

Discontinuations Due to Adverse Reactions

Schizophrenia Trials

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

Among the adverse reactions in the 6-week, fixed-dose, placebo-controlled study in adolescents with schizophrenia, only dystonia led to discontinuation (<1% of paliperidone-treated subjects).

Schizoaffective Disorder Trials

The percentages of subjects who discontinued due to adverse reactions in the two schizoaffective disorder placebo-controlled 6-week studies in adults were 1% and <1% in paliperidone- and placebo-treated subjects, respectively. The most common reasons for discontinuation were gastrointestinal disorders (1% and 0% in paliperidone- and placebo-treated subjects, respectively).

Dose-Related Adverse Reactions

Schizophrenia Trials

Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with paliperidone, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

In the 6-week, fixed-dose, placebo-controlled study in adolescents with schizophrenia, among the adverse reactions that occurred with >2% incidence in the subjects treated with paliperidone, the incidences of the following adverse reactions increased with dose: tachycardia, akathisia, extrapyramidal symptoms, somnolence, and headache.

Schizoaffective Disorder Trials

In a placebo-controlled, 6-week, high- and low-dose study in adult subjects with schizoaffective disorder, akathisia, dystonia, dysarthria, myalgia, rash/pruritus, rhinitis, cough, and pharyngolaryngeal pain occurred more frequently (i.e., a difference of at least 2%) in subjects who received higher doses of paliperidone compared with subjects who received lower doses.

Demographic Differences

An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia and in the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder did not reveal any evidence of clinical relevance differences in safety on the basis of gender or race alone; there was also no difference on the basis of age [see *Use in Specific Populations* (8.5)].

Extrapyramidal Symptoms (EPS)

Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale (global clinical rating score [mean change from baseline] which evaluates akathisia), (3) use of anticholinergic medications to treat emergent EPS (Table 7), and (4) incidence of spontaneous reports of EPS (Table 8). For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and paliperidone 3 mg and 6 mg doses for any of these EPS measures.

Table 7. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

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

* For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items)

^b For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2

^c Percent of patients who received anticholinergic medications

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

EPS Group	Percentage of Patients Paliperidone				
	Placebo (N=355)	3 mg once daily (N=127)	6 mg once daily (N=235)	9 mg once daily (N=246)	12 mg once daily (N=242)
Overall percentage of patients with EPS-related AE	11	13	10	25	26
Dyskinesia	3	5	3	8	9
Dystonia	1	1	1	5	5
Hyperkinesia	4	4	3	8	10
Parkinsonism	2	3	3	7	6
Tremor	3	3	3	4	3

Dyskinesia group includes: Dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms, oculogyration, trismus

Hyperkinesia group includes: Akathisia, hyperkinesia

Parkinsonism group includes: Bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism

Tremor group includes: Tremor

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

Table 9. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies in Adults

EPS Group	Percentage of Patients Paliperidone			
	Placebo (N=202)	3-6 mg once-daily flexible-dose range (N=108)	9-12 mg once-daily flexible-dose range (N=98)	3-12 mg once-daily flexible dose range (N=214)
Overall percentage of patients with EPS-related AE	11	23	22	17
Dyskinesia	1	3	1	1
Dystonia	1	2	3	2
Hyperkinesia	5	5	8	7
Parkinsonism	3	14	7	7
Tremor	3	12	11	5

Dyskinesia group includes: Dyskinesia, muscle twitching

Dystonia group includes: Dystonia, muscle spasms, oculogyration

Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness

Parkinsonism group includes: Bradykinesia, drooling, hypertonia, muscle rigidity, muscle lightness, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, parkinsonism

Tremor group includes: Tremor

The incidences of EPS-related adverse events in the adolescent schizophrenia studies showed a similar dose-related pattern to those in the adult studies. There were notably higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescent population as compared to the adult studies (Table 10).

Table 10. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizophrenia Studies in Adolescent Subjects

EPS Group	Percentage of Patients Paliperidone				
	Placebo (N=51)	1.5 mg once daily (N=54)	3 mg once daily (N=16)	6 mg once daily (N=45)	12 mg once daily (N=35)
Overall percentage of patients with EPS-related AE	0	6	25	22	40
Hyperkinesia	0	4	6	11	17
Dystonia	0	2	0	11	14
Tremor	0	2	6	7	11
Parkinsonism	0	0	6	2	14
Dyskinesia	0	2	6	2	6

Hyperkinesia group includes: Akathisia

Dystonia group includes: Dystonia, muscle contracture, oculogyric crisis, tongue paralysis, torticollis

Tremor group includes: Tremor

Parkinsonism group includes: Cogwheel rigidity, extrapyramidal disorder, muscle rigidity

Dyskinesia group includes: Dyskinesia, muscle contractions involuntary

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscles groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities

In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in adult subjects with schizophrenia and from the two placebo-controlled, 6-week studies in adult subjects with schizoaffective disorder, between-group comparisons revealed no medically important differences between paliperidone and placebo in the proportions of subjects experiencing statistically clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between paliperidone 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, paliperidone was associated with increases in serum prolactin [see *Warnings and Precautions* (5.7)].

