

PRODUCT MONOGRAPH

PrINVEGA®* SUSTENNA®*

paliperidone palmitate Prolonged-Release Injectable Suspension,
paliperidone as paliperidone palmitate

Supplied as pre-filled syringes containing 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL, and 150 mg/1.5 mL paliperidone as paliperidone palmitate

Antipsychotic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Nonmedicinal Ingredients
Intramuscular injection	Prolonged-Release Injectable Suspension/supplied as prefilled syringes containing 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL, and 150 mg/1.5 mL paliperidone as paliperidone palmitate	Citric acid monohydrate, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection

INDICATIONS AND CLINICAL USE

INVEGA® SUSTENNA® (paliperidone palmitate) is indicated for the treatment of schizophrenia. In controlled clinical trials, INVEGA® SUSTENNA® 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® SUSTENNA® in children under the age of 18 have not been established.

CONTRAINDICATIONS

INVEGA[®] SUSTENNA[®] is contraindicated in patients who are hypersensitive to paliperidone, risperidone, or to any ingredient in the formulation or component of the container.

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

Administration

Care must be taken to avoid inadvertent injection of INVEGA[®] SUSTENNA[®] into a blood vessel.

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 oral 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 time points during the day. Least square mean changes from baseline in QTcLD were calculated at each scheduled ECG assessment time point 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 ($C_{\max ss} = 113$ ng/mL) was more than 2-fold the exposure predicted for the maximum recommended 150 mg dose of INVEGA[®] SUSTENNA[®] administered in the deltoid muscle (predicted median $C_{\max ss} = 50$ ng/mL).

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.

In the four fixed-dose, double-blind, placebo-controlled studies of INVEGA[®] SUSTENNA[®] in which 1293 subjects received active drug, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the long-term study, in which 849 subjects received INVEGA[®] SUSTENNA[®] no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

Concomitant Use of INVEGA[®] SUSTENNA[®] with Risperidone or Oral Paliperidone

Concomitant use of INVEGA[®] SUSTENNA[®] with oral paliperidone or oral or injectable risperidone has not been studied. Since paliperidone (9-hydroxy-risperidone) is the major active metabolite of risperidone, concomitant use of INVEGA[®] SUSTENNA[®] with risperidone or oral paliperidone is not recommended since the combination of any of these medications will lead to additive paliperidone exposure.

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[®] SUSTENNA[®] 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 can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with INVEGA[®] SUSTENNA[®] in the recommended dose range of 25 mg–150 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the long-term study, syncope was not reported as an adverse event in the open-label transition/maintenance phases or the subsequent double-blind phase. However, presyncope was reported as an adverse event in one subject (< 1% [1/849]) in the open-label transition/maintenance phase and syncope was reported as an adverse event in one subject (< 1%) during the open-label extension phase of the study.

In the four fixed-dose, double-blind, placebo-controlled studies, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA[®] SUSTENNA[®]-treated subjects. Further, 2% (29/1293) of INVEGA[®] SUSTENNA[®]-treated subjects in the recommended dose range of 25 mg–150 mg and 2% (11/510) of placebo-treated subjects met predefined criteria for orthostatic hypotension based on vital signs measurements.

In the long-term study, there were no reported adverse events of orthostatic hypotension. No more than 1% of INVEGA[®] SUSTENNA[®]-treated subjects met the predefined criteria for orthostatic hypotension based on vital signs measurements (1% [6/849]) during the open-label transition/maintenance phases, < 1% [1/205] during the double-blind phase, and 1% [4/388] during the open-label extension phase) compared with 1% (2/203) of placebo-treated subjects in the double-blind phase.

INVEGA[®] SUSTENNA[®] should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia). 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

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, 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 hyperglycemia or diabetes (< 3%) in subjects treated with INVEGA[®] SUSTENNA[®].

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[®] SUSTENNA[®], suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA[®] SUSTENNA[®] was not marketed at the time these studies were performed, it is not known if INVEGA[®] SUSTENNA[®] is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite

discontinuation of the suspect drug. 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.

Hyperprolactinemia

As with other atypical antipsychotics that antagonize dopamine D₂ receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone.

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 D₂ 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 the four fixed-dose, double-blind, placebo-controlled studies with INVEGA[®] SUSTENNA[®] (25 mg–150 mg), the proportion of subjects who experienced potentially prolactin-related adverse events was similar for the placebo (1%) and INVEGA[®] SUSTENNA[®] (1–2%) groups.

Gastrointestinal **Antiemetic Effect**

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

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.

Although no cases of priapism have been reported in clinical trials with INVEGA[®] SUSTENNA[®], priapism has been reported with oral paliperidone during post-marketing surveillance.

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.

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 frequently during the first few months of therapy and discontinuation of INVEGA[®] SUSTENNA[®] 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 10⁹ /L) should discontinue INVEGA[®] SUSTENNA[®] and have their WBC followed until recovery (see **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions**).

Hepatic/Biliary/Pancreatic

Paliperidone is not extensively metabolized in the liver. In a study with oral paliperidone 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[®] SUSTENNA[®], 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[®] SUSTENNA[®] should be prescribed in a manner that is most likely to minimize the risk of TD. As with any antipsychotic, INVEGA[®] SUSTENNA[®] 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[®] SUSTENNA[®], withdrawal of the drug should be considered. However, some patients may require treatment with INVEGA[®] SUSTENNA[®] despite the presence of the syndrome.

Potential Effect on Cognitive and Motor Performance

Somnolence, sedation and dizziness were reported as adverse reactions in subjects treated with INVEGA[®] SUSTENNA[®] (see **ADVERSE REACTIONS**). Antipsychotics, including INVEGA[®] SUSTENNA[®], have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures

Antipsychotic drugs are known to lower the seizure threshold. In the four fixed-dose, double-blind, placebo-controlled studies, < 1% (1/1293) of subjects treated with INVEGA[®] SUSTENNA[®] in the recommended dose range of 25 mg–150 mg experienced an adverse event of convulsion compared with < 1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

In the long-term study, < 1% (3/849) INVEGA[®] SUSTENNA[®]-treated subjects in the open-label transition/maintenance phase reported adverse events of convulsion (2 subjects) or epilepsy (1 subject). In the double-blind phase, < 1% (1/205) of INVEGA[®] SUSTENNA[®]-treated subjects

reported an adverse event of epilepsy compared with 0% (0/203) of placebo-treated subjects. No cases of epilepsy or convulsion were reported in the open-label extension phase of this study.

As with other antipsychotic drugs, INVEGA[®] SUSTENNA[®] 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[®] SUSTENNA[®], 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.

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. INVEGA[®] SUSTENNA[®] is to be administered by a health care professional (see **DOSAGE AND ADMINISTRATION**); therefore, suicide due to an overdose is unlikely.

Renal

INVEGA[®] SUSTENNA[®] has not been systematically studied in patients with renal impairment. Based on a limited number of observations with INVEGA[®] SUSTENNA[®] in subjects with mild renal impairment and pharmacokinetic simulations, the dose of INVEGA[®] SUSTENNA[®] should be reduced in patients with mild renal impairment (see **DOSAGE AND ADMINISTRATION**). INVEGA[®] SUSTENNA[®] is not recommended in patients with moderate or severe renal impairment.

The disposition of oral 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).

Special Populations

Pregnant Women:

Teratogenic Effects

The safety of intramuscularly-injected paliperidone palmitate or orally-dosed paliperidone for use 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. Pregnancy parameters were not affected in rats given the intramuscular injection of paliperidone palmitate. The high doses were toxic to the mothers. The offspring were not affected

at exposures 20- to 22-fold the maximum human exposure, or intramuscular exposures 6-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 following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

INVEGA[®] SUSTENNA[®] 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[®] SUSTENNA[®] 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[®] SUSTENNA[®].

Pediatrics (< 18 years of age): The safety and efficacy of INVEGA[®] SUSTENNA[®] in children under the age of 18 years has not been established.

Geriatrics (> 65 years of age): Clinical studies of INVEGA[®] SUSTENNA[®] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment who should be given reduced doses. 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[®] SUSTENNA[®] 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[®] SUSTENNA[®] 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[®] SUSTENNA[®] and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Events

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.

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects with schizophrenia who received at least one dose of INVEGA[®] SUSTENNA[®] in the recommended dose range of 25 mg to 150 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA[®] SUSTENNA[®]-treated subjects, 1293 received INVEGA[®] SUSTENNA[®] in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA[®] SUSTENNA[®] in the long-term trial (of whom 205 continued to receive INVEGA[®] SUSTENNA[®] during the double-blind placebo-controlled phase of this study), and 1675 received INVEGA[®] SUSTENNA[®] in five non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 150 mg INVEGA[®] SUSTENNA[®] initiation dose followed by treatment with either 25 mg, 100 mg, or 150 mg every 4 weeks.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

A causal association for INVEGA[®] SUSTENNA[®] often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The majority of all adverse events were mild to moderate in severity.

Short-Term, Placebo-Controlled Studies

The most common adverse events (reported by $\geq 5\%$ in any INVEGA[®] SUSTENNA[®] dose group in the four fixed-dose, double-blind, placebo-controlled trials and at least twice that for placebo) were: injection site reactions, dizziness, extrapyramidal disorder, somnolence and akathisia.

