Paliperidone palmitate: Once-monthly treatment option for schizophrenia

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Fast onset of action and long half-life simplifies administration

Paliperidone palmitate (9-hydroxy-risperidone) is an injectable, once-monthly atypical antipsychotic medication, FDA-approved in July 2009 for acute and/or maintenance treatment of schizophrenia. This aqueous-based, extremely slowly dissolving depot medication is well tolerated and causes few drug-drug interactions.[1] Clinically, paliperidone palmitate and its parent drug, intramuscular (IM) risperidone, have similarities and differences.

Clinical information

Paliperidone palmitate is available in 39-mg, 78-mg, 117-mg, 156-mg, and 234-mg formulations. Once administered, it hydrolyzes and diffuses slowly and provides paliperidone doses equivalent to 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg, respectively. The 234-mg dose of paliperidone palmitate is equivalent to 12 mg oral paliperidone, 117 mg to 6 mg, and 39 to 78 mg to 3 mg, respectively (visit this article at CurrentPsychiatry.com to learn more about paliperidone palmitate).

Pharmacokinetics. This palmitate ester of paliperidone is an aqueous suspension utilizing nanocrystal molecules. The increased surface area leads to rapid medication release and a short time to steady state. Active paliperidone plasma levels were detected at day 1, meaning co-administration with the oral formulation is not necessary. Paliperidone palmitate's slow dissolution rate results in a half-life of 25 to 49 days. The fast onset of action and long half-life simplifies administration.

Co-administration with carbamazepine decreases paliperidone levels, whereas divalproex causes an increase. Up to 60% of paliperidone is excreted unchanged through the kidneys, which means patients with impaired renal function require a lower dosage. Because the liver has only a minimal role in paliperidone palmitate's metabolism, dose adjustment is needed only for patients with severe hepatic dysfunction.[1]

Administration. Before starting this medication, test for allergy with a dose of oral paliperidone. Then administer 2 consecutive loading doses of paliperidone palmitate by deltoid IM injection; first 234 mg, and then a 156-mg dose after 7 to 10 days. Monthly injections of 117 mg are recommended, although higher or lower dosages can be used depending on the clinical situation. The first 2 injections should be in the deltoid muscle because plasma concentrations are 28% higher with deltoid vs gluteal administration. Subsequent injections can alternate between gluteal and deltoid sites.

If a dose is missed within 6 weeks of the last injection, administer the most recently used dosage. For discontinuation of 6 weeks to 6 months, administer 2 injections of the previously stabilized dose separated by 1 week, followed by the regular monthly dosage. After >6 months, begin the initial loading dose regimen.[1]

Paliperidone palmitate is available in prefilled syringes that do not require refrigeration or reconstitution. Use a 22-gauge needle for deltoid injections and for patients weighing >200 lbs. Use a 23-gauge

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needle for gluteal injections in non-obese individuals. Do not inject into a blood vessel, and alternate injection sites between sides of the body each month.[1]

Efficacy

In a 9-week, phase II, double-blind study, mean Positive and Negative Syndrome Scale (PANSS) scores improved in patients receiving paliperidone, 78 mg or 156 mg (mean change -5.2 and -7.8, respectively) compared with placebo (6.2). Two percent of the paliperidone group discontinued the agent, compared with 10% of placebo. Although extrapyramidal symptoms were comparable in all groups (1%), 5% of patients receiving 78 mg and 8% of patients receiving 156 mg reported parkinsonian adverse events, compared with 1% with placebo.[2]

In other double-blind, placebo-controlled trials, paliperidone dosages from 25 mg to 150 mg were associated with a decrease in positive and negative symptoms in 1,540 subjects.[1] During a 1-year study, 18% of patients taking paliperidone palmitate relapsed, compared with 48% for placebo.[1]

In a 53-week study, both paliperidone palmitate and IM risperidone were effective in decreasing positive and negative symptoms; however, risperidone-treated patients showed greater therapeutic response.[3] Mean PANSS score changes in patients receiving paliperidone were -11.6, compared with -14.4 with risperidone. Psychotic relapse occurred in 14% of IM risperidone patients and 18% of paliperidone palmitate patients.[3]

In an unpublished 13-week, randomized, double-blind study conducted by the drug's manufacturer, paliperidone palmitate, 78 mg to 234 mg once monthly, and long-acting risperidone, 25 mg to 50 mg every other week with supplemental oral risperidone for 2 to 3 weeks, were reported as equivalent.[1] Both groups showed similar decrease in PANSS scores (-18.6 vs -17.9); however, reported adverse events were slightly higher in patients receiving paliperidone (57.9% vs 52.8%).[1]

Adverse events

Common side effects include insomnia (15%), anxiety (10%), and headaches (9%). Dizziness, agitation, gastrointestinal upset, hypotension, and urinary tract infection have been reported. Rarely, tachycardia, clinically nonsignificant QTc prolongation, and tardive dyskinesia occur. Increased prolactin levels have been observed, particularly in females. This drug should not be prescribed to pregnant or lactating women or elderly patients with dementia-related psychosis. In the 13-week trial, patients gained up to 3.3 lbs. Other adverse effects include allergic reactions, blood dyscrasias, elevated liver enzymes, lower seizure thresholds, body temperature dysregulation, neuroleptic malignant syndrome, dysphagia, and motor impairments.[1]

Clinically significant adverse effects were reported in 25% of paliperidone-treated subjects compared with 20% in the risperidone IM group. The discontinuation rate was 5% for paliperidone palmitate, compared with 3% for IM risperidone. Hyperkinesia with paliperidone (6%) was less prominent than with risperidone (10%).[3]

References

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3. Fleischhacker W. A randomized, double blind, parallel-group comparative study of flexibly dosed paliperidone palmitate (25, 50, 75, or 100 mg eq.) administered every 4 weeks and flexibly dosed Risperdal® Consta® (25, 37.5, or 50 mg) administered every 2 weeks in subjects with schizophrenia. Available at: http://download.veritasmedicine.com/PDF/CR004195_CSR.pdf. Accessed November 23, 2009.

Drug Brand Names

Carbamazepine • Tegretol
Divalproex • Depakote
Paliperidone • Invega
Paliperidone palmitate • Invega Sustenna
Risperidone IM • Risperdal Consta

Disclosure

Dr. Lindenmayer has received grant support from AstraZeneca, Otsuka, Pfizer Inc., Dainippon Sumitomo, Azur, Janssen, Eli Lilly and Company, and National Institute of Mental Health. He is a consultant to Eli Lilly and Company and Janssen. Drs. Sedky, Nazir, and Lippmann report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Acknowledgments

The authors thank Dr. Roop Parlapalli, an observer physician at University of Louisville School of Medicine, for his editorial revision.

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Table

Paliperidone palmitate: Fast facts

Brand name: Invega Sustenna

Indication: Acute and/or maintenance treatment of patients with schizophrenia

Approval date: July 31, 2009

Manufacturer: Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Dosing forms: 39-, 78-, 117-, 156-, and 234-mg doses of injectable solutions

Cost: Is not covered by private insurance and requires prior authorization for Medicare or Medicaid coverage. According to Internet pharmacies, monthly paliperidone costs:

- $255 for 39 mg
- $509 for 78 mg
- $763 for 117 mg
- $1,017 for 156 mg
- $1,525 for 234 mg.

Monthly costs for IM risperidone are:

- $302 for 12.5 mg
- $642 for 25 mg
- $934 for 37.5 mg
- $1,280 for 50 mg.