Other Adverse Reactions Observed During Premarketing Evaluation of Paliperidone

The following additional adverse reactions occurred in <2% of paliperidone-treated subjects in the above schizophrenia and schizoaffective disorder clinical trials. Similarly, there were no differences between paliperidone 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, paliperidone was associated with increases in serum prolactin [see *Warnings and Precautions* (5.7)].

Cardiac Disorders: bradycardia, palpitations

Eyes disorders: eye movement disorder

Gastrointestinal disorders: flatulence

General disorders: edema

Immune system disorders: anaphylactic reaction

Infections and infestations: urinary tract infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity

Nervous system disorders: ophthalmorus

Psychiatric disorders: agitation, insomnia, nightmare

Reproductive system and breast disorders: Breast discomfort, menstruation irregular, retrograde ejaculation

Skin and mucous membrane disorders: nasal congestion

Renal and subcutaneous tissue disorders: pruritus, rash

Vascular disorders: hypertension

The safety of paliperidone was also evaluated in a long-term trial designed to assess the maintenance of effect with paliperidone in adults with schizophrenia [see *Clinical Studies* (14)]. In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of paliperidone; because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency; accordingly, cataplexy, ileus, priapism, somnambulum, swollen tongue, tardive dyskinesia, thrombotic thrombocytopenic purpura, urinary incontinence, urinary retention.

6.3 Adverse Reactions Reported with Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

7. DRUG INTERACTIONS

7.1 Potential for Paliperidone to Affect Other Drugs

Given the primary CNS effects of paliperidone [see *Adverse Reactions* (6.1, 6.2)], paliperidone should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when paliperidone is administered with other therapeutic agents that have this potential [see *Warnings and Precautions* (5.9)].

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 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, CYP2C9/9/10, 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. Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Pharmacokinetic interaction between lithium and paliperidone is unlikely.

In a drug interaction study, co-administration of paliperidone (12 mg once daily for 5 days) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics (AUC_{0-∞} and C_{max}) of valproate in 13 patients stabilized on valproate. In a clinical study, subjects on stable doses of valproate had comparable valproate average plasma concentrations when administered with or without paliperidone. On initiation of carbamazepine, the dose of paliperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of paliperidone should be re-evaluated and decreased if necessary.

7.2 Potential for Other Drugs to Affect Paliperidone

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of paliperidone 6 mg once daily with carbamazepine, a strong inducer of both CYP3A4 and P-glycoprotein (P-gp), at 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of paliperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of paliperidone should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 [see *Clinical Pharmacology* (12.3)]. In an interaction study in healthy subjects in which a single 3 mg dose of paliperidone was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (95% CI, 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

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

Pharmacokinetic interaction between lithium and paliperidone is unlikely.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including paliperidone, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [see *Clinical Considerations*]. Overall, available data from published epidemiological studies of pregnant women exposed to paliperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes [see *Data*]. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including paliperidone, during pregnancy [see *Clinical Considerations*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated with paliperidone during the period of organogenesis with up to 8 times the maximum recommended human dose (MRHD) based on mg/m² body surface area. Additional reproductive toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

Disease-Associated Maternal and/or Embryo/Fetal Risk

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including paliperidone, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m² body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Clot papilla was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 16 mg based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. When the offspring of pregnant rats, treated with risperidone at 0.6 times the MRHD based on mg/m² body surface area, reached adulthood, learning was impaired, increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m² body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams (see RISPERDAL, package insert).

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant, or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone's parent compound, risperidone [see *Clinical Considerations*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for paliperidone and any potential adverse effects on the breastfed child from paliperidone or from the mother's underlying condition.

Clinical Considerations

Infants exposed to paliperidone through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of paliperidone (D₂ receptor antagonism), treatment with paliperidone may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see *Warnings and Precautions* (5.7)].

8.4 Pediatric Use

Safety and effectiveness of paliperidone in the treatment of schizophrenia were evaluated in 150 adolescent subjects 12-17 years of age with schizophrenia who received paliperidone in the dose range of 1.5 mg to 12 mg/day in a 6-week, double-blind, placebo-controlled trial.