Discontinuations Due to Adverse Events

In the four fixed-dose, double-blind placebo controlled trials, 5.0% of subjects treated with INVEGA[®] SUSTENNA[®] discontinued due to adverse events as compared to 7.8% of subjects

treated with placebo. Schizophrenia (1.5%), psychotic disorder (0.5%), suicidal ideation (0.5%), and agitation (0.5%) were the most common adverse events leading to discontinuation in the INVEGA[®] SUSTENNA[®] treatment group. In the overall clinical trial program, one INVEGA[®] SUSTENNA[®]-treated subject also discontinued due to neuroleptic malignant syndrome.

Commonly Observed Adverse Drug Events in Double-Blind, Placebo-Controlled Trials

Table 1.1 enumerates the adverse events reported in $\geq 2\%$ of patients treated with INVEGA[®] SUSTENNA[®] in the four fixed-dose, double-blind, placebo-controlled studies.

Table 1.1 Adverse Events in $\geq 2\%$ of INVEGA® SUSTENNA®-Treated Subjects and Equal or Greater Than Placebo with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

Body System or Organ Class Preferred Term	Placebo	R092670 25 mg eq.	R092670 50 mg eq.	R092670 100 mg eq.	R092670 150/25 mg eq.	R092670 150/100 mg eq.	R092670 150/150 mg eq.	Total Pali
	(N=510)	(N=130)	(N=302)	(N=312)	(N=160)	(N=165)	(N=163)	(N=1232)
	%	%	%	%	%	%	%	%
Total percentage of subjects with adverse events	70	75	68	69	63	60	63	67
Infections and infestations								
Bronchitis	1	2	<1	1	0	1	1	1
Influenza	<1	0	0	<1	2	1	0	<1
Nasopharyngitis	2	0	2	2	4	2	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4	2
Urinary tract infection	1	0	1	<1	1	1	2	1
Metabolism and nutrition disorders								
Decreased appetite	1	2	1	1	0	1	1	1
Psychiatric disorders								
Agitation	7	10	5	9	8	5	4	6
Anxiety	7	8	5	3	5	6	6	5
Depression	1	1	2	1	1	0	1	1
Hallucination, auditory	1	2	2	1	1	1	1	1
Insomnia	15	15	15	13	12	10	13	13
Nightmare	<1	2	0	0	0	0	0	<1
Suicidal ideation	2	0	1	2	2	2	1	1

Note: The following preferred terms were combined: “Somnolence” and “Sedation” into “Somnolence”; “Injection site pain”, “Injection site pruritus”, “Injection site nodule”, “Injection site induration”, “Administration site pain”, “Administration site reaction”, “Application site erythema”, “Application site swelling”, “Injection site bruising”, “Injection site discomfort”, “Injection site erythema”, “Injection site extravasation”, “Injection site inflammation”, “Injection site irritation”, “Injection site mass”, “Injection site oedema”, “Injection site reaction”, “Injection site swelling”, “Injection site haematoma”, “Injection site joint pain”, “Vessel puncture site pain”, and “Vessel puncture site reaction” into “Injection site reactions”; and “Abdominal discomfort”, “Stomach discomfort” and “Abdominal pain upper” into “Abdominal discomfort/Abdominal pain upper”.

Note: The adverse events in the studies were coded using the MedDRA version 12.0.

Note: The cut-off criteria (incidence $\geq 2\%$ and \geq placebo) are based on percentages after rounding.

Table 1.1 Adverse Events in $\geq 2\%$ of INVEGA[®] SUSTENNA[®]-Treated Subjects and Equal or Greater Than Placebo with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

Body System or Organ Class Preferred Term	Placebo	R092670 25 mg eq.	R092670 50 mg eq.	R092670 100 mg eq.	R092670 150/25 mg eq.	R092670 150/100 mg eq.	R092670 150/150 mg eq.	Total Pali
	(N=510) %	(N=130) %	(N=302) %	(N=312) %	(N=160) %	(N=165) %	(N=163) %	(N=1232) %
Psychiatric disorders (continued)								
Tension	1	2	1	1	0	0	0	1
Nervous system disorders								
Akathisia	3	2	2	3	1	5	6	3
Dizziness	1	6	2	4	1	4	2	3
Dyskinesia	1	1	2	1	0	1	1	1
Extrapyramidal disorder	1	5	2	3	1	0	0	2
Headache	12	11	11	15	11	7	6	11
Hypertonia	<1	1	2	1	0	0	0	1
Somnolence	3	5	7	4	1	5	5	5
Eye disorders								
Eye swelling	0	2	0	0	0	0	0	<1
Cardiac disorders								
Conduction disorder	1	0	2	1	0	0	0	1
Sinus bradycardia	1	0	1	<1	2	0	0	<1
Tachycardia	<1	1	0	1	1	1	2	1
Vascular disorders								
Hypertension	1	2	1	1	1	1	0	1
Respiratory, thoracic and mediastinal disorders								
Cough	1	2	3	1	0	1	1	1
Dyspnoea	1	2	<1	1	1	0	0	1

See footnotes on the first page of the table.

Table 1.1 Adverse Events in $\geq 2\%$ of INVEGA® SUSTENNA®-Treated Subjects and Equal or Greater Than Placebo with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

Body System or Organ Class Preferred Term	Placebo	R092670 25 mg eq.	R092670 50 mg eq.	R092670 100 mg eq.	R092670 150/25 mg eq.	R092670 150/100 mg eq.	R092670 150/150 mg eq.	Total Pali
	(N=510) %	(N=130) %	(N=302) %	(N=312) %	(N=160) %	(N=165) %	(N=163) %	(N=1232) %
Respiratory, thoracic and mediastinal disorders (continued)								
Oropharyngeal pain	1	1	2	<1	1	1	0	1
Gastrointestinal disorders								
Abdominal discomfort/abdominal pain upper	2	2	4	4	1	2	4	3
Constipation	5	3	5	5	2	4	1	4
Diarrhoea	2	0	3	2	1	2	2	2
Dry mouth	1	3	1	0	1	1	1	1
Gastroesophageal reflux disease	0	2	<1	<1	0	0	0	<1
Nausea	3	4	4	3	2	2	2	3
Toothache	1	1	1	3	1	2	3	2
Vomiting	4	5	4	2	3	2	2	3
Skin and subcutaneous tissue disorders								
Pruritus	1	1	2	1	1	0	1	1
Rash	1	2	1	<1	2	1	2	1
Musculoskeletal and connective tissue disorders								
Back pain	2	2	1	3	1	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2	1
Myalgia	1	2	1	<1	1	0	2	1
Pain in extremity	1	0	2	2	2	3	0	2
General disorders and administration site conditions								
Asthenia	0	2	1	<1	0	1	1	1
Fatigue	1	1	2	2	1	2	1	2
Injection site reactions	2	0	4	6	9	7	10	6

See footnotes on the first page of the table.

Table 1.1 Adverse Events in $\geq 2\%$ of INVEGA[®] SUSTENNA[®]-Treated Subjects and Equal or Greater Than Placebo with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

Body System or Organ Class Preferred Term	Placebo	R092670 25 mg eq.	R092670 50 mg eq.	R092670 100 mg eq.	R092670 150/25 mg eq.	R092670 150/100 mg eq.	R092670 150/150 mg eq.	Total Pali
	(N=510) %	(N=130) %	(N=302) %	(N=312) %	(N=160) %	(N=165) %	(N=163) %	(N=1232) %
General disorders and administration site conditions (continued)								
Pain	1	0	2	1	0	1	1	1
Investigations								
Alanine aminotransferase increased	2	0	2	1	1	1	1	1
Aspartate aminotransferase increased	1	0	2	0	1	1	2	1
Blood cholesterol increased	<1	2	1	0	0	0	0	<1
Electrocardiogram qt prolonged	1	1	1	1	2	2	0	1
Low density lipoprotein increased	<1	2	1	0	0	1	0	<1
Weight increased	1	4	4	1	1	1	2	2
Injury, poisoning and procedural complications								
Skin laceration	<1	2	<1	0	1	0	0	<1

See footnotes on the first page of the table.

Less Common Clinical Trial Adverse Drug Reactions

The following additional adverse events occurred in $< 2\%$ of INVEGA[®] SUSTENNA[®]-treated subjects in the above four fixed-dose, double-blind, placebo-controlled trials. In addition, the following also includes adverse events reported in INVEGA[®] SUSTENNA[®]-treated subjects with schizophrenia at any rate who participated in other trials. All events assessed as possible drug-related adverse events are included. In addition, medically/clinically meaningful events, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Although the events reported occurred during treatment with INVEGA[®] SUSTENNA[®], they were not necessarily caused by it.

