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FORMULARY DRUG REVIEWS

Paliperidone

Dennis J. Cada, PharmD, FASHP, FASCP (Editor), Danial E. Baker, PharmD, FASCP, FASHP,† and Terri Levien, PharmD‡*

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Generic Name:
PALIPERIDONE EXTENDED-RELEASE TABLETS
Proprietary Name: ***Invega*** (Janssen)
Approval Rating: **1S**
Therapeutic Class: **Atypical Antipsychotics**
Similar Drugs: **Risperidone**
Sound- or Look-Alike Names: ***Neumega, Invagesic***

INDICATIONS

Paliperidone has received Food and Drug Administration (FDA) approval for use in the treatment of schizophrenia.[1] See Table 1 for a comparison of the FDA-approved indications for paliperidone and risperidone.

CLINICAL PHARMACOLOGY

Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone.[2,3] It exists as a mixture of two equally potent enantiomers, with interconversion observed between the enantiomers.[4] The pharmacologic activity of the two enantiomers is qualitatively and quantitatively similar in vitro.[1]

Paliperidone binds to the central dopamine D_2 receptors and serotonin $5\text{-}HT_{2A}$ receptors; antagonism at these receptors is the proposed mechanism of action.[5,6] The striatal D_2 occupancy after the administration of a 6 mg extended-release tablet in healthy subjects is 64% at 22 hours and 53% at 46 hours.[6,7] Paliperidone is also active as an antagonist at $alpha_1$- and $alpha_2$-adrenergic receptors and H_1 histaminergic receptors.[1] Paliperidone has no affinity for cholinergic muscarinic or $beta_1$- or $beta_2$-adrenergic receptors.[1]

PHARMACOKINETICS

The tablets are formulated using the Alza OROS delivery system, utilizing osmotic pressure to deliver paliperidone.[2] Peak plasma concentrations occur at 23.1 to 29 hours after the oral administration of a paliperidone extended-release tablet.[5] Steady-state concentrations occur after 4 to 5 days of dosing in most patients.[1] The pharmacokinetics are dose-proportional over the 3 to 12 mg dosage range.[1] The oral bioavailability of this formulation is 28%.[4] Administration of the 12 mg extended-release tablet with a standard high-fat/high-caloric meal increased the peak concentration 60% and the area under the curve (AUC) 54% compared with administration under fasting conditions. Although administration with meals may result in increased exposure, paliperidone was not dosed with regard to meals in clinical trials and such dosing is not required.[1] Plasma protein binding of paliperidone is 74%.[1]

Paliperidone is a substrate and

*Executive Editor, *The Formulary;* †Director, Drug Information Center and Professor of Pharmacy Practice; College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495; ‡Clinical Associate Professor of Pharmacotherapy, Drug Information Center, Washington State University Spokane, Wash.

Table 1. Comparison of Indications for Paliperidone and Risperidone[1,2]

Indication	*Paliperidone*	*Risperidone*
Bipolar mania		X
Irritability associated with autistic disorder		X
Schizophrenia	X	X

Table 2. Comparison of the Pharmacokinetic Parameters for Paliperidone and Risperidone[1,2,4,5,9-12]

	Paliperidone	*Risperidone*
Time to peak (h)	24	1
Oral bioavailability (%)	28	70
Half-life (h)	23	3 to 20[a]
Hepatic metabolism	Limited	Extensive
Metabolized by CYP2D6	-	Yes
% excreted unchanged in the urine	59%	NS[b]
Protein binding (%)	74	90

[a]Depends on the metabolizer status; extensive metabolizers = 3 hours and poor metabolizers = 20 hours.