Safety and effectiveness of paliperidone for the treatment of schizophrenia in patients < 12 years of age were not been established. Safety and effectiveness of paliperidone for the treatment of schizoaffective disorder in patients < 18 years of age have not been established.

Juvenile Animal Studies

In a study in which juvenile rats were treated with oral paliperidone from days 24 to 27 of age, a reversible impairment of performance in a test of learning and memory was seen. In females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents at MRHD of 12 mg/day. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

The long-term effects of paliperidone on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

The safety, tolerability, and efficacy of paliperidone were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older) in this study; subjects received flexible doses of paliperidone (3 mg to 12 mg once daily). In addition, a small number of subjects (65 years of age and older) were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of paliperidone (3 mg to 15 mg once daily) [see *Clinical Studies* (14)]. There were no subjects ≥ 65 years of age in the schizoaffective disorder studies.

Overall, of the total number of subjects in schizophrenia clinical studies of paliperidone (n=1796), including those who received paliperidone or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical patient experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to paliperidone. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Paliperidone is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once a small number of subjects (65 years of age and older) were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of paliperidone (3 mg to 15 mg once daily) [see *Clinical Studies* (14)]. There were no subjects ≥ 65 years of age in the schizoaffective disorder studies.

9.3 Dependence

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

10. OVERDOSAGE

10.1 Human Experience

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of paliperidone was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gut upset/nauseas. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacologic effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Width: 17.0" Length: 18.75" Fold: 1.25" x 1.25"

9.125"

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HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use PALIPERIDONE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for PALIPERIDONE EXTENDED-RELEASE TABLETS.

Initial U.S. Approval: 2006
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS See full prescribing information for complete boxed warning. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Paliperidone extended-release tablets are not approved for use in patients with dementia-related psychosis. (5.1)

RECENT MAJOR CHANGES Dosage and Administration (2.5) 1/2025 Warnings and Precautions (5.7) 1/2025

INDICATIONS AND USAGE Paliperidone extended-release tablets are an atypical antipsychotic agent indicated for Treatment of Schizophrenia (1.1)
Adults: Efficacy was established in three 6-week trials and one maintenance trial. (14.1)
Adolescents (ages 12-17): Efficacy was established in one 6-week trial. (14.1)
Treatment of schizophrenia disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants. (1.2)
Efficacy was established in two 6-week trials in adult patients. (14.2)

Table with 4 columns: Dosage Form, Initial Dose, Recommended Dose, Maximum Dose. Rows include Schizophrenia - adults (2.1), Schizophrenia-adolescents (2.1), and Schizophrenia disorder - adults (2.2).

CONTRAINDICATIONS Known hypersensitivity to paliperidone, risperidone, or to any excipients in paliperidone. (4)
WARNINGS AND PRECAUTIONS Cerebrovascular Adverse Reactions: An increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) has been seen in elderly patients with dementia-related psychosis treated with atypical antipsychotic agents. (5.1)
Neuroleptic Malignant Syndrome: Manage with immediate discontinuation of drug and close monitoring. (5.3)
QT Prolongation: Increase in QT interval, avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. (5.4)
Orthostatic Hypotension and Syncope (5.9)
Falls (5.10)
Leukopenia, Neutropenia, and Agranulocytosis (5.11)
Seizures (5.13)
Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes which may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.6)

ADVERSE REACTIONS Commonly observed adverse reactions (incidence > 5% and at least twice that for placebo) were (6)
Adults with schizophrenia: extrapyramidal symptoms, tachycardia, and akathisia.
Adults with schizophrenia: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia.
Adults with schizophrenia disorder: extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.
Central-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol. (7.1)
Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with paliperidone. (7.1)
Strong CYP2A6 and CYP2D6 (P-gp) inducers: It may be necessary to increase the dose of paliperidone when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of paliperidone. (7.2)
Co-administration of divalproex sodium increased Cmax and AUC of paliperidone by approximately 50%. Adjust dose of paliperidone if necessary based on clinical assessment. (7.2)
USE IN SPECIFIC POPULATIONS Renal Impairment: Dosing must be individualized according to renal function status. (2.5)
Elderly: Same as for younger adults (adjust dose according to renal function status). (2.4)
Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
Pediatric Use: Safety and effectiveness in the treatment of schizophrenia not established in patients less than 12 years of age. Safety and effectiveness in the treatment of schizophrenia disorder not established in patients less than 18 years of age. (8.4)