Events are categorized by organ class and listed in order of decreasing frequency according to the following definitions:

Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$, including isolated reports

Immune system disorders: *Uncommon:* hypersensitivity

Endocrine disorders: *Uncommon:* hyperprolactinemia

Metabolism and nutrition disorders: *Uncommon:* hyperglycemia, hyperinsulinemia, increased appetite

Psychiatric disorders: *Uncommon:* restlessness

Nervous system disorders: *Common:* tremor; *Uncommon:* bradykinesia, convulsion, dizziness postural, drooling, dysarthria, dystonia, lethargy, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope, tardive dyskinesia; *Rare:* cerebrovascular accident, neuroleptic malignant syndrome

Eye disorders: *Uncommon:* oculogyric crisis, vision blurred; *Rare:* eye movement disorder, eye rolling

Ear and labyrinth disorders: *Uncommon:* vertigo

Cardiac disorders: *Uncommon:* atrioventricular block first degree, bradycardia, palpitations, bundle branch block, postural orthostatic tachycardia syndrome, sinus tachycardia

Vascular disorders: *Uncommon:* orthostatic hypotension

Gastrointestinal disorders: *Uncommon:* salivary hypersecretion

Skin and subcutaneous tissue disorders: *Uncommon:* pruritus generalized, urticaria; *Rare:* drug eruption

Musculoskeletal and connective tissue disorders: *Uncommon:* joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching; *Rare:* nuchal rigidity

Reproductive system and breast disorders: *Uncommon:* amenorrhea, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction; *Rare:* breast discharge

Investigations: *Common:* blood glucose increased, blood triglycerides increased; *Uncommon:* electrocardiogram abnormal

In the long-term trial, the nature and frequencies of adverse events during the open-label phases of this study were generally comparable to those observed in the four placebo-controlled fixed-dose studies shown in Table 1.1. The nature of adverse events reported during the double-blind phase of this study were also generally similar to those observed in the open-label phases.

Dose-Related Adverse Events

Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials, among the adverse events that occurred at $\geq 2\%$ incidence in the subjects treated with INVEGA[®] SUSTENNA[®], only akathisia and injection site reactions display a clear dose-related trend. Hyperprolactinemia also exhibited a dose relationship, but did not occur at $\geq 2\%$ incidence in subjects treated with INVEGA[®] SUSTENNA[®].

Demographics

An examination of population subgroups in the double-blind, placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects ≥ 65 years of age.

Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline or score at the end of trial) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, (4) the Abnormal Involuntary Movement Scale scores (mean change from baseline or scores at the end of trial) (Table 1.2), and (5) incidence of spontaneous reports of EPS (Table 1.3).

Table 1.2. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication

Scale	Percentage of Subjects			
	Placebo (N=262)	INVEGA [®] SUSTENNA [®] 25 mg (N=130)	50 mg (N=223)	100 mg (N=228)
Parkinsonism ^a	9	12	10	6
Akathisia ^b	5	5	6	5
Dyskinesia ^c	3	4	6	4
Use of Anticholinergic Medications ^d	12	10	12	11

- a: For Parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)
b: For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint
c: For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint
d: Percent of subjects who received anticholinergic medications to treat emergent EPS

Table 1.3. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term

EPS Group	Percentage of Subjects			
	Placebo (N=262)	INVEGA [®] SUSTENNA [®] 25 mg (N=130)	50 mg (N=223)	100 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism	5	6	6	4
Hyperkinesia	2	2	2	4
Tremor	3	2	2	3
Dyskinesia	1	2	3	1
Dystonia	0	1	1	2

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the long-term trial exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of Parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA[®] SUSTENNA[®] 100 mg group (18% and 11%, respectively) than in the INVEGA[®] SUSTENNA[®] 50 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study involving 150 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA[®] SUSTENNA[®] 150/25 mg, 150/100 mg, and 150/150 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA[®] SUSTENNA[®] 150/100 mg (4.8%) and 150/150 mg (5.5%) groups, but at a lower rate in the 150/25 mg group (1.3%). The percentage of subjects who required use of an anticholinergic medication was low and similar across the placebo and paliperidone palmitate groups (11% to 13%).

Table 1.4. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term in a 13-week 150 mg Initiation Dose Study

EPS Group	Percentage of Subjects			
	Placebo (N=164)	150/25 mg ^a (N=160)	150/100 mg ^a (N=165)	150/150 mg ^a (N=163)
Hyperkinesia	4.9	1.3	4.8	5.5
Parkinsonism	1.8	3.1	3.0	4.3
Tremor	2.4	0.6	1.8	1.2
Dyskinesia	0.6	0	1.2	0.8
Dystonia	0.6	1.9	0	0

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms

^a Initial deltoid injection of 150 mg followed by either 25 mg, 100 mg, or 150 mg every 4 weeks by deltoid or gluteal injection. (See **PRODUCT MONOGRAPH Part II: CLINICAL TRIALS**)

Weight Gain

In the 13-week study involving the recommended initiation regimen (i.e., the initial 150 mg and 100 mg deltoid injections), the proportions of subjects with a weight increase from baseline of $\geq 7\%$ were more common among subjects in the INVEGA[®] SUSTENNA[®] groups than in the placebo group. The proportion of subjects with an abnormal weight increase $\geq 7\%$ showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA[®] SUSTENNA[®] 25 mg, 100 mg, and 150 mg groups, respectively.

In the two 13-week, fixed-dose, double-blind, placebo-controlled trials (pooled data), the proportions of subjects meeting a weight gain criterion of $\geq 7\%$ of body weight were 6%, 9%, and 10% in the INVEGA[®] SUSTENNA[®] 25 mg, 50 mg, and 100 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, 8% and 6% in the INVEGA[®] SUSTENNA[®] 50 mg and 100 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label transition/maintenance period of the long-term trial, 12% of INVEGA[®] SUSTENNA[®]-treated subjects met this criterion; the mean weight change from open-label baseline was +0.7 kg. In the variable length double-blind phase, this criterion (weight gain of $\geq 7\%$ from double-blind phase to endpoint) was met by 6% of INVEGA[®] SUSTENNA[®]-treated subjects (median duration 171 days [range 1 day - 407 days]) compared with 3% of placebo-

treated subjects (median duration 105 days [range 8 days - 441 days]); the mean weight change from double-blind baseline was +0.5 kg for INVEGA[®] SUSTENNA[®] compared with -1.0 kg for placebo. Similar results were observed in the open-label extension phase of this study. Abnormal Hematologic and Clinical Chemistry Findings

In the pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials, a between-group comparison revealed no medically important differences between INVEGA[®] SUSTENNA[®] 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[®] SUSTENNA[®] 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[®] SUSTENNA[®] was associated with increases in serum prolactin (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**). Observed increases in serum prolactin concentrations were mostly asymptomatic and infrequently associated with reports of potentially prolactin-related adverse events. The results from the 13-week study involving 150 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the long-term trial exhibited comparable findings.

Pain Assessment and Local Injection Site Reactions

In the 13-week study involving the recommended initiation regimen (i.e., the initial 150 mg and 100 mg deltoid injections), the mean intensity of injection pain reported by subjects using a visual analog scale (0 mm = no pain to 100 mm = unbearably painful) at first injection was 22 and 18 for INVEGA[®] SUSTENNA[®] and placebo groups, respectively. Throughout the rest of the study when injections could be administered in either the gluteal or deltoid site, mean pain scores ranged between 10–15 mm for gluteal injections, and from 15–21 mm for deltoid injections. Thus, pain at the deltoid site tended to be greater, although still usually mild. Investigator ratings of pain were consistent with the subject ratings. Although less frequent, there was also more swelling at the deltoid site as compared to the gluteal site.

Overall, occurrences of pain, induration, redness, or swelling, at injection sites, as assessed by blinded study personnel, were infrequent, generally mild, and tended to decrease over time.

Adverse Events Reported with Oral Paliperidone

The following is a list of additional adverse events that have been reported with oral paliperidone:

Infections and infestations: rhinitis, viral infection

Immune system disorders: anaphylactic reaction

Psychiatric disorders: aggression, sleep disorder

Nervous system disorders: cogwheel rigidity, grand mal convulsion, parkinsonian gait, transient ischemic attack

Eye disorders: dry eye

Cardiac disorders: bundle branch block left, sinus arrhythmia

Vascular disorders: hypotension, ischemia

Respiratory, thoracic and mediastinal disorders: nasal congestion, pneumonia aspiration

Gastrointestinal disorders: dyspepsia, flatulence, small intestinal obstruction

Skin and subcutaneous tissue disorders: rash papular

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, neck pain, shoulder pain, torticollis, trismus

Reproductive system and breast disorders: breast engorgement, breast pain, breast tenderness, retrograde ejaculation

General disorders and administration site conditions: edema, edema peripheral, pyrexia

Injury, poisoning and procedural complications: fall

Investigations: blood creatine phosphokinase increased, blood insulin increased, blood pressure increased, electrocardiogram QT corrected interval prolonged, electrocardiogram T wave abnormal, electrocardiogram T wave inversion, heart rate increased, insulin C-peptide increased, weight decreased

Post-Market Adverse Drug Reactions

Adverse events first identified as ADRs during postmarketing experience with paliperidone are included in Table 1.5. In this table, the frequencies are provided according to the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$, including isolated reports

In Table 1.5, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 1.5 Adverse Drug Reactions Identified During Post-Marketing Experience with Paliperidone by Frequency Category Estimated from Spontaneous Reporting Rates	
Immune System Disorders	
<i>Rare</i>	Angioedema
Gastrointestinal Disorders	
<i>Very rare</i>	Swollen tongue
Renal and Urinary Disorders	
<i>Very rare</i>	Urinary incontinence
<i>Very rare</i>	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
<i>Very rare</i>	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
<i>Very rare</i>	Priapism

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[®] SUSTENNA[®] are considerably different from those observed with oral immediate-release risperidone formulations, as well as those from risperidone long-acting injection (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 oral risperidone and risperidone long-acting injection in clinical trials and postmarketing experience that may be relevant to INVEGA[®] SUSTENNA[®] can be found in local labelling for risperidone.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Since paliperidone palmitate is hydrolyzed to paliperidone (see **ACTION AND CLINICAL PHARMACOLOGY**), results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Potential for INVEGA[®] SUSTENNA[®] 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 from a study using oral paliperidone extended-release 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[®] SUSTENNA[®] 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[®] SUSTENNA[®] is administered with other therapeutic agents that have this potential.