[b]NS = not specified; both parent drug and metabolites are renally excreted.

weak inhibitor of P-glycoprotein, which makes it predisposed to pharmacokinetic drug interactions with P-glycoprotein inhibitors.[3,8] However, at therapeutic concentrations, paliperidone did not inhibit P-glycoprotein and, therefore, is not expected to inhibit P-glycoprotein-mediated transport of other drugs to a clinically important extent.[1]

Paliperidone undergoes limited hepatic metabolism.[9] Approximately 60% of the dose is excreted in the urine as unchanged drug (range, 51% to 67%), with another 32% recovered as metabolites.[1] Following administration of an immediate-release paliperidone formulation, four metabolites were identified in the urine, each accounting for up to 6.5% of the administered dose. Fecal metabolites accounted for only 0.4% to 0.9% of the administered dose.[9,10] The elimination half-life is approximately 23 hours.[1,10] Pharmacokinetic analysis revealed no difference in exposure or clearance between extensive and poor metabolizers of CYP-450 2D6 substrates.[1]

A comparison of the pharmacokinetic parameters for paliperidone and risperidone in healthy adults can be found in Table 2.

Plasma concentrations of free paliperidone were similar in patients with moderate hepatic function impairment (Child-Pugh class B) and in healthy subjects, although total paliperidone exposure decreased because of a reduction in protein binding. No dosage adjustment is necessary in patients with mild or moderate hepatic function impairment. The effects of severe hepatic function impairment have not been assessed.[1]

The dose of paliperidone should be reduced in patients with moderate or severe renal function impairment. Elimination of paliperidone is reduced with declining creatinine clearance (CrCl). Total paliperidone clearance was reduced 32% in patients with mild renal function impairment (CrCl 50 to 79 mL/min), 64% in patients with moderate renal function impairment (CrCl 30 to 49 mL/min), and 71% in patients with severe renal function impairment (CrCl 10 to 29 mL/min), corresponding to an average increase in AUC of 1.5-, 2.6-, and 4.8-fold, respectively. The mean terminal elimination half-life was 24, 40, and 51 hours in patients with mild, moderate, and severe renal function impairment, respectively, compared with 23 hours in subjects with healthy renal function (CrCl 80 mL/min or greater).[1]

No differences in pharmacokinetics were observed in a pharmacokinetic study enrolling Japanese and white subjects.[1] No differences in pharmacokinetics were observed in a pharmacokinetic study enrolling men and women.[1]

COMPARATIVE EFFICACY

Most of the efficacy data for paliperidone extended-release tablets are from three 6-week studies enrolling patients with acute schizophrenia. The results of long-term studies are not available.

Placebo-Controlled Studies

Paliperidone 6 and 12 mg extended-release tablets were assessed in a 6-week, multicenter, double-blind, randomized study enrolling 444 patients with schizophrenia. All patients were experiencing an acute episode of schizophrenia and agreed to hospitaliza-

tion for the first 14 days of the study. The intent-to-treat population included 432 patients with a mean age of 41.6 years, was 55% black and 74% male, and had a baseline Positive and Negative Syndrome Scale (PANSS) total score of 93.7. Patients received paliperidone 6 or 12 mg, placebo, or olanzapine 10 mg once daily. The primary study end point was change in PANSS total score. PANSS total score was reduced 15.7 points in the paliperidone 6 mg group (P = 0.006) and 17.5 points in the paliperidone 12 mg group (P < 0.001) compared with a reduction of eight points in the placebo group. Improvement in Personal and Social Performance (PSP) scores was observed with paliperidone 6 mg (8.8; P = 0.008) compared with placebo (2.9).[13]

Paliperidone extended-release was also assessed in a 6-week, double-blind, placebo-controlled study enrolling 114 patients 65 years of age and older (mean, 70 years of age) with a mean PANSS total score of 70 to 120 (mean, 92.6). Patients received paliperidone extended-release 6 mg or placebo. The paliperidone dose was increased to 9 mg/day after 7 days if tolerated, then adjusted in 3 mg increments over the range of 3 to 12 mg. The mean modal paliperidone dose was 8.3 mg/day. The mean change in PANSS total score was –14.6 in the paliperidone group and –9.9 in the placebo group (least squares mean difference, –5.5; 95% confidence interval [CI], –9.85 to –1.12). The overall incidence of adverse reactions was similar in the paliperidone and placebo groups, although extrapyramidal disorders occurred more frequently in the paliperidone group. No prolactin- or glucose-related adverse reactions were observed. Weight change at end point was similar in the two groups (–0.05 kg with paliperidone vs –0.01 kg in the placebo group).[14]

