland development, prominent luteal cells in the ovaries, and endometrial gland hyperplasia in the uterus in females. Reduced body weight gain at all dose levels correlated with reduced long bone growth at 1.25 and 5 mg/kg; however all effects were reversible and 0.31 mg/kg was a NOAEL. Mainly CNS-related clinical signs and increased heart rate at all dose levels were transient and/or reversible.

The carcinogenic potential of paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be of little predictive value to humans.

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PART III: CONSUMER INFORMATION

PrINVEGA®
paliperidone Extended-release Tablets

This leaflet is Part III of a three-part "Product Monograph" published when INVEGA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INVEGA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
INVEGA® belongs to a group of medicines called antipsychotic drugs.

INVEGA® is a prescription medicine used to treat the symptoms of schizophrenia and related psychotic disorders.

The doctor has prescribed INVEGA®, also known as paliperidone, to help relieve the symptoms that are bothering you/the patient you are caring for. Although INVEGA® cannot cure the illness, it can keep the symptoms under control and reduce the risk of relapse as you/the patient you are caring for continues treatment.

Not all people with schizophrenia and related psychotic disorders have the same symptoms. Some of the most common symptoms of schizophrenia and related psychotic disorders may include:

- hallucinations
  - seeing, feeling, hearing, or smelling things that are not there
- delusions
  - believing things that are not true
- paranoia
  - feeing paranoid or not trusting others and feeling very suspicious
- avoiding family and friends and wanting to be alone

Related psychotic disorders may also include:

- mania
  - being very over-active or over-excited
- symptoms of depression
  - feeling sad, hopeless, helpless, tired, or sleeping a lot or not enough.

What it does:
Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how INVEGA® works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:
Do not take/give INVEGA® if you/the patient you are caring for has had an allergic reaction to paliperidone, or a related drug (risperidone), or any of the nonmedicinal ingredients. Symptoms of an allergic reaction may include: itching, skin rash, swelling of the face, lips or tongue, shortness of breath. **If you experience any of these symptoms/if these symptoms are experienced by the patient you are caring for, your doctor/the treating physician should be contacted immediately.**

INVEGA® is not recommended for use in children under 18 years of age.

What the medicinal ingredient is:
Paliperidone

What the nonmedicinal ingredients are:
The following inactive ingredients are common to all tablet strengths: butylated hydroxytoluene, carnauba wax, cellulose acetate, ferric oxide red, ferric oxide yellow, hydroxyethyl cellulose, hypromellose, iron oxide black, polyethylene oxides, polyethylene glycol, propylene glycol, povidone, sodium chloride, stearic acid, and titanium dioxide.
The 3 mg tablets also contain lactose and triacetin.

What dosage forms it comes in:
Tablets: 3 mg, 6 mg, 9 mg and 12 mg‡.

‡ Not available in Canada

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Studies with various medicines of the group to which INVEGA® belongs, have been associated with an increased rate of death when used in elderly patients with dementia. Some of these studies included treatment with a related drug, RISPERDAL (risperidone). INVEGA® is not indicated in elderly patients with dementia.

BEFORE you use INVEGA®, talk to your doctor or pharmacist if you:

- have had serious allergic reactions to other medications, including risperidone
- have a history of stroke, mini-stroke, high cholesterol or high blood pressure
- were previously diagnosed with a condition known as Neuroleptic Malignant Syndrome (high temperature and muscle stiffness) or Tardive Dyskinesia (abnormal movements of the tongue or face). Both of these are conditions caused by antipsychotic drugs.
- have diabetes or are at a risk for diabetes or a family history of diabetes
- are pregnant or planning to become pregnant
- are breast-feeding or planning to breast feed
- have a history of problems with the heart and/or blood vessels;
- have/had a heart disease or heart disease treatment that makes you prone to low blood pressure or feeling dizzy or faint when you stand up from lying or sitting positions

- have/have ever had blackouts or seizures
- have or have had low white blood cell counts in your blood. Let your doctor know right away if you develop a fever or infection while being treated with INVEGA®
- have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reasons, or take oral contraceptives ("The Pill").
- have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or large or small intestine)
- have diseases associated with diarrhea
- have Parkinson's disease or Dementia with Lewy Bodies (DLB)
- are taking or planning to take any other medicines (prescription or over-the-counter)
- drink alcoholic beverages or use drugs
- suffer from lactose intolerance because INVEGA® tablets contain lactose
- are taking RISPERDAL® (risperidone)
- have a history of kidney problems
- have liver problems
- suffer from Alzheimer's disease
- are dehydrated
- exercise strenuously
- have or have had breast cancer;
- have pituitary tumours
- are planning to have an operation on the eye
- are feeling thirsty and unwell

Elderly Patients with Dementia
Studies in elderly patients with dementia have shown that a related drug, RISPERDAL®, taken by itself or with furosemide, is associated with a higher rate of death (see **Serious Warnings and Precautions** box).

