

Invega: prolonged-release paliperidone for schizophrenia

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KEY POINTS

- paliperidone, the active metabolite of risperidone, is licensed for the treatment of schizophrenia
- available as a modified-release formulation for once-daily administration; 3mg – £97.28 (28), 6mg – £97.28 (28), 9mg – £145.92 (28)
- in short-term randomised trials in patients with schizophrenia of at least one year's duration, paliperidone improved the symptoms of schizophrenia with response rates of 40-50 per cent compared with 18-34 per cent with placebo
- efficacy and adverse effects of paliperidone appear to be comparable with olanzapine
- once-daily regimen should improve adherence



Paliperidone (Invega) is a new atypical antipsychotic available as modified-release tablets for once-daily administration. Here, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Martin Livingston comments on its place in the treatment of schizophrenia.

The atypical antipsychotics, with the exception of clozapine, are recommended as first-line treatments for newly-diagnosed schizophrenia and for those whose treatment with older antipsychotics is effective but poorly tolerated.¹ Risperidone (Risperdal) and olanzapine (Zyprexa) have similar efficacy.^{2,3} However, the atypicals are particularly distinguished by their adverse effects: olanzapine is associated with weight gain³ and a higher risk of altered glycaemic control,³ whereas risperidone is associated with greater effects on prolactin,³ ejaculatory dysfunction² and drug treatment for extrapyramidal effects.²

Risperidone is an antagonist at dopamine D₂ and serotonin 5HT₂ receptors, and also has some alpha₁- and alpha₂-blocking activity and antihistamine H₁ activity.⁴ Its activity is due both to the parent compound and its active metabo-

lite paliperidone, which has a similar receptor-binding profile.⁵

Paliperidone (Invega) is now licensed for the treatment of schizophrenia and is available as modified-release tablets, using the OROS osmotic system, for once-daily administration. The prolonged-release formulation uses osmosis technology to provide constant plasma levels over 24 hours (see Figure 1).

The recommended dose is 6mg daily, adjusted within the range 3-12mg daily according to response. Patients with mild renal impairment should receive 3mg daily and older patients may therefore need dose adjustment. The dose should be taken consistently with or without food, because absorption is increased by a fatty meal. Prescribing precautions are similar to those of risperidone. Paliperidone may increase the QT interval.

Clinical trials

Three randomised, double-blind, placebo-controlled six-week trials in a total of 1692 patients provide the key efficacy data for paliperidone.⁶⁻⁸ Each included patients with schizophrenia diagnosed at least one year previously with active symptoms and a PANSS (Positive and Negative Syndrome Scale) score of 70-120, thereby excluding patients with severely disabling symptoms. The primary end-point was the change in PANSS score. All included olanzapine 10mg daily as an active comparator.

Overall, the change in PANSS score was similar for doses ranging from 3-12mg daily and significantly greater than with placebo, with a nonsignificant trend for greater effects at higher doses. There was no significant difference in efficacy at any dose compared with olanzapine. Response rates, defined as at least a 30 per cent reduction in base-

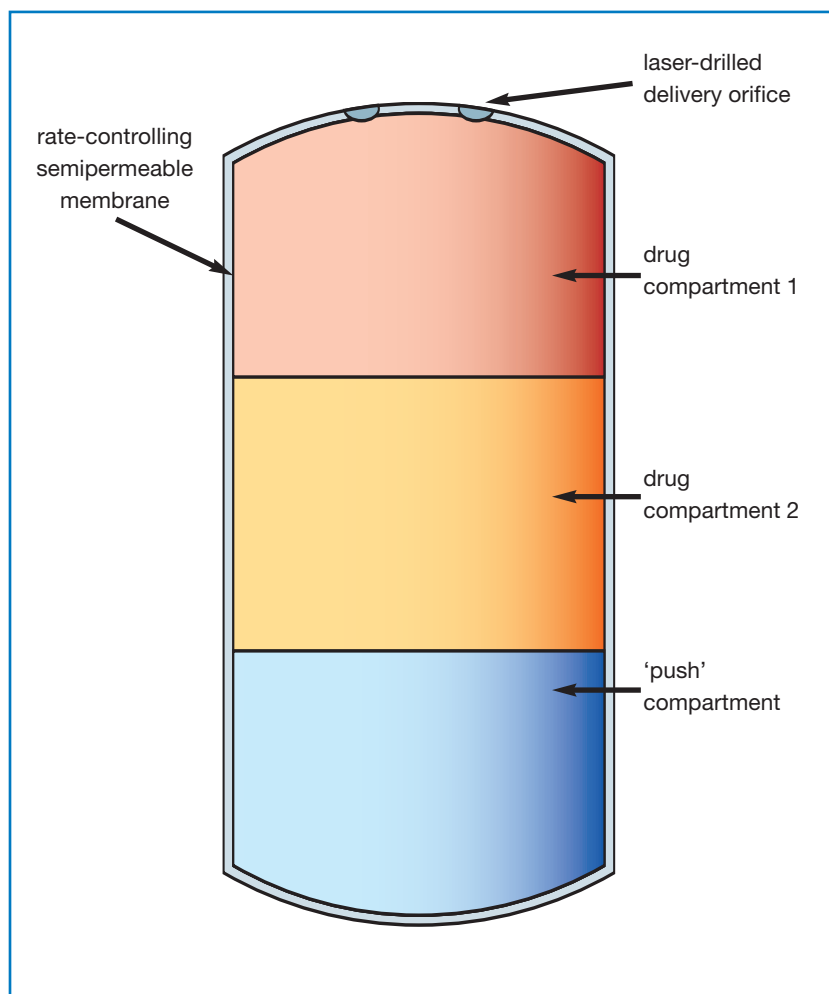


Figure 1. OROS technology includes a liquid drug compartment, an osmotic 'push' compartment, a semipermeable membrane and a drug delivery orifice. In the gut, water passes through the semipermeable membrane, expanding the 'push' compartment and forcing the drug through the delivery orifice

line PANSS score, were 40-51 per cent compared with 18-34 per cent with placebo. The effects of paliperidone on positive and negative symptoms, and on quality of life, were similar to those of olanzapine.