DRUG INTERACTIONS
DRUGS THAT MAY CAUSE ORTHOSTATIC HYPOTENSION
DRUGS THAT MAY CAUSE EXTRAPYRAMIDAL AND/OR WITHDRAWAL SYMPTOMS IN NEONATES WITH THIRD TRIMESTER EXPOSURE
DRUGS THAT MAY INCREASE THE EFFECTS OF PALIPERIDONE
DRUGS THAT MAY DECREASE THE EFFECTS OF PALIPERIDONE

HOW SUPPLIED/STORAGE AND HANDLING
PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

9 mg - Light yellow to yellow film coated, round cylindrical biconvex tablets printed with "9" in black ink.
4 CONTRAINDICATIONS Paliperidone extended-release tablets are contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the paliperidone extended-release tablets (see Warnings and Precautions (5.1)).

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5.4 QT Prolongation Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, anti-cholinergic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., piperacillin, 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. The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single-dose, multicenter QT study) in adults with schizophrenia and schizophrenia disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

5.5 Tardive Dyskinesia In the QT study (n=141), the 6 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9, 15.6) on day 9 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 6 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of paliperidone (Cmax = 11.9 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6, 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during the study.

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Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.6)
Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.6)
Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. (5.7)
Gastrointestinal Narrowing: Obstructive symptoms may result in patients with gastrointestinal disease. (5.9)
Orthostatic Hypotension and Syncope: Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension. (5.9)
Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotics, including paliperidone. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of paliperidone should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.11)
Potential for Cognitive and Motor Impairment: Use caution when operating machinery. (5.12)
Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.13)

ADVERSE REACTIONS Commonly observed adverse reactions (incidence > 5% and at least twice that for placebo) were (6)
Adults with schizophrenia: extrapyramidal symptoms, tachycardia, and akathisia.
Adults with schizophrenia: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia.
Adults with schizophrenia disorder: extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.
Central-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol. (7.1)
Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with paliperidone. (7.1)
Strong CYP2A6 and CYP2D6 (P-gp) inducers: It may be necessary to increase the dose of paliperidone when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of paliperidone. (7.2)
Co-administration of divalproex sodium increased Cmax and AUC of paliperidone by approximately 50%. Adjust dose of paliperidone if necessary based on clinical assessment. (7.2)
USE IN SPECIFIC POPULATIONS Renal Impairment: Dosing must be individualized according to renal function status. (2.5)
Elderly: Same as for younger adults (adjust dose according to renal function status). (2.4)
Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
Pediatric Use: Safety and effectiveness in the treatment of schizophrenia not established in patients less than 12 years of age. Safety and effectiveness in the treatment of schizophrenia disorder not established in patients less than 18 years of age. (8.4)

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Based on comparison to the normative data, these changes are not considered to be clinically significant.
Schizophrenia Disorder Trials
In the pooled data from the two placebo-controlled, 6-week studies in adult patients with schizophrenia, a higher percentage of paliperidone-treated subjects (5%) had an increase in body weight of > 7% compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of > 7% was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

5.7 Hyperprolactinemia Like other drugs 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, a drug that is associated with higher levels of prolactin than other antipsychotic drugs. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

5.8 Potential for Gastrointestinal Obstruction Because the paliperidone extended-release tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, paliperidone should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (obstructive or idiopathic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, post-surgical strictures, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, paliperidone should only be used in patients who are able to swallow the tablet whole (see Dosage and Administration (2.3) and Patient Counseling Information (17)).

5.9 Orthostatic Hypotension and Syncope Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blockading activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with paliperidone (3 mg, 6 mg, 9 mg, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. Paliperidone 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, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.10 Falls Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including paliperidone, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Leukopenia, Neutropenia, and Agranulocytosis In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporarily related to antipsychotic agents, including paliperidone. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC/absolute neutrophil count) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of paliperidone at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if any symptoms or signs occur. Discontinue paliperidone in patients with severe neutropenia (absolute neutrophil count < 1000/mm3) and follow the WBC until recovery.

5.12 Potential for Cognitive and Motor Impairment Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with paliperidone (see Warnings and Precautions (5.7)). Antipsychotics, including paliperidone, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating heavy machinery or driving a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.13 Seizures During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with paliperidone (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. Like other antipsychotic drugs, paliperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

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

5.15 Priapism Drug with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

5.16 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 paliperidone 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.

