



Paliperidone

Long-acting antipsychotic can be taken once daily

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Paliperidone, a second-generation antipsychotic (SGA), was awaiting FDA approval for treating schizophrenia (*Table 1*) at press time. FDA issued an approvable letter September 29.

The long-acting oral medication can be given once daily, without the plasma level peaks and troughs associated with other SGAs.

CLINICAL IMPLICATIONS

Paliperidone—the active metabolite of risperidone (9-hydroxy risperidone)—produces the same effects

as its parent compound. Because it is metabolized less by the liver, however, paliperidone will likely have a lower risk of drug-drug interactions than risperidone.

Paliperidone can help patients with hallucinations, delusions, and other florid psychotic symptoms. Once-daily dosing could also make it easier for patients with schizophrenia to adhere to treatment.

Paliperidone caused relatively few side effects in clinical trials, indicating that the drug could be started at therapeutic dosages. A 6-mg dose reaches clinically effective plasma levels in approximately 22 hours; a higher dosage might take less time.

Table 1

Paliperidone: Fast facts

Class: Second-generation antipsychotic
Prospective indication: Schizophrenia
FDA action: Issued approvable letter September 29, 2006
Manufacturer: Janssen Pharmaceutica
Dosing forms: Not determined
Recommended dosage: Data suggest that 6 mg/d is a suitable starting dosage for most patients. ¹⁻³ No formal recommendation issued

HOW IT WORKS

As with all antipsychotics, paliperidone blocks dopamine uptake (D2 receptors) and—as with other newer SGAs—it has a high affinity for 5-HT (serotonin) receptors. This serotonergic action may help modulate side effects.

Paliperidone has shown antipsychotic effectiveness at 3 to 15 mg/d, and a 6-mg dosage is no more likely to cause extrapyramidal symptoms (EPS) or other adverse events than olanzapine, 10 mg/d, or placebo.¹⁻³ This finding suggests that 6 mg/d might be a suitable starting dosage for most patients.

CLINICAL FINDINGS

Efficacy. The drug showed efficacy for treating acute schizophrenia in three randomized, double-blind, controlled trials.

In a 6-week study,¹ 444 patients who were experiencing acute schizophrenia episodes and had Positive and Negative Syndrome Scale (PANSS) scores between 70 and 120 received paliperidone, 6 or 12 mg/d, olanzapine, 10 mg/d, or placebo. The study was powered to compare paliperidone and placebo; the olanzapine group was included to confirm study sensitivity.

Mean baseline total and negative symptom PANSS scores improved twice as much among the paliperidone and olanzapine groups compared with placebo (*Table 2*). Personal and Social Performance (PSP) scale scores also improved significantly among patients receiving paliperidone, 6 mg/d. The PSP scale gauges function, ability to perform socially useful activities such as self-care and work, and disturbing and aggressive behavior.

In two similarly designed, 6-week studies (N=1,248),^{2,3} paliperidone at 3, 6, 9, or 12 mg/d produced statistically significant improvement in total and negative symptom PANSS scores and PSP scale scores compared with placebo.

Relapse prevention. Kramer et al⁴ measured paliperidone's ability to prevent or delay schizophrenia recurrence among 205 patients experiencing an episode. Participants had been diagnosed with schizophrenia at least 1 year earlier and had PANSS total scores between 70 and 120. Patients with substance dependence or other axis I disorders were excluded.

Over an 8-week run-in period, patients were hospitalized for 2 weeks and started on

open-label paliperidone, 9 mg/d; dosages then were titrated to 3 to 15 mg/d depending on efficacy and tolerability. Once stable for 2 weeks, subjects were discharged and maintained on paliperidone for 6 weeks, then were randomized to a double-blind phase during which they received a similar dosage of paliperidone or placebo. Regimen duration varied during the double-blind phase.

The study was stopped after 2 months when an interim analysis showed significant efficacy for paliperidone. Among patients who relapsed, mean time to relapse was 68 days among patients taking paliperidone (n=14, 25%), compared with 25 days in the placebo group (n=29, 53%).

Recurrence was defined as:

- psychiatric hospitalization
- total PANSS score ≥ 40 at randomization decreased by 25% for 2 days, or total PANSS score <40 at randomization fell ≥ 10 points
- Clinical Global Impression of Severity (CGI-S) score ≥ 3 at randomization increased to ≥ 4 for 2 days, or CGI-S score ≥ 4 at randomization rose to ≥ 5
- individual-item PANSS baseline score ≥ 3 increased to ≥ 5 for 2 days, or baseline score ≥ 4 rose to ≥ 6
- self injury, suicidal or homicidal thoughts, or clinically significant aggressive behavior.