Most withdrawals from treatment (n=720) were due to lack of

efficacy, with higher rates at lower doses of paliperidone. Discontinuation rates were similar for paliperidone and olanzapine.

A fourth trial to determine the efficacy of paliperidone in preventing recurrence was terminated early when an interim analysis

demonstrated a twofold higher recurrence rate among patients randomised to placebo after having been treated with paliperidone for 14 weeks (see Figure 2).⁹

Adverse effects

In clinical trials the commonest adverse effects were headache (13 per cent), tachycardia (7 per cent) and sinus tachycardia (6 per cent), akathisia (7 per cent), extrapyramidal disorder (5 per cent) and somnolence or sedation (4-5 per cent). The only clinically relevant difference from olanzapine in these trials was a lower rate of somnolence. The effects of paliperidone on prolactin levels were dose related and similar to those of risperidone, resulting in adverse effects in fewer than 4 per cent of patients. Other dose-dependent, but uncommon, adverse effects in these trials included weight gain and orthostatic hypotension.

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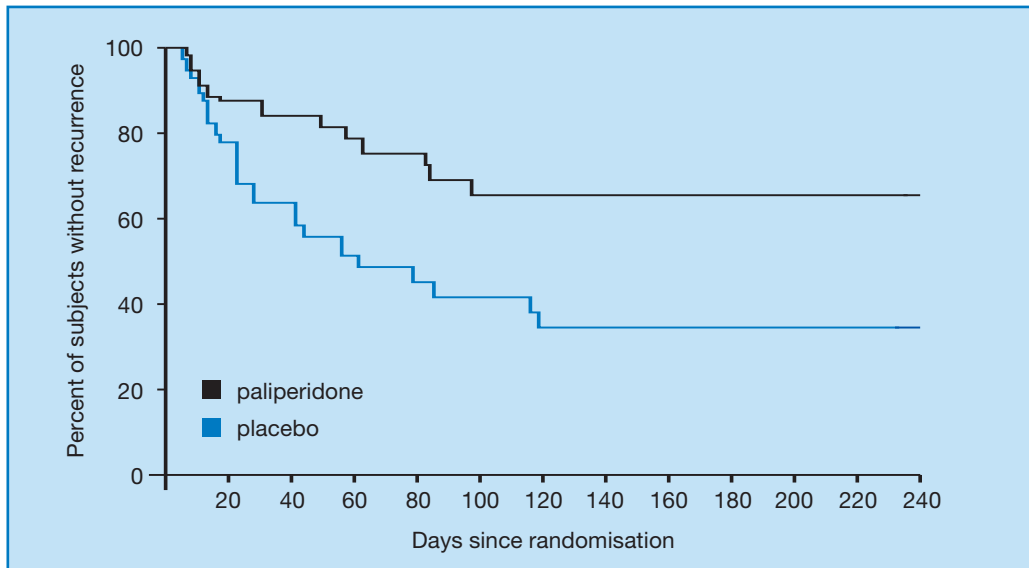


Figure 2. Time to symptom recurrence, paliperidone vs placebo.⁹ Patients were randomised to paliperidone or placebo after a 14-week paliperidone stabilisation phase. The trial was terminated at the interim analysis phase, at which time 25 per cent of paliperidone-treated patients had had a recurrence versus 53 per cent of patients taking placebo

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

In the UK, second-generation (atypical) antipsychotic drugs have become the mainstay in the treatment of patients with psychotic illnesses. This is especially true in early intervention programmes in first-onset psychosis. Their main advantage is that they are less likely to induce extrapyramidal movement disorder. This benefit, perhaps more than any other, has encouraged many GPs to initiate treatment in primary care with antipsychotics.

Meta-analyses of clinical trials have not, however, supported the contention of superior efficacy of the newer antipsychotics in treatment, with the exception of clozapine, which is reserved for treatment-resistant patients. Concern about the link between

some second-generation antipsychotics, olanzapine and clozapine especially, and the onset of the metabolic syndrome has led many community mental health teams to establish physical-health and well-being clinics.

It is salutary to note that over 70 per cent of patients discontinue antipsychotics within 18 months, regardless of whether they are on a first- or second-generation preparation, although significantly fewer stopped olanzapine given in high dose (average 20.1mg).¹

Paliperidone, the active metabolite of risperidone, shares its receptor-binding properties. It is available as a once-daily extended-release preparation that utilises an osmotic technology for consistent and continual drug delivery. Paliperidone is effective in trials of at least one-year duration in comparison with the rather

low dose of 10mg olanzapine. A relapse prevention study was terminated early due to the evident superiority of paliperidone over placebo. Paliperidone shares the side-effect profile of risperidone and therefore similar cautions in prescribing apply.

Paliperidone is simple to titrate, a useful feature in acute psychotic illness, and the once-daily regimen should enhance adherence, a major problem in the long-term management of psychosis.

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