priapism. Although priapism has not been reported in clinical trials of paliperidone, the drug possesses α-adrenergic blocking activity and may therefore be associated with this risk.

Hematologic Effects. Thrombotic thrombocytopenic purpura (TTP) has not been reported in clinical trials of paliperidone. TTP has been reported in association with risperidone therapy; however, the relationship of this adverse event to risperidone is unknown.

Body Temperature Regulation. Disruption of the body's ability to reduce core body temperature has been associated with the use of antipsychotic agents. Use caution when paliperidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

Antiemetic Effects. Antiemetic effects were observed in preclinical studies with paliperidone; these effects also may occur in humans and mask signs of overdosage of other drugs or obscure cause of vomiting in various disorders (e.g., intestinal obstruction, Reye's syndrome, brain tumor).

Patients with Concomitant Illness. Clinical experience with paliperidone in patients with certain concomitant illnesses is limited.

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including paliperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and features consistent with NMS. (For additional information on extrapyramidal adverse effects and NMS, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Paliperidone has not been adequately evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease to date and patients with these conditions were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension associated with paliperidone, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease. (See Orthostatic Hypotension and Syncope under Warnings/Precautions/General Precautions, in Cautions.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Paliperidone is distributed into milk in animals. Both risperidone and 9-hydroxyrisperidone, which is the major active metabolite of risperidone and the same drug as paliperidone, distribute into milk following risperidone administration in humans. The manufacturer states that women receiving paliperidone should not breast-feed.

Pediatric Use. Safety and effectiveness not established in pediatric patients younger than 18 years of age.

Geriatric Use. In clinical studies, approximately 7% of nearly 1800 patients were 65 years of age or older. In addition, the short-term efficacy and safety of paliperidone have been demonstrated in a placebo-controlled trial of 6 weeks' duration in 114 geriatric patients with schizophrenia. While no substantial differences in efficacy or safety relative to younger adults were observed in these studies or in other clinical experience with the drug, increased sensitivity cannot be ruled out.

Because geriatric patients may have reduced renal function, dosage adjustment may be required based on renal function status; consider monitoring renal function. (See Dosage and Administration: Special Populations.)

Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Paliperidone is *not* approved for the treatment of dementia-related psychosis. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Patients with moderate hepatic impairment (Child-Pugh class B) exhibited similar plasma concentrations of free paliperidone as healthy individuals, although total paliperidone exposure decreased because of decreased protein binding. Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). The effect of severe hepatic impairment on paliperidone pharmacokinetics is not known. (See Dosage and Administration: Special Populations.)

Renal Impairment. Clearance decreased by an average of 32, 64, and 71% in patients with mild, moderate, and severe renal impairment, respectively. Dosage adjustment is recommended in patients with moderate or severe renal impairment. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients receiving paliperidone include tremor, headache, orthostatic hypotension, tachycardia, somnolence, akathisia, insomnia, anxiety, extrapyramidal reaction, dizziness, dystonia, QT_c interval prolongation, nausea, dyspepsia, and weight gain.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) isoenzymes 2D6, 3A4, 1A2, 2A6, 2C9, and 2C19: pharmacokinetic interaction unlikely.

■ **Drugs Affecting Hepatic Microsomal Enzymes** Substrates of CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, or CYP3A5: pharmacokinetic interaction unlikely.

■ **Drugs Inhibiting P-glycoprotein Transport System** At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein; clinically relevant interactions unlikely.

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT-interval prolongation); avoid concomitant use of other drugs known to prolong the QT interval (e.g., amiodarone, quinidine, procainamide, sotalol, other Class Ia and III antiarrhythmics, chlorpromazine, thioridazine, gatifloxacin, moxifloxacin).

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

■ **Alcohol** Potential pharmacologic interaction (additive sedative effects). Avoid alcoholic beverages during paliperidone therapy.

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Paroxetine** Concomitant administration of paroxetine (20 mg daily) and a single dose of paliperidone (3 mg as extended-release tablets) caused a small, clinically insignificant increase in paliperidone area under the concentration-time curves (AUCs) compared with paliperidone administration alone. Therefore, dosage adjustment of paliperidone is not necessary.

■ **Risperidone** Concurrent use of paliperidone with risperidone has not been studied to date. However, because paliperidone is the principal active metabolite of risperidone, consideration should be given to additive paliperidone exposure if risperidone and paliperidone are concomitantly administered.

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effects). Use with caution.

■ **Smoking** Pharmacokinetic interaction unlikely. Dosage adjustment in patients who smoke is not necessary.

Description

Paliperidone is a benzisoxazole-derivative antipsychotic agent that differs chemically from other currently available first-generation (typical) antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The drug is the major active metabolite of risperidone, another atypical antipsychotic agent.

The exact mechanism of paliperidone's antipsychotic action, like that of other antipsychotic agents, has not been fully elucidated, but may involve antagonism of central dopamine type 2 (D_2) and serotonin type 2 (5-hydroxytryptamine [$5\text{-}HT_{2A}$]) receptors. Antagonism at α_1- and α_2-adrenergic and histamine (H_1) receptors may contribute to other therapeutic and adverse effects observed with the drug. Paliperidone possesses no affinity for cholinergic muscarinic and β_1- and β_2-adrenergic receptors.

In vitro studies have suggested a role for cytochrome P-450 (CYP) isoenzymes 2D6 and 3A4 in the metabolism of paliperidone; however, the results of in vivo studies indicate that these isoenzymes play a limited role in the overall elimination of the drug from the body.

Approximately 80% and 11% of a single 1-mg oral dose of radiolabeled, immediate-release paliperidone is recovered in urine and feces, respectively, within 1 week. About 59% of the administered dose is recovered as unchanged drug and 32% recovered as metabolites. Following single-dose oral administration as extended-release tablets, paliperidone appears to have a mean terminal elimination half-life of about 23 hours.

Advice to Patients

Importance of reading manufacturer's patient information.

Risk of orthostatic hypotension, particularly during initial dosage titration and at times of reinitiation of therapy or increases in dosage. Importance of advising patients who experience dizziness or fainting during therapy to get up slowly when sitting or lying down.

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with paliperidone, patients should be cautioned about driving, operating machinery, or performing hazardous tasks while taking paliperidone until they gain experience with the drug's effects. Importance of avoiding alcohol during paliperidone therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs that Prolong QT Interval) and OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus, seizures).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients that paliperidone tablets should be swallowed whole with the aid of liquids, and should not be chewed, divided or crushed. Patients should not be concerned if they notice a tablet-like substance in their stool.

Importance of informing patients of other important precautionary information. (See Cautions.)