Table 2

Mean PANSS score reductions among patients taking paliperidone, olanzapine, or placebo

	Paliperidone, 6 mg/d	Paliperidone, 12 mg/d	Olanzapine, 10 mg/d	Placebo
Total PANSS score	17.5	17.5	18.4	8.0
Negative symptom PANSS score	4.4	3.9	4.4	2.2

Source: Reference 1

continued

Related resources

- ▶ Karlsson P, Dencker E, Nyberg S, et al. Pharmacokinetics, dopamine D2 and serotonin 5-HT2A receptor occupancy and safety profile of paliperidone extended-release in healthy subjects. Poster presented at: Winter Workshop on Schizophrenia (WWS); February 5-11, 2006; Davos, Switzerland.

DRUG BRAND NAMES

Olanzapine • Zyprexa
Risperidone • Risperdal

DISCLOSURES

Dr. Simpson receives grant support from AstraZeneca Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, and Johnson & Johnson. He is a consultant to Janssen Pharmaceutica, Johnson & Johnson, Merck and Co., and Pfizer, and is a speaker for Janssen Pharmaceutica and Pfizer.

A final analysis showed a 22% relapse rate among patients taking paliperidone vs. 52% of the placebo group. Paliperidone was associated with improvements in PANSS, CGI-S, PSP, and quality of life measures at all dosages.

SAFETY

Compared with placebo, mean prolactin levels in the long-term study were four times as high among men (40 vs. 10 ng/mL) and five times as high among women (100 vs. 20 ng/mL) who received paliperidone at any dosage.⁴ Also, EPS such as dystonia and hyperkinesia were more prevalent at 12 mg/d (10%) than at 6 mg/d (5%).^{1,2}

During paliperidone therapy, patients should be asked if they are experiencing abnormal movements, sexual dysfunction, breast enlargement, or irregular menstruation (women). If so, decrease the dosage by 3 mg and monitor for side effects and clinical efficacy.

Paliperidone, a second-generation antipsychotic awaiting FDA approval, has reduced schizophrenia's positive and negative symptoms in clinical trials. Data suggest the drug can be taken once daily with low side-effect risk.

BottomLine

Among other reported adverse effects in the efficacy studies:

- somnolence was less prevalent among patients receiving either paliperidone, 3 to 12 mg/d, or placebo (13%) than among those receiving olanzapine, 10 mg/d (25%)³
- tachycardia was more prevalent among the paliperidone and olanzapine groups (14% to 20%) compared with placebo (0%)¹⁻³
- headache prevalence (10% to 20%) was similar in all groups¹⁻³
- mean body weight changes after 6 weeks were more pronounced in the olanzapine group (1.3±2.8 kg) than among patients receiving placebo (-0.7±2.4 kg) or paliperidone at 6 mg/d (0.2±2.4 kg), 9 mg/d (0.6±2.7 kg), or 12 mg/d (0.6±2.6 kg).²

In the relapse prevention study,⁴ potential neuroleptic malignant syndrome was reported in 1 patient taking paliperidone 3 days after the patient withdrew from the study. The patient had received paliperidone for 19 days and was treated for EPS with an unknown medication during the run-in period. Medical status returned to normal at endpoint except for elevated creatine kinase.

Discontinuation rates in the relapse prevention study's double-blind phase were greater among the paliperidone group (n=20, 19%) compared with placebo (n=8, 8%).⁴ The reasons paliperidone group patients withdrew consent were not available.

References

1. Marder S, Kramer M, Ford L, et al. Efficacy and safety of oral paliperidone extended-release tablets in treatment of schizophrenia: a 6-week placebo control study. Poster presented at: Winter Workshop on Schizophrenia (WWS); February 5-11, 2006; Davos, Switzerland.
2. Kane J, Kramer J, Ford L, et al. Treatment of schizophrenia using oral paliperidone extended-release tablets: a 6-week placebo-controlled study. Poster presented at: WWS; February 5-11, 2006; Davos, Switzerland.
3. Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and effect on functioning of paliperidone extended-release in healthy subjects. Poster presented at: WWS; February 5-11, 2006; Davos, Switzerland.
4. Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended release tablets for prevention of symptom recurrence in patients with schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* (in press).