Potential for Other Drugs to Affect INVEGA[®] SUSTENNA[®]

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 oral paliperidone extended-release once daily 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 oral paliperidone extended-release 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[®] SUSTENNA[®] should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA[®] SUSTENNA[®] 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.

Concomitant Use of INVEGA[®] SUSTENNA[®] with Risperidone or Oral Paliperidone

Concomitant use of INVEGA[®] SUSTENNA[®] with oral paliperidone or oral or injectable risperidone has not been studied. Since paliperidone (9-hydroxy-risperidone) is the major active metabolite of risperidone, concomitant use of INVEGA[®] SUSTENNA[®] with risperidone or oral paliperidone is not recommended since the combination of any of these medications will lead to additive paliperidone exposure.

Drug-Food Interactions

Interactions with food have not been established.

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 statistically significant differences between smokers and non-smokers in an analysis performed with oral paliperidone extended-release tablets.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adult

For patients who have never taken oral paliperidone or oral/injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA[®] SUSTENNA[®].

Recommended **initiation regimen** of INVEGA[®] SUSTENNA[®] is with a dose of 150 mg on treatment day 1 and 100 mg on day 8 (one week later), both administered in the deltoid muscle in order to attain therapeutic concentrations rapidly (see **ACTION AND CLINICAL PHARMACOLOGY**). Recommendations for switching from other antipsychotics are provided in the subsection **“For Patients Who are SWITCHING from Other Antipsychotic Agents”** to follow.

The recommended subsequent monthly maintenance dose is 75 mg; this dose can be higher or lower within the range of 25 to 150 mg based on individual patient tolerability and/or efficacy.

Following the initiation regimen, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA[®] SUSTENNA[®] should be considered (see **ACTION AND CLINICAL PHARMACOLOGY**), as the full effect of the dose adjustment may not be evident for several months.

Administration Information

INVEGA[®] SUSTENNA[®] is intended for intramuscular use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

The recommended needle size for administration of INVEGA[®] SUSTENNA[®] into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg (≥ 200 lb), the 1½-inch, 22 gauge needle is recommended. For those < 90 kg (< 200 lb), the 1-inch, 23 gauge needle is recommended. Deltoid injections should be alternated between the two deltoid muscles.

The recommended needle size for administration of INVEGA[®] SUSTENNA[®] into the gluteal muscle is the 1½-inch, 22 gauge needle. Administration should be made into the upper-outer quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

Concomitant use of INVEGA[®] SUSTENNA[®] with oral paliperidone or oral or injectable risperidone has not been studied. Since paliperidone (9-hydroxy-risperidone) is the major active metabolite of risperidone, concomitant use of INVEGA[®] SUSTENNA[®] with risperidone or oral paliperidone is not recommended since the combination of any of these medications will lead to additive paliperidone exposure.

Missed Doses

Guidance for Avoiding Missed Doses It is recommended that the second dose of the initiation regimen of INVEGA[®] SUSTENNA[®] be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

Missed Dose (1 Month to 6 Weeks) After administration of the initiation regimen, the recommended injection cycle of INVEGA[®] SUSTENNA[®] is monthly. If less than 6 weeks have elapsed since the last injection, then the previous maintenance dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed Dose (> 6 Weeks to 6 Months)

If more than 6 weeks have elapsed since the last injection of INVEGA[®] SUSTENNA[®], the recommendation is as follows:

For patients with previous maintenance doses of 25 to 100 mg:

1. a deltoid injection as soon as possible at the same maintenance dose the patient was previously

- on,
2. another deltoid injection (same dose) one week later (day 8),
 3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg.

For patients with previous maintenance dose of 150 mg:

1. a deltoid injection as soon as possible at the 100 mg dose
2. another deltoid injection one week later (day 8) at the 100 mg dose
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg.

Missed Dose (> 6 Months) Subsequent to administration of the initiation regimen, if more than 6 months have elapsed since the last injection of INVEGA[®] SUSTENNA[®], initiate dosing as described for the initial recommended initiation of INVEGA[®] SUSTENNA[®] above.

Patients with Hepatic Impairment

INVEGA[®] SUSTENNA[®] has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Patients with Renal Impairment

INVEGA[®] SUSTENNA[®] has not been systematically studied in patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), recommended initiation of INVEGA[®] SUSTENNA[®] is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 50 mg in either the deltoid or gluteal muscle.

INVEGA[®] SUSTENNA[®] is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Elderly

In general, recommended dosing for elderly patients with normal renal function (≥ 80 mL/min) is the same as for younger adults with normal renal function. As 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[®] SUSTENNA[®] in patients < 18 years of age have not been studied.

Other Special Populations

No dose adjustment for INVEGA[®] SUSTENNA[®] is recommended based on gender, race, or smoking status.

For Patients Who are SWITCHING from Other Antipsychotic Agents

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to INVEGA® SUSTENNA®, or concerning concomitant administration with other antipsychotics.

Switching from Oral Antipsychotics

For patients who have never taken oral paliperidone or oral/injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®.

Previous oral antipsychotics can be discontinued at the time of initiation of treatment with INVEGA® SUSTENNA®. INVEGA® SUSTENNA® should be started according to the one-week initiation dosing regimen (i.e., the initial 150 mg and 100 mg deltoid injections) as described in **Recommended Dose and Dosage Adjustment**.

Patients previously stabilized on different doses of INVEGA® Extended-Release Tablets can attain similar paliperidone steady-state exposure with INVEGA® SUSTENNA® following administration of the initiation regimen as described in **Recommended Dose and Dosage Adjustment** and subsequent monthly doses as shown below:

Table 1.6 Doses of INVEGA® and INVEGA® SUSTENNA® Needed to Attain Similar Paliperidone Exposure at Steady-State

Formulation	INVEGA® Extended-Release Tablets	INVEGA® SUSTENNA® Prolonged-Release Suspension
Dosing Frequency	Once Daily	Once every 4 weeks
Dose (mg)	12 6 3	150 75 25-50

Switching from Long-Acting Injectable Antipsychotics

For patients who have never taken oral paliperidone or oral/injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®.

When switching patients from previous long-acting injectable antipsychotics (including RISPERDAL® CONSTA®), initiate INVEGA® SUSTENNA® therapy in place of the next scheduled injection. INVEGA® SUSTENNA® should then be continued at monthly intervals.

The one-week initiation dosing regimen (i.e., the initial 150 mg and 100 mg deltoid injections) as described at the beginning of the DOSAGE AND ADMINISTRATION section above is not required.

Patients previously stabilized on different doses of RISPERDAL® CONSTA® risperidone powder for Injectable Prolonged-Release Suspension can attain similar active drug steady-state exposure during maintenance treatment with INVEGA® SUSTENNA® monthly doses according to the following:

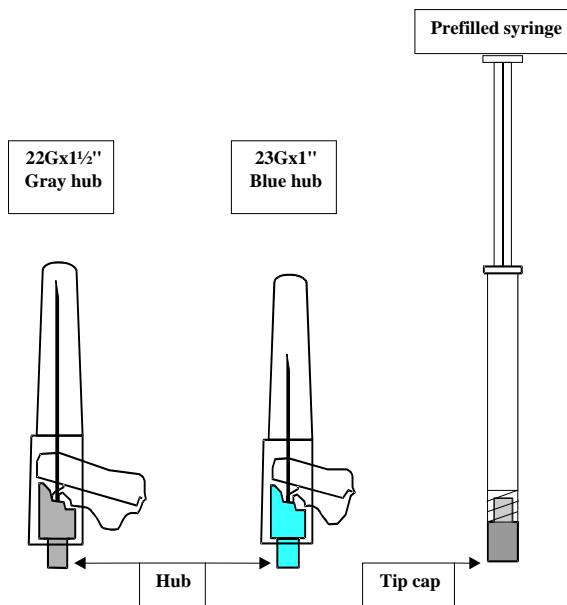
Table 1.7 Doses of RISPERDAL® CONSTA® and INVEGA® SUSTENNA® needed to attain similar paliperidone exposure at steady-state

Previous RISPERDAL® CONSTA® Dose	INVEGA® SUSTENNA® Dose
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

If INVEGA® SUSTENNA® is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

Instructions for Use

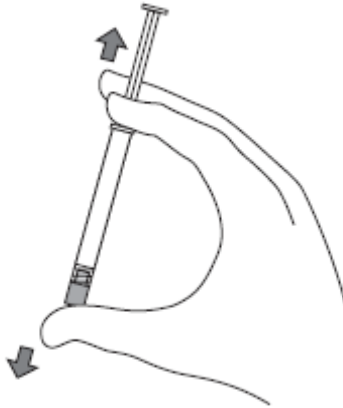
The kit contains a prefilled syringe and 2 safety needles (a 1½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.