Tell your doctor if you are taking a furosemide. Furosemide is a drug which is sometimes used to treat high blood pressure, some heart problems, or to treat swelling of parts of the body caused by the build-up of too much fluid.

In elderly patients with dementia, medicines in the same group as INVEGA® have been associated with side effects including sudden change in mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, slurred speech or vision problems. If any of these should occur, even for a short period of time, seek medical attention right away.

Effects on newborns
In some cases, babies born to a mother taking paliperidone during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

If you are taking blood pressure medication
Low blood pressure can result from using INVEGA® together with medications used to treat high blood pressure. If you need to use both INVEGA® and medications used to reduce blood pressure, consult your doctor.

Other cautions
Very rarely, a state of confusion, reduced consciousness, high fever or stiff muscles might occur. If this should happen, get emergency help right away and tell the doctor that you are receiving INVEGA®.

During long-term treatment, INVEGA® might cause involuntary twitching in the face or other body regions. Should this happen, consult your doctor.

Since medications of this type may interfere with the ability of the body to adjust to heat, it is best to avoid becoming overheated or dehydrated (for example with vigorous exercise or exposure to extreme heat) while taking INVEGA®.

INVEGA® should be used with caution, and only after consultation with your doctor, if you have heart problems, particularly irregular heart rhythm, abnormalities in electrical activity of the heart, or if you are using medications that can change the heart's electrical activity.

Some people experience drowsiness or blurred vision while taking INVEGA®. Do not drive or operate machinery until you know how you respond to INVEGA®.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

It is important for the doctor to have all the above information before prescribing treatment and dosage. This list should be carefully reviewed by you and discussed with the doctor.

INTERACTIONS WITH THIS MEDICATION

Inform all doctors, dentists and pharmacists who are treating you that you are taking INVEGA®. Inform them if you are taking or are planning on taking any other medicine, including prescription, over-the-counter, or natural health products. They will tell you which medicines you can take with INVEGA®.

Since INVEGA® works primarily in the brain, interference with other drugs that work in the brain (including alcohol) could occur. It is recommended that you DO NOT drink alcohol and only take drugs prescribed by your doctor.

Inform your doctor if you start or stop taking any of the following medications:

- Valproate (drugs used to treat seizures, manic-depression and migraines)

- INVEGA® should be used with caution when taking medications that may change the electrical activity of the heart, such as but not restricted to: medicines for malaria, heart rhythm disorders, allergies, other antipsychotics, antidepressants, water tablets or other medicines affecting body salts (sodium, potassium, magnesium)

- Phenothiazines and some heart medications (e.g., medication for high blood pressure, antiarrhythmics, or beta-blockers), as these may interact with INVEGA® to cause your blood pressure to drop too low

- Dopamine agonists, e.g. levodopa (antiparkinsonian agent), may decrease the effect of INVEGA®.

- Carbamazepine (an anticonvulsant) has been shown to decrease the levels of INVEGA® in your blood.

PROPER USE OF THIS MEDICATION

Do not chew, crush or divide the tablets. Swallow INVEGA® tablets whole with water or other liquids.

Take INVEGA® once each day preferably in the morning with or without food.

The INVEGA® tablet does not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

It is very important that you take/give INVEGA® the way the doctor has prescribed it.

The doctor has decided on the best dosage for you/the patient you are caring for based on individual needs. Dosage may be increased or decreased depending on the response.

It is important that you keep taking/giving INVEGA® even after your/the symptoms have improved or disappeared. Do not change or stop taking/giving INVEGA® without consulting the doctor.

DO NOT give INVEGA® to anyone else. The doctor has prescribed it for you/the patient you are caring for.

Usual adult dose:

The usual starting dose is 6 mg once daily.

For patients with impaired kidney function:

Mild impairment: the recommended initial dose is 3 mg once daily; your doctor may later decide to increase the dose to 6 mg once daily.

Moderate to severe impairment: the recommended initial dose is 3 mg every other day; your doctor may later decide to increase the dose to 3 mg once daily

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

One or more of the following signs may occur in an overdose: sleepiness, drowsiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, abnormal heartbeats, rapid heartbeat, reduced consciousness, and excessive trembling or excessive muscle stiffness.

Missed dose:
If you miss a dose, do not take a double dose to make up for a forgotten dose.

If you miss one dose, take your next dose on the day following the missed dose.

If you miss two or more doses, contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, INVEGA® can cause some side effects. These side effects are most likely to be minor and temporary. However, some may be serious and need medical attention. Many of the side effects are dose related, so it is important not to exceed your prescribed dose. Should you experience these symptoms, please consult your doctor.