The effects of paliperidone extended-release on symptom recurrence were assessed in another double-blind study enrolling 530 patients. Patients with acute schizophrenia (PANSS total score between 70 and 132) were initially enrolled in an 8-week, run-in treatment period and received open-label, flexible paliperidone extended-release doses (3 to 15 mg once daily; starting dose 9 mg/day). Patients who achieved symptomatic control during the last 2 weeks of the run-in phase entered a 6-week, open-label stabilization phase (n = 312) and were continued on the same dose of paliperidone. Patients who remained stable during the stabilization phase entered a double-blind phase (n = 207) and were randomly assigned to paliperidone extended-release (at the same dose as in the stabilization phase) or placebo. The primary study end point was the time to first recurrence event in the double-blind phase. An interim analysis was scheduled at the 43rd recurrence event, and, at that time, the study was terminated at the recommendation of the monitoring committee based on a prespecified threshold for significance versus placebo. Among patients entering the double-blind phase, recurrence events occurred in 52% of placebo-treated patients compared with 22% of paliperidone-treated patients (P < 0.001). The time point at which 25% of patients experienced a recurrence event was 23 days with placebo compared with 68 days with paliperidone. Results for the primary end point were not presented in the meeting abstract. Mean PANSS total score in the double-blind phase was increased 15.1 points in the placebo group compared with an increase of 6 in the paliperidone group (P < 0.001).[15,16]

Placebo-Controlled Comparator Group Studies

The efficacy and safety of paliperidone were assessed in a 6-week, multicenter, double-blind, randomized, placebo-controlled study including 628 patients with acute schizophrenia. Enrolled patients were 18 years of age and older (mean, 37.1 years of age) and experiencing an acute episode of schizophrenia, as represented by a PANSS total score between 70 and 120 (mean, 93.9). All patients were diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria at least 1 year prior to screening and agreed to a voluntary hospitalization for a minimum of 14 days. The patient population was 52% male and 86% white, 42% of patients were previously hospitalized for psychosis four or more times, 61% received previous therapy with atypical antipsychotics, and 57% received conventional antipsychotics. The primary comparison was between paliperidone 6 mg (123 patients), 9 mg (122 patients), or 12 mg (129 patients) extended-release tablets once daily or placebo once daily (126 patients). Another group of patients received olanzapine 10 mg once daily (128 patients) with results compared with placebo as an assay sensitivity group to confirm study validity. The study was completed by 66% of patients (46% of patients in the placebo group and 65% to 78% in the active-treatment groups). Lack of efficacy prompted early discontinuation two and a half to four times more frequently in the placebo group (40% of discontinuations in

the placebo group vs 10% to 16% of discontinuations in the active-treatment groups). Compared with placebo, all doses of paliperidone were associated with improvement in PANSS total score, all PANSS Marder factor scores, and personal and social functioning. PANSS total score also improved in the olanzapine group. PANSS total score decreased 17.9 points in the 6 mg group, 17.2 points in the 9 mg group, 23.3 points in the 12 mg group (all $P < 0.001$ vs placebo), 19.9 points in the olanzapine group, and 4.1 points in the placebo group. Similar improvements compared with placebo (all $P < 0.001$) were seen in all PANSS Marder factor scores (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression). A 30% or greater reduction in PANSS total score was achieved in 52% of patients treated with olanzapine, 56% of patients treated with paliperidone 6 mg, 51% treated with paliperidone 9 mg, and 61% treated with paliperidone 12 mg compared with 30% of placebo recipients ($P < 0.001$ for all paliperidone groups vs placebo). A 50% or greater reduction was achieved in 32% of patients treated with paliperidone 12 mg compared with 15% treated with placebo ($P = 0.001$). The incidence of movement disorder-related adverse reactions and rating scale measurements were similar to placebo in the paliperidone 6 mg group, but more common in the 9 and 12 mg groups. There were no reports of glucose-related adverse reactions, clinically important lipid changes, or changes in body weight of more than 1 kg in the paliperidone-treated patients, although the study duration was only 6 weeks.[2]