INVEGA® SUSTENNA® is for single use only.

Note: The 1½-inch 22 gauge needle hub colour appears gray but corresponds to ISO needle hub colour “black”.

1. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.

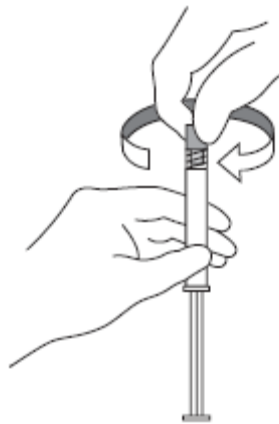


2. Select the appropriate needle.

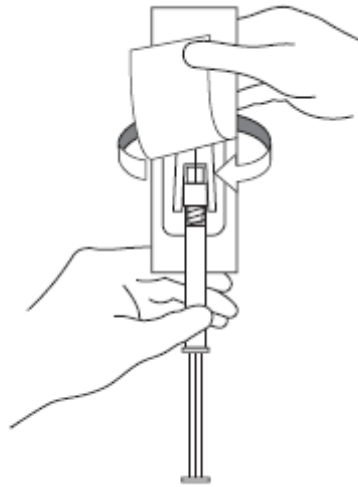
For DELTOID injection, if the patient weighs < 200 lb (< 90 kg), use the 1-inch **23** gauge needle (needle with **blue** coloured hub); if the patient weighs \geq 200 lb (\geq 90 kg), use the 1½-inch **22** gauge needle (needle with **gray** coloured hub).

For GLUTEAL injection, use the 1½-inch **22** gauge needle (needle with **gray** coloured hub).

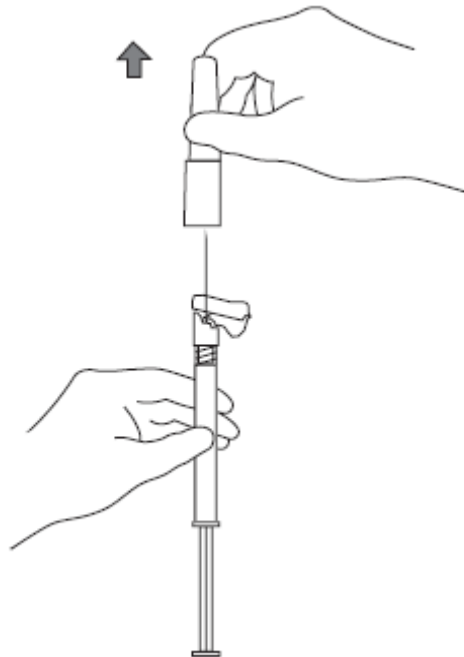
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



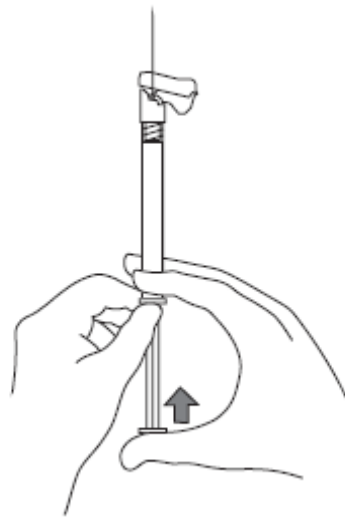
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



5. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.

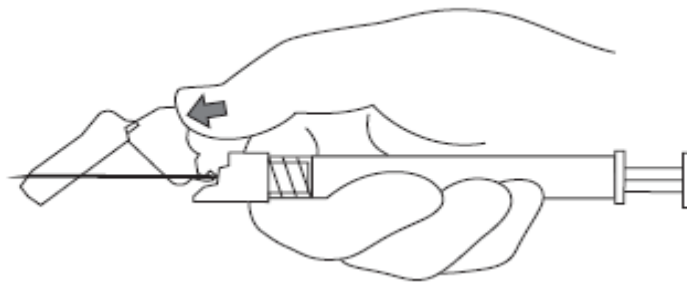


6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.

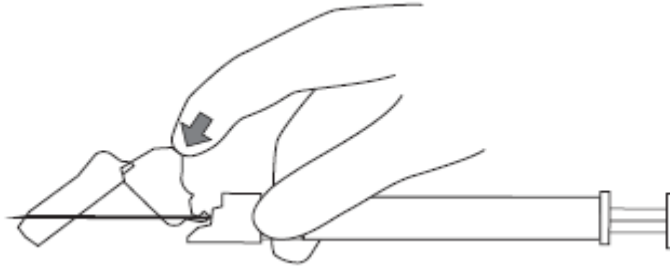


7. Inject the entire contents intramuscularly into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**
8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle protection system. The needle protection system is fully activated when a “click” is heard. Discard the syringe with needle appropriately.

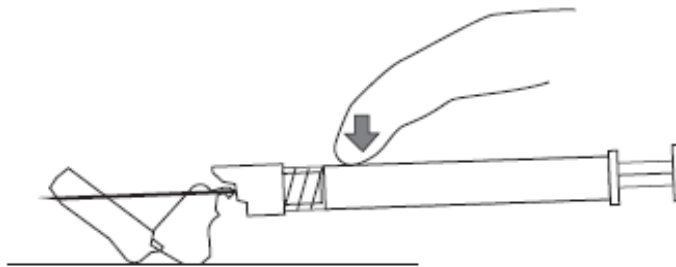
8a



8b



8c



OVERDOSAGE

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

Because INVEGA[®] SUSTENNA[®] is to be administered by health care professionals, the potential for overdose by patients is low.

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 with oral paliperidone. In the case of acute overdose, the possibility of multiple drug involvement should be considered.

Treatment

Consideration should be given to the prolonged-release nature of INVEGA[®] SUSTENNA[®] and the long apparent half-life of paliperidone 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 fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone (see **Pharmacokinetics**). The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism. Antagonism at receptors other than D₂ and 5HT_{2A} may explain some of the other effects of paliperidone.

Pharmacodynamics

Paliperidone is a centrally active dopamine D₂ antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H₁ 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.

Pharmacokinetics

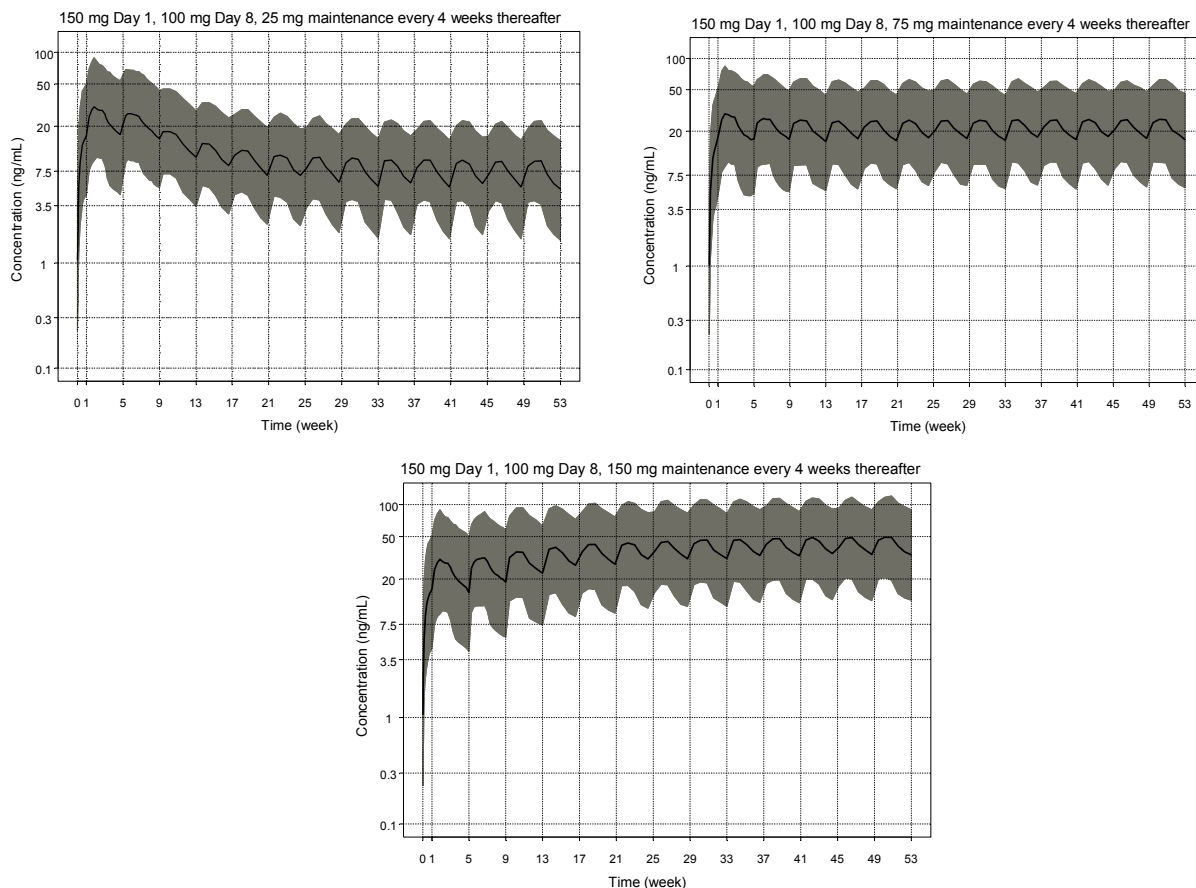
Absorption and Distribution

Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median t_{max} of 13 days. The release of the drug starts as early as day 1 and lasts for as long as 126 days.