Very commonly headache, or feeling sleepy or less alert may be experienced.

Common side effects may include: common cold symptoms, sinus infection, difficulty falling or staying asleep, mania, irritability, depression, anxiety, faster heart rate, slowed heart rate, heartbeat irregularities, lack of energy, restlessness, feeling dizzy, stuffy nose, drop in blood pressure upon standing, high blood pressure, stomach ache, dry mouth, itching, increased saliva, being sick (vomiting), diarrhea, uncontrollable movements of the face, eyes or body, trembling, slowness of movement, muscle stiffness or spasm, and increased appetite.

Weight gain has been reported with INVEGA®. Your doctor should check your body weight before starting INVEGA® and continue to monitor it for as long as you are being treated.

Uncommon side effects may include: urinary tract infection, feeling like you have the flu, weight loss, anemia, high blood triglycerides (a fat), nightmares, swelling of legs or other body area, increased liver transaminases in your blood, rash, a restless urge to move parts of your body, fainting, sensation the room is spinning, sensation your heart is racing, variation in heart rate, heart rhythm changes, decreased blood pressure, decreased blood flow, rigid muscles, muscle weakness, and

joint swelling.

INVEGA® can raise your levels of a hormone called "prolactin" (measured with a blood test). Women may experience leakage of fluid or milk from the breast even if they are not pregnant, breast discomfort, or missed or irregular periods, or other problems with your cycle. Men may experience breast swelling/enlargement or difficulty getting or maintaining an erection or other sexual dysfunction.

High blood sugar has been reported. See your doctor if you experience symptoms such as excessive thirst or urination.

Your doctor should take blood tests before starting INVEGA®. They will monitor blood sugar, and the number of infection-fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

In rare cases, the following may happen: low blood sugar, diabetes mellitus or worsening of diabetes, increased cholesterol, loss of consciousness, heartbeat irregularities, joint stiffness, and vaginal discharge.

Lack of bowel muscle movement that causes blockage may occur very rarely.

Side effects where the frequency is not known include glaucoma (increased pressure within the eyeball), and problems with the movement of your eyes**.**

During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you take or have taken INVEGA®. If you need to have cataract surgery, be sure to tell your eye doctor if you take or have taken INVEGA®.

Since paliperidone is a compound resulting from the breakdown of risperidone in the human body, any side effects that may occur after taking risperidone may also occur with INVEGA®.

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Do not be alarmed by this list of possible side effects. You may not experience any of them. If any of these side effects are experienced, they are usually mild and temporary. However, do not hesitate to report undesired side effects to your doctor.

If you have taken INVEGA® in the last three months of your pregnancy and you notice that your newborn baby develops shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems or difficulty in feeding, seek immediate emergency medical attention**.**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Call your doctor or pharmacist		Stop taking drug and seek immediate medical emergency help
		Only if severe	In all cases	
Common	New or worsening constipation		✓	
Uncommon	Skin rash on its own		✓	
	Allergic Reaction: fever, itching, rash, hives, swelling of the face, lips, throat or tongue, difficulty swallowing or breathing, shortness of breath			✓
	Seizure (i.e., loss of consciousness with uncontrolled shaking)			✓
Rare	**Rhabdomyolysis: v**ery dark ("tea coloured") urine, muscle tenderness and/or aching			✓
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains and flu-like symptoms		✓	
	Tardive Dyskinesia: muscle twitching or abnormal movements of the face or tongue		✓	
	Strokes and Transient Ischemic Attacks: sudden change in mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, slurred speech or vision problems, even for a short period of time			✓
Very Rare	A state of confusion, reduced consciousness, high fever, or pronounced muscle stiffness			✓
	Marked changes in body temperature (generally as a result of several factors together including extreme heat or cold)			✓
	Long-lasting (greater than 4 hours in duration) and painful erection of the penis.			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
	Blood Clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		✓	
Unknown	**Inflammation of the pancreas:** severe abdominal pain, fever, nausea, vomiting			✓
	Jaundice: yellowing of the skin and eyes, dark urine			✓
	Life-threatening complications of uncontrolled diabetes such as shortness of breath, confusion and loss of consciousness			✓
	Bruise easily, excessive bleeding		✓	

This is not a complete list of side effects. For any unexpected effects while taking INVEGA®, contact your doctor or pharmacist.

HOW TO STORE IT

Store INVEGA® in its original package.

INVEGA® tablets should be stored between 15–30°C. Protect from moisture.

Keep out of the sight and reach of children.

The expiry date for INVEGA® is printed on the package. Do not use the medicine in the package after this date.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect® (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions, concerns, or the full Product Monograph go to:
www.janssen.com/canada
or contact the manufacturer, Janssen Inc., at:
1-800-567-3331 or 1-800-387-8781

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