Paliperidone extended-release was also assessed in a 6-week, double-blind, placebo-controlled study enrolling 618 patients with an episode of acute schizophrenia. Patients received paliperidone extended-release 3, 9, or 15 mg, placebo, or olanzapine 10 mg once daily. The primary efficacy end point was the change from baseline to end point in PANSS total score. The enrolled population was 49% white and 68% male, with a mean age of 36.8 years and a mean PANSS total score of 93. At end point, PANSS total score was reduced 18.1 in the olanzapine group, 2.8 in the placebo group, 15 in the 3 mg group, 16.3 in the 9 mg group, and 19.9 in the 15 mg group ($P < 0.001$ for paliperidone vs placebo). Improvement in PANSS total score was observed within 4 days of initiation of paliperidone therapy. PSP scores were also improved at each paliperidone dose compared with placebo (8.3 at 3 mg, 7.6 at 9 mg, 12.2 at 12 mg, and 1.5 with placebo ($P < 0.001$).[17]

Pooled Analysis

A pooled analysis of these three 6-week studies was also conducted with results from 1,306 patients included in the intent-to-treat analysis. Mean patient age was 38.3 years; 62% were white and 62% were male. Baseline PANSS total score was 93.5. Mean PANSS total score at end point was improved at each paliperidone dose (–15 with 3 mg, –16.9 with 6 mg, –16.8 with 9 mg, –20.6 with 12 mg, –19.9 with 15 mg compared with –4.8 with placebo; $P < 0.001$). All PANSS Marder factor scores were also improved for paliperidone compared with placebo ($P \leq 0.001$). Response was achieved in 39.8% of patients treated with paliperidone 3 mg, 53.2% treated with paliperidone 6 mg, 48.2% treated with paliperidone 9 mg, 56.7% treated with paliperidone 12 mg, and 52.7% treated with paliperidone 15 mg, compared with 27.4% treated with placebo; $P < 0.001$). Mean changes in body weight with placebo and paliperidone 3, 6, 12, and 15 mg, respectively, were –0.4, 0.6, 0.6, 1, 1.1, and 1.9 kg.[18]

A post hoc pooled analysis from these three 6-week paliperidone studies also assessed the efficacy of paliperidone in 270 patients with predominant negative symptoms. At end point, improvements in PANSS negative factor scores were greater in the paliperidone groups (–6.3 in the 3 mg group, –5.5 in the 9 mg group, and –5.6 in the 12 mg group compared with –2.8 in the placebo group [$P < 0.02$]). PANSS total, Clinical Global Impression-Severity (CGI-S), and PSP scores were also improved in all three paliperidone dose groups compared with placebo.[19] In an additional post hoc pooled assessment of the effects of paliperidone on negative symptoms, improvement in negative symptoms was determined to be directly related to paliperidone effects on negative symptoms as well as secondary to indirect paliperidone effects on both positive and depressive symptomatology.[20]

In another post hoc pooled analysis from the three 6-week paliperidone studies, including 1,306 patients, paliperidone extended-release 3, 6, 9, 12, and 15 mg doses were associated with greater improvements in quality of sleep than placebo, as assessed by a visual analog scale (VAS). VAS scores were improved 9 points in the paliperidone 3 mg group, 11.1 points with 6 mg, 11.4 points with 9 mg, 9.7 points with 12 mg, and 11.3 points with 15 mg, compared

with a change of 0.6 on placebo ($P < 0.05$). Daytime drowsiness, also assessed by mean change in VAS, was not observed at any paliperidone dose compared with placebo.[21]