Following intramuscular injection of single doses (25 mg–150 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 150 mg on day 1 and 100 mg on day 8 help attain therapeutic concentrations rapidly.

This dosing regimen and the release profile of INVEGA[®] SUSTENNA[®] results in rapid attainment of sustained therapeutic concentrations similar to the steady state concentrations obtained by monthly dosing at 75 mg. At lower or higher monthly doses of INVEGA[®] SUSTENNA[®], plasma concentrations gradually decrease or increase respectively until steady state for the lower or higher doses is achieved; see Figure 1.1.

Figure 1.1. Population PK simulations of plasma paliperidone concentrations with a range of maintenance doses. The solid line and the shaded area represent the median and the 90% prediction interval based on the population PK simulation.



The AUC of paliperidone following INVEGA[®] SUSTENNA[®] administration was dose-proportional over a 25 mg–150 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 50 mg. The mean steady-state peak: trough ratio for an INVEGA[®] SUSTENNA[®] dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. The median apparent half-life of paliperidone following INVEGA[®] SUSTENNA[®] administration increased over the dose range of 25 mg–150 mg from 25–49 days.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6–1.8.

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

Metabolism and Elimination

The following data are based on a human mass balance study using oral solution of ¹⁴C-paliperidone which has approximately 100% bioavailability. One week following administration of a single 1 mg dose of oral solution ¹⁴C-paliperidone, 59% of the 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, none of which accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence in vivo that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernable difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. In vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No in vivo data are available and the clinical relevance is unknown.

Long-Acting Paliperidone Palmitate Injection versus Oral Extended-Release Paliperidone

INVEGA® SUSTENNA® is designed to deliver paliperidone over a monthly period while extended-release oral paliperidone is administered on a daily basis. Figure 1.2 presents the median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA® SUSTENNA® administration using the recommended initiation regimen compared to the administration of an oral extended-release tablet (6 mg or 12 mg). The initiation regimen for INVEGA® SUSTENNA® (150 mg/100 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

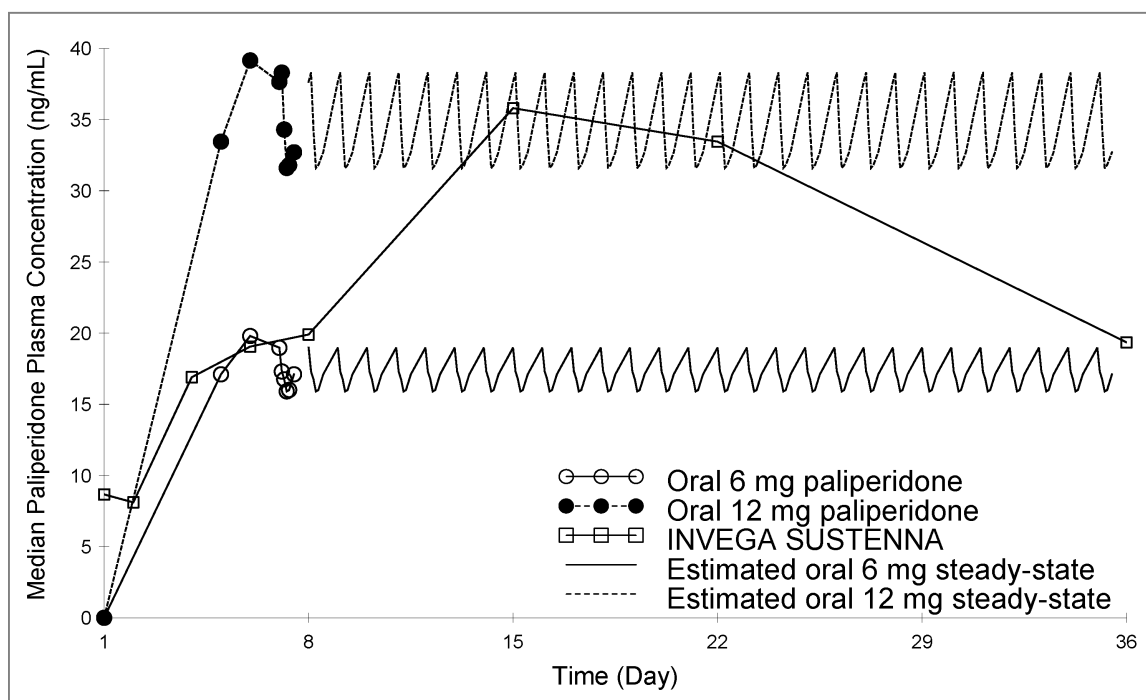


Figure 1.2: Median plasma concentration-time profiles following median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA® SUSTENNA® administration using the recommended initiation regimen (initiating with paliperidone palmitate equivalent to paliperidone 150 mg/100 mg in the deltoid muscle on Day 1/Day 8) compared to the daily administration of an oral extended-release tablet (6 mg or 12 mg).

In general, overall initiation plasma levels with INVEGA[®] SUSTENNA[®] were within the exposure range observed with 6–12 mg extended-release oral paliperidone. The use of the INVEGA[®] SUSTENNA[®] initiation regimen allowed patients to stay in this exposure window of 6–12 mg extended-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from INVEGA[®] SUSTENNA[®] was lower relative to the variability determined from extended-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Special Populations and Conditions

Pediatrics: No data available.

Geriatrics: No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see **Renal Insufficiency** below and **DOSAGE AND ADMINISTRATION**).

Gender: No clinically significant differences were observed between men and women.

Race: Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA[®] SUSTENNA[®] administration.

Hepatic Insufficiency: Paliperidone is not extensively metabolized in the liver. Although INVEGA[®] SUSTENNA[®] was not studied in patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. 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. Paliperidone has not been studied in patients with severe hepatic impairment.

Renal Insufficiency: INVEGA[®] SUSTENNA[®] has not been systematically studied in patients with renal impairment. Based on a limited number of observations with INVEGA[®] SUSTENNA[®] in subjects with mild renal impairment and pharmacokinetic simulations, the dose of INVEGA[®] SUSTENNA[®] should be reduced in patients with mild renal impairment; INVEGA[®] SUSTENNA[®] is not recommended for use in patients with moderate or severe renal impairment (see **DOSAGE AND ADMINISTRATION**).

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

≥ 80 mL/min). Paliperidone has not been studied in subjects with creatinine clearance < 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 statistically significant differences between smokers and non-smokers in an analysis performed with oral paliperidone extended-release tablets.

STORAGE AND STABILITY

INVEGA[®] SUSTENNA[®] should be stored at room temperature (15–30°C).

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

INVEGA[®] SUSTENNA[®] paliperidone palmitate Prolonged-Release Injectable Suspension is available in pre-filled syringes as a white to off-white sterile aqueous prolonged-release suspension for intramuscular injection in dose strengths of 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1 mL or 150 mg/1.5 mL paliperidone (as 78, 117, 156 or 234 mg of paliperidone palmitate respectively). The product is supplied as a kit and contains a prefilled syringe and 2 safety needles, a 1½-inch 22 gauge safety needle, and a 1-inch 23 gauge safety needle. The pre-filled syringes are for single use only.