6. ADVERSE REACTIONS The following adverse reactions are discussed in more detail in other sections of the labeling:
Increased mortality in elderly patients with dementia-related psychosis (see Boxed Warning and Warnings and Precautions (5.1))
Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis (see Warnings and Precautions (5.2))
Neuroleptic malignant syndrome (see Warnings and Precautions (5.3))
QT prolongation (see Warnings and Precautions (5.4))
Potential for gastrointestinal obstruction (see Warnings and Precautions (5.8))
Orthostatic hypotension and syncope (see Warnings and Precautions (5.9))
Falls (see Warnings and Precautions (5.10))
Leukopenia, neutropenia, and agranulocytosis (see Warnings and Precautions (5.11))
Potential for cognitive and motor impairment (see Warnings and Precautions (5.12))
Seizures (see Warnings and Precautions (5.13))
Dysphagia (see Warnings and Precautions (5.14))
Priapism (see Warnings and Precautions (5.15))
Disruption of body temperature regulation (see Warnings and Precautions (5.16))

6.1 Clinical Trials Experience The most common adverse reactions in clinical trials in adult patients with schizophrenia (reported in 5% or more of subjects treated with paliperidone and at least twice the placebo rate in any of the dose groups) were extrapyramidal symptoms, tachycardia, and akathisia. The most common adverse reactions in clinical trials in adult patients with schizophrenia disorder (reported in 5% or more of subjects treated with paliperidone and at least twice the placebo rate) were extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

The most common adverse reactions that were associated with discontinuation from clinical trials in adult patients with schizophrenia (causing discontinuation in 2% of paliperidone-treated subjects) were nervous system disorders. The most common adverse reactions that were associated with discontinuation from clinical trials in adult patients with schizophrenia disorder (causing discontinuation in 2% of subjects treated with paliperidone and at least twice the placebo rate) were extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

The safety of paliperidone was evaluated in 1205 adult subjects with schizophrenia who participated in three placebo-controlled, 6-week, double-blind trials, of whom 850 subjects received paliperidone at fixed doses ranging from 3 mg to 12 mg once daily. The information presented in this section was derived from pooled data from these three trials. Additional safety information from the placebo-controlled phase of the long-term maintenance study, in which subjects received paliperidone at daily doses with the range of 3 mg to 15 mg (n=104), is included in (14.2).

The safety of paliperidone was evaluated in 150 adolescent subjects 12-17 years of age with schizophrenia who received paliperidone in the dose range of 1.5 mg to 12 mg/day in a 6-week, double-blind, placebo-controlled trial. The safety of paliperidone was also evaluated in 622 adult subjects with schizophrenia disorder who participated in two placebo-controlled, 6-week, double-blind trials. In one of these trials, 206 subjects were assigned to one of two dose levels of paliperidone: 6 mg with the option to reduce to 3 mg (n=108) or 12 mg with the option to reduce to 9 mg (n=98) once daily. In the other study, 214 subjects received flexible doses of paliperidone (3-12 mg once daily). Both studies included subjects who received paliperidone either as monotherapy or in association with mood stabilizers and/or antidepressants. Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology. Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for paliperidone often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia (Adults and Adolescents) Table 4 enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies in adults, listing those that occurred in 2% or more of subjects treated with paliperidone in any of the dose groups, and for which the incidence in paliperidone-treated subjects in any of the dose groups was greater than that in the placebo group.

Table 4. Adverse Reactions Reported by > 2% of Paliperidone-Treated Adult Subjects with Schizophrenia in Three Short-Term, Fixed-Dose, Placebo-Controlled Clinical Trials *
Percentage of Patients Paliperidone
Placebo 3 mg once daily (N=127) 6 mg once daily (N=235) 9 mg once daily (N=246) 12 mg once daily (N=242)

Table with 5 columns: Body System or Organ Class, Dictionary-Derived Term, Total percentage of subjects with adverse reactions, Placebo (N=355), 3 mg once daily (N=127), 6 mg once daily (N=235), 9 mg once daily (N=246), 12 mg once daily (N=242).

Table with 5 columns: Body System or Organ Class, Dictionary-Derived Term, Total percentage of subjects with adverse reactions, Placebo (N=51), 1.5 mg once daily (N=54), 3 mg once daily (N=16), 6 mg once daily (N=45), 12 mg once daily (N=35).

* Table includes adverse reactions that were reported in 2% or more of subjects in any of the paliperidone dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies: one study included once-daily paliperidone doses of 3 mg and 9 mg, the second study included 6 mg, 9 mg, and 12 mg, and the third study included 6 mg and 12 mg (see Clinical Studies (14.2)). Extrapyramidal symptoms includes the terms dyskinesia, dystonia, extrapyramidal symptoms, muscle rigidity, cogwheel, parkinsonism, and tremor. Somnolence includes the terms somnolence and som