In another post hoc pooled assessment, including 1,192 patients from these three 6-week studies, improvement in PANSS total score compared with placebo was observed for all paliperidone doses by treatment day 4 (–2.9 for placebo vs –5.8, –5.6, –5.1, and –5.8 for paliperidone 3, 6, 9, and 12 mg, respectively; $P < 0.05$). Sustained improvement was observed over the duration of the studies. Improvement in all PANSS Marder factor scores was also observed by day 4 in at least one paliperidone group. Improvement in CGI-S score for all doses compared with placebo was observed on day 8, with sustained improvement also observed over the duration of the studies.[22,23]

Another post hoc pooled assessment from these three 6-week studies examined paliperidone compared with placebo in 384 patients diagnosed with schizophrenia within 5 years of study entry. The mean time since diagnosis was 2.8 years. Mean baseline PANSS total scores ranged from 90.7 to 93.4. At end point, mean PANSS total scores improved from baseline at each paliperidone dose compared with placebo (–15.5, –16.4, –18.7, –17.7, –7.4 for paliperidone 3, 6, 9, and 12 mg, and placebo, respectively; $P < 0.02$). Similar improvement was also observed for CGI-S scores and PSP scores.[24]

CONTRAINDICATIONS

Paliperidone is contraindicated in patients with a history of hypersensitivity to paliperidone, risperidone, or any of the product ingredients (eg, carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, iron oxides).[1]

WARNINGS AND PRECAUTIONS

The warnings and precautions associated with paliperidone are similar to those of risperidone.[1,12]

Paliperidone labeling contains the class warnings regarding tardive dyskinesia, neuroleptic malignant syndrome, hyperglycemia, and diabetes mellitus, and the class black box warning regarding increased mortality in elderly patients with dementia-related psychosis.[1] Labeled precautions are also similar to those of risperidone and include orthostatic hypotension and syncope, seizures, dysphagia, hyperprolactinemia, potential for cognitive and motor impairment, priapism, body temperature regulation disruption, suicide risk, and renal function impairment.[1,12] Because of the risk of orthostatic hypotension with paliperidone, the agent should be used with caution in patients with known cardiovascular disease.[1]

Paliperidone causes a modest increase in corrected QT interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc, including class 1A (eg, quinidine, procainamide) or class 3 (eg, amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (eg, chlorpromazine, thioridazine), antibiotics (eg, 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. In a study of the effects of paliperidone on QTc interval, paliperidone 8 mg immediate-release showed a mean placebo-subtracted increase from baseline of 12.3 msec (90% CI, 8.9, 15.6) on day 8 at 1.5 hours postdose. The mean steady-state peak plasma concentration with this 8 mg dose (113 ng/mL) was more than twice the exposure for the 12 mg extended-release formulation (45 ng/mL). With a 4 mg immediate-release tablet (peak concentration, 35 ng/mL), the placebo-subtracted QTc was 6.8 msec (90% CI, 3.6, 10.1) on day 2 at 1.5 hours postdose. No subjects in this study had a change exceeding 60 msec or a QTc exceeding 500 msec at any time during the study. While in the efficacy studies with the extended-release formulation, only one subject treated with the 12 mg dose had a QTc change exceeding 60 msec and no subjects had a QTc exceeding 500 msec at any time in any of the three placebo-controlled studies.[1]

The paliperidone extended-release tablet is nondeformable and does not change shape in the gastrointestinal (GI) tract, therefore it should not be administered to patients with pre-existing severe GI narrowing (eg, esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel diverticulum) to minimize the risk of a bowel obstruction.[1]

Oral bioavailability from the tablet formulations may be reduced with conditions that decrease GI transit time (eg, diarrhea), while bioavailability may be increased with conditions that increase GI transit time (eg, GI neuropathy and diabetic gastro-

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