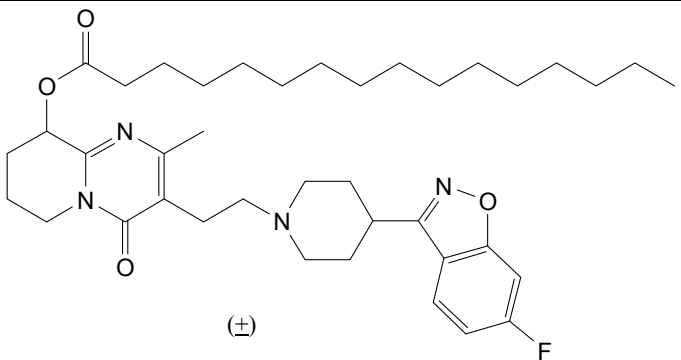
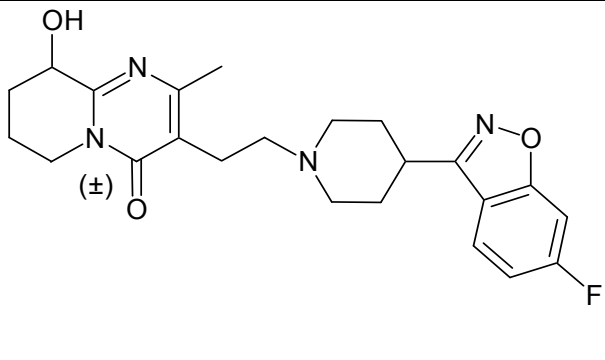
Composition

The following inactive ingredients in INVEGA[®] SUSTENNA[®] are citric acid monohydrate, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name	Paliperidone palmitate (prodrug)	Paliperidone (active moiety)
Chemical name	(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate	(±)-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	C ₃₉ H ₅₇ FN ₄ O ₄	C ₂₃ H ₂₇ FN ₄ O ₃
Molecular mass	664.8	426.49
Structural formula		
Physical Appearance	Paliperidone palmitate is a white to almost white powder.	Paliperidone is a white to yellow powder.
Dissociation Constants	pK _{a1} = 8.3 (piperidone moiety) pK _{a2} < 3 (pyrimidine moiety)	pK _{a1} = 8.2 (piperidone moiety) pK _{a2} = 2.6 (pyrimidine moiety)
Partition Coefficients	log p > 5	log p = 2.39
Solubility	Paliperidone palmitate is insoluble in 0.1N HCl, 0.1N NaOH, and water; very slightly soluble in ethanol, methanol, and 2-propanol; freely soluble in dichloromethane.	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

The efficacy of INVEGA[®] SUSTENNA[®] was established in three 13-week double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult patients who met DSM-IV criteria for schizophrenia. The fixed doses of INVEGA[®] SUSTENNA[®] in these studies

were given on days 1, 8, 36, and 64 of these studies, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression-Severity (CGI-S) Scale.

In a 13-week study (n=636) comparing three fixed doses of INVEGA[®] SUSTENNA[®] (initial deltoid injection of 150 mg followed by 3 gluteal or deltoid doses of either 25 mg/4 weeks, 100 mg/4 weeks or 150 mg/4 weeks) to placebo, all three doses of INVEGA[®] SUSTENNA[®] were superior to placebo in improving the PANSS total score. Based on the ITT LOCF analysis of the primary efficacy variable, PANSS total score, the improvement in all 3 INVEGA[®] SUSTENNA[®] dose groups reached statistical significance (25 mg: p=0.034; 100 mg: p<0.001; 150 mg: p<0.001). The 100 mg and 150 mg doses were superior to placebo on the CGI-S scale (p=0.005 and p<0.001 respectively) but not the 25 mg dose.

In another 13-week study (n=349) comparing three fixed doses of INVEGA[®] SUSTENNA[®] (50 mg/4 weeks, 100 mg/4 weeks, and 150 mg/4 weeks) to placebo, only 100 mg/4 weeks of INVEGA[®] SUSTENNA[®] was superior to placebo in improving the PANSS total score (p=0.019). The 50 mg dose group was numerically superior to placebo, but the difference was not statistically significant. The 100 mg dose was superior to placebo on the CGI-S scale (p=0.010). Although a 150 mg dosage arm was included in this study, due to a medication allocation error affecting this arm only there were insufficient numbers of subjects receiving this dose to allow definitive conclusions concerning the efficacy of this dose.

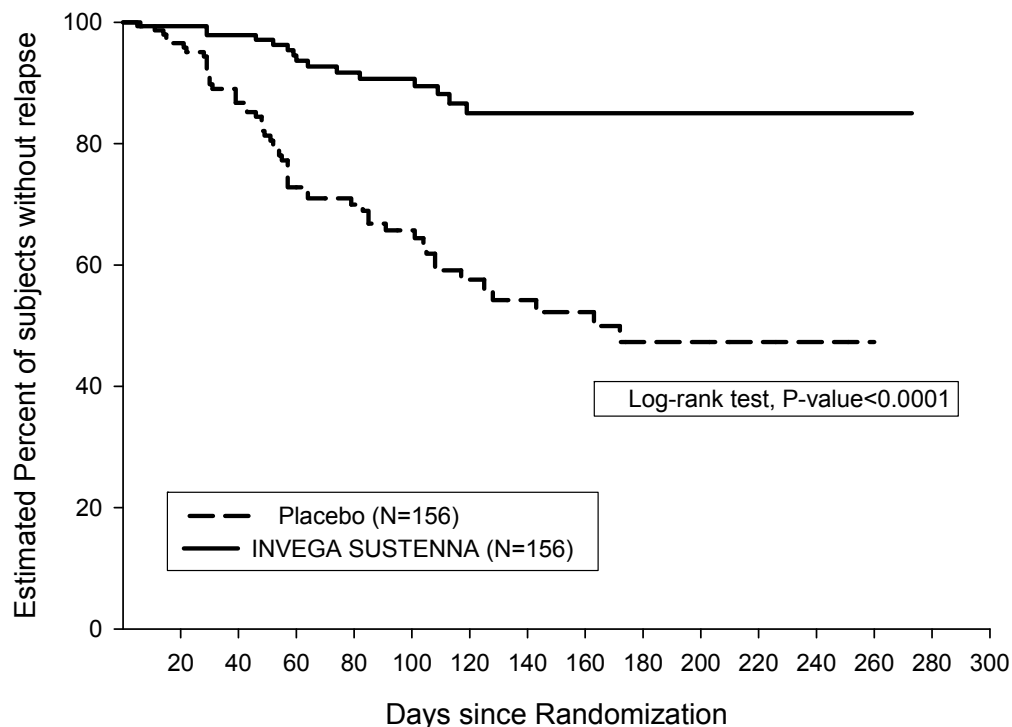
In a third 13-week study (n=513) comparing three fixed doses of INVEGA[®] SUSTENNA[®] (25 mg/4 weeks, 50 mg/4 weeks, and 100 mg/4 weeks) to placebo, all three doses of INVEGA[®] SUSTENNA[®] were superior to placebo in improving the PANSS total score (25 mg: p=0.015; 50 mg: p=0.017; 100 mg: p<0.001). All doses were superior to placebo on the CGI-S scale (25 mg: p=0.003; 50 mg: p=0.006; 100 mg: p=0.002).

In a pooled analysis of the latter two 13-week studies, all paliperidone palmitate groups (25 mg, 50 mg and 100 mg) were statistically significantly superior to placebo for the mean change from baseline to endpoint in the PANSS total score (p≤0.009). The least squares mean difference from placebo ranged from -4.9 to -8.2 in the paliperidone palmitate groups, with the greatest difference in the highest dose group (i.e., 100 mg group).

The efficacy of INVEGA[®] SUSTENNA[®] in maintaining symptomatic control and delaying relapse of schizophrenia was established in a longer-term, double-blind, placebo-controlled, flexible-dose study involving 849 non-elderly adult subjects who met DSM-IV criteria for schizophrenia. This study included a 33-week open-label acute treatment and stabilization phase, and a randomized, placebo-controlled phase to observe for relapse and a 52-week open-label extension period. In this study, doses of INVEGA[®] SUSTENNA[®] included 25, 50, 75 and 100 mg administered monthly; the 75 mg dose was allowed only in the 52-week open-label extension. Subjects initially received flexible doses (25 – 100 mg) of INVEGA[®] SUSTENNA[®] during a 9-week transition period. In order to enter the 24-week maintenance period, subjects were required to have a PANSS score of ≤ 75. Dosing adjustments were only allowed in the first 12 weeks of the maintenance period. During the variable length double-blind phase, patients were randomized to either the same dose of INVEGA[®] SUSTENNA[®] (median duration 171 days [range 1 day - 407 days]) they received during the stabilization phase, i.e., 25 mg, 50 mg, or 100 mg administered every 4 weeks, or to placebo (median duration 105 days [range 8 days - 441 days]). A total of 410 stabilized patients

were randomized to either INVEGA® SUSTENNA® or to placebo until they experienced a “relapse” of schizophrenia symptoms. “Relapse” was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization, $\geq 25\%$ increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behaviour, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behaviour), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness). The primary efficacy variable was time to “relapse”. A pre-planned interim analysis (after 68 recurrence events occurred) showed a significantly longer time to “relapse” in patients treated with INVEGA® SUSTENNA® compared to placebo (Figure 2.1), and the study was stopped early because maintenance of efficacy was demonstrated.

**Figure 2.1: Kaplan-Meier Plot of Time to “Relapse” (Interim Analysis)
: Intent-to-Treat Analysis Set)**



The results of the analysis based on the final data, including all data up to the date of the study termination, was consistent with that of the primary efficacy analysis based on the interim data.

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

DETAILED PHARMACOLOGY

Preclinical Pharmacodynamics

I.m. injected paliperidone palmitate is converted to paliperidone, with minimal systemic exposure to paliperidone palmitate in animals as well as in humans. Systemic effects following i.m. administered paliperidone palmitate is mediated through paliperidone.

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}, D₂, 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 D₂ 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 D₂ 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

After i.m. administration of paliperidone palmitate, the exposure to the unhydrolyzed prodrug is very low, whereas a prolonged release of paliperidone, with a duration of at least one month, is observed both in humans and all animal species tested. Nonclinical animal models were also used to simulate the consequences of accidental partial intravenous administration or intralipomatous injection. Following i.v. administration, there was no instantaneous release of the entire dose, but a prolonged release of paliperidone. An injection in the subcutaneous fat layer produced a similar profile, but with lower paliperidone plasma concentrations to that observed after i.m. dosing.

After i.m. injection, paliperidone palmitate forms an agglomerate of nanoparticles. There is a dissociation of the product, most likely by hydrolysis, in the muscle cells surrounding this depot. After hydrolysis paliperidone enters the systemic circulation, whereas the palmitate moiety is probably oxidized in the muscle cells.

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 D₂-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 palmitate and paliperidone were 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 systemic toxicity profile of paliperidone palmitate and paliperidone mainly consisted of findings related to exaggerated pharmacodynamic effects of CNS- and PRL-mediated actions.

In the repeat-dose toxicity studies with paliperidone palmitate, NOAELs could not be established due to injection site tolerability issues which in the animal studies occurred at all dose levels. This poor injection site tolerability does not translate to humans.

In the repeat-dose toxicity studies with paliperidone, 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.

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 conducted with paliperidone. 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.

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.

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 10, 30, and 60 mg/kg/month, which is 0.5, 2, and 4 times, respectively, the maximum recommended human 150 mg dose of INVEGA[®] SUSTENNA[®] on a mg/m² basis. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 30 and 60 mg/kg/month. These findings are considered to be of little relevance in terms of human risk.

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PART III: CONSUMER INFORMATION

Pr INVEGA®* SUSTENNA®*
paliperidone palmitate Prolonged-Release Injectable
Suspension

This leaflet is Part III of a three-part “Product Monograph” published when INVEGA® SUSTENNA® 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® SUSTENNA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

The doctor has prescribed INVEGA® SUSTENNA®, also known as paliperidone, to help relieve the symptoms that are bothering you/the patient you are caring for. Although INVEGA® SUSTENNA® 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.

INVEGA® SUSTENNA® belongs to a group of medicines called antipsychotic drugs. INVEGA® SUSTENNA® is used to treat the symptoms of schizophrenia, which may include hallucinations (hearing, seeing or sensing things that are not there), mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech, and behavioural and emotional flatness. People suffering from schizophrenia may also feel depressed, anxious, guilty or tense.

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® SUSTENNA® works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:

INVEGA® SUSTENNA® should not be given if an allergic reaction to the medicine, or a related drug (risperidone), or any of the nonmedicinal ingredients has occurred.

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.

The safety and efficacy of INVEGA® SUSTENNA® in children under the age of 18 have not been established.

What the medicinal ingredient is:

paliperidone palmitate

What the nonmedicinal ingredients are:

Citric acid monohydrate, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

What dosage forms it comes in:

INVEGA® SUSTENNA® Prolonged-Release Injectable Suspension is available in pre-filled syringes in the following dosage strengths: 50 mg, 75 mg, 100 mg, 150 mg paliperidone as paliperidone palmitate.

WARNINGS AND PRECAUTIONS **Serious Warnings and Precautions**

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

BEFORE starting treatment with INVEGA® SUSTENNA®, talk to your doctor or pharmacist if you or the patient you are caring for:

- 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 a family history of diabetes
- are pregnant or planning to become pregnant
- are breast-feeding
- have/had a heart disease or heart disease treatment that makes you prone to low blood pressure
- have a history of heart problems, any problems with the way your heart beats, or are being treated for high blood pressure
- have/have ever had blackouts or seizures
- have Parkinson’s disease or dementia with Lewy bodies (DLB)
- have/had breast cancer
- have pituitary tumours
- are taking any other medicines (prescription, over-the-counter, or natural health products)
- drink alcoholic beverages or use drugs
- are taking RISPERDAL® (risperidone)
- have a history of kidney problems
- suffer from Alzheimer’s disease
- are feeling thirsty and unwell
- exercise strenuously

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[®] SUSTENNA[®] 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.

If you are taking blood pressure medication

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

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.

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[®] SUSTENNA[®].

During long-term treatment, INVEGA[®] SUSTENNA[®] 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[®] SUSTENNA[®].

INVEGA[®] SUSTENNA[®] 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.

Because some people experience drowsiness, you should not drive or operate machinery until you are reasonably certain

that INVEGA[®] SUSTENNA[®] does not affect your ability to carry out these activities.

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 or the patient you are caring for that you/the patient you are caring for are/is taking INVEGA[®] SUSTENNA[®]. 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[®] SUSTENNA[®].

Since INVEGA[®] SUSTENNA[®] 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.

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

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

Since INVEGA[®] SUSTENNA[®] can lower blood pressure, care should be taken when INVEGA[®] SUSTENNA[®] is taken with other drugs that lower blood pressure.

PROPER USE OF THIS MEDICATION

Usual dose:

INVEGA[®] SUSTENNA[®] is a long-acting medicine that a health care professional will give to you by injection. This means that you do not have to take this medicine every day.

When you receive your first dose of INVEGA[®] SUSTENNA[®] you will need to get a second dose one week later. After that you will only need to get a dose once a month.

If you were previously treated with a long-acting injectable antipsychotic medication and are being switched to INVEGA[®] SUSTENNA[®], you will only need to get a dose once a month.

Your doctor or health care provider will give you the injection into the upper arm or buttocks.

Your doctor will tell you when to come into the doctor's office or clinic for the injection. It is important not to miss

your scheduled dose. If you cannot keep your appointment with the doctor, make sure you call him/her right away so another appointment can be made as soon as possible.

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

Overdose:

Immediately contact your doctor or go to the nearest hospital emergency department.

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 heart beats, rapid heartbeat, reduced consciousness, and excessive trembling or excessive muscle stiffness.

Missed dose:

If you stop coming for your injections, your symptoms may return. You should not stop this medicine unless told to do so by your doctor as your symptoms may return.

If you cannot keep your appointment with the doctor, make sure you call him/her right away so another appointment can be made as soon as possible. Your doctor or treatment team will decide what you should do next.

If you have any further questions on the use of this product, ask your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, INVEGA® SUSTENNA® 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.

Side effects that may occur very commonly are headache and trouble falling asleep or waking up during the night or too early in the morning.

Side effects that may occur commonly include faster heart rate, stomach ache, constipation, diarrhea, nausea, vomiting, lack of energy, fatigue, injection site pain, increased weight, feeling of inner restlessness, dizziness, uncontrollable movements of the face or body, sleepiness, rash and high blood pressure.

Uncommon side effects include slowed heart rate, heartbeat irregularities, blurred vision, dry mouth, increased saliva, decreased or increased appetite, seizures, feeling dizzy upon standing, drooling, rigid muscles, slowness of movement and muscle stiffness or spasm, and itching. While women may experience leakage of fluid or milk from the breast, men may

develop breast swelling. Women may experience missed or irregular periods. Men may experience difficulty getting or maintaining an erection. High blood sugar has also been reported. See your doctor if you experience symptoms such as excessive thirst or urination.

Rare side effects include painful eye movement.

Because some people experience drowsiness or blurred vision, you should not drive or operate machinery until you are reasonably certain that INVEGA® SUSTENNA® does not affect your ability to carry out these activities.

Your doctor may check your body weight before starting INVEGA® SUSTENNA® and during treatment.

Your doctor may take blood tests before starting INVEGA® SUSTENNA® and during treatment, and may monitor blood sugar, and the number of infection fighting white blood cells.

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.

If you have taken INVEGA® SUSTENNA® 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.

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® SUSTENNA®.

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.

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

Symptom / effect	Call your doctor or pharmacist		Stop taking the drug and seek immediate medical emergency assistance.
	Only if severe	In all cases	
Common			

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

Skin rash on its own		✓	
Swelling at the injection site, injection site pain		✓	
Uncommon			
Symptoms of allergic reaction, such as itching, skin rash, swelling of the mouth, face, lips, or tongue, or shortness of breath ¹			✓
Seizure (i.e., loss of consciousness with uncontrollable shaking)			✓
Muscle twitching or abnormal movements of the face or tongue		✓	
Marked changes in body temperature (generally as a result of several factors together including extreme heat or cold)			✓
Rare			
A state of confusion, reduced consciousness, high fever, or pronounced muscle stiffness, pain and swelling			✓
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			✓
Symptoms of pancreas inflammation such as severe abdominal pain, fever, nausea, vomiting		✓	
Side effects with an unknown frequency²			
Long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Symptoms of jaundice, such as yellowing of the skin and eyes			✓
Life-threatening complications of uncontrolled diabetes such as shortness of breath, confusion and loss of consciousness			✓
Bruise easily, excessive bleeding		✓	

¹ Reported with oral paliperidone.

² These events may not have occurred with INVEGA[®] SUSTENNA[®] but are known to occur with this kind of medicine.

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

HOW TO STORE IT

Store INVEGA[®] SUSTENNA[®] in its original package.

INVEGA[®] SUSTENNA[®] should be stored between 15–30°C.

Keep INVEGA[®] SUSTENNA[®] out of the reach of children.

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect[™] Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

<http://www.janssen.ca>

or by contacting the sponsor, Janssen Inc., at 1-800-567-3331.

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