

# NEW DRUG EVALUATION

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## PALIPERIDONE

Paliperidone, the major metabolite of risperidone, is a new atypical antipsychotic licensed for the management of schizophrenia. Paliperidone should not be used in place of adequate therapeutic trials of more established and evaluated atypical antipsychotics. In short-term studies paliperidone has been shown to be effective, demonstrating improvements in symptom scores, compared with placebo. There are limited comparative data with other less costly atypical antipsychotics which suggest similar efficacy and tolerability. Fully published longer-term safety and efficacy data are currently lacking.

### What is it?

Paliperidone (Invega<sup>®</sup>, Janssen-Cilag Ltd) is the major metabolite of risperidone. It is a prolonged release oral atypical antipsychotic licensed for the treatment of schizophrenia in adults. The recommended dose is 6mg once daily, administered in the morning, though doses range from 3 to 12 mg once daily. When administered with food, plasma concentrations of paliperidone are increased by 50 - 60% compared with administration in the fasting state.<sup>1</sup> A generic version of risperidone became available in 2007.

Paliperidone prolonged release tablets must be swallowed whole and must not be chewed, divided or crushed.<sup>1</sup>

### How effective is it?

Three multi-centre, randomised, double-blind, placebo-controlled trials examined the efficacy and safety of paliperidone in subjects who met DSM-IV criteria for schizophrenia. Paliperidone doses, which varied across the three studies, ranged from 3 mg to 15 mg once daily. The primary endpoint was decrease in total Positive and Negative Syndrome Scale (PANSS) score from baseline assessment, for which  $\geq 30\%$  reduction is defined as clinically significant. Secondary endpoints included the Personal and Social Performance (PSP) scale and the Clinical Global Impression - Severity (GCI-S) scale.

A 6-week study assessed the efficacy and safety of once-daily paliperidone (6 mg, 9 mg and 12 mg) versus placebo or olanzapine 10 mg in 630 patients, 66% of whom completed the study. All doses of paliperidone demonstrated significant improvement in total PANSS score, with significantly more patients attaining  $\geq 30\%$  reduction in PANSS total score (51-61%) compared with placebo (30%;  $p < 0.001$ ).<sup>2</sup>

A second 6-week study randomised 618 patients to once-daily paliperidone (3 mg, 9 mg and 15 mg), placebo or olanzapine 10mg, with 59% of patients completing the study. All doses of paliperidone demonstrated significant improvement in total PANSS score ( $p < 0.001$ ), with 40 - 53% of the treatment groups achieving  $\geq 30\%$  reduction in total PANSS score compared with 18% of the placebo group ( $p \leq 0.005$ ). Significant improvements in personal and social functioning were also demonstrated compared with placebo.<sup>3</sup>

A further 6-week study randomised 444 patients to once-daily paliperidone (6 mg and 12 mg), placebo and olanzapine 10 mg, with 43% of patients completing the study. Both doses of paliperidone demonstrated significant improvement in total PANSS score, from baseline, when compared with placebo ( $p = 0.006$  and  $p < 0.001$ , respectively).<sup>4</sup> Lack of efficacy was the most commonly reported reason for withdrawal from each of these studies (19-24% of total study population).<sup>2,4</sup>

All three studies included an active treatment group receiving olanzapine 10 mg.<sup>2,4</sup> This was to provide a concurrent active control group to confirm that the studies were adequate to detect a drug effect in the event of negative findings for paliperidone compared with placebo. Although the studies were not designed for statistical comparison, the efficacy of paliperidone and olanzapine was similar.<sup>5</sup>

A fourth study evaluated the efficacy and safety of paliperidone in delaying symptom recurrence in patients who had been stabilized after an acute episode of schizophrenia. In this randomised, double-blind, placebo-controlled study 530 patients were stabilized during an 8-week run-in phase using open-label, flexibly dosed once-daily paliperidone (3 mg - 15 mg, starting dose 9 mg) and a 6-week stabilization phase. The study was terminated early at the pre-planned interim analysis when 43 patients from the intention-to-treat population ( $n = 113$ ) experienced a relapse (14 patients (25%) in the paliperidone group and 29 patients (53%) in the placebo group). Time to recurrence significantly favoured the paliperidone group ( $p = 0.005$ ).<sup>6</sup> The European Medicines Agency indicated that relapse rather than recurrence prevention had been demonstrated and the study is not sufficient to support a recurrence prevention claim. The study did however support a maintained effect for patients who initially respond.

Results from a study comparing paliperidone (9 - 12 mg) and quetiapine (600 - 800 mg) have been presented in abstract form.<sup>7</sup> The reported data suggest a significant change in PANSS score compared with placebo after two weeks of treatment, with the reduction significantly better with paliperidone compared with quetiapine (-23.4 and -17.1,  $p < 0.001$ ). As the data have not been fully published, detailed critical appraisal is not possible.

## How safe is it?

The most frequently reported adverse drug reaction (ADR) in clinical trials was headache ( $\geq 1$  in 10). The following ADRs were reported as common ( $\geq 1$  in 100 to  $< 1$  in 10): tachycardia, akathisia, sinus tachycardia, extrapyramidal disorder, somnolence, dizziness, sedation, tremor, hypertonia, dystonia, orthostatic hypotension and dry mouth. The ADRs that appeared to be dose-related included weight gain, headache, salivary hypersecretion, vomiting, dyskinesia, akathisia, dystonia, extrapyramidal disorder, hypertonia and Parkinsonism.<sup>1</sup> Long term safety data are currently lacking. All suspected ADRs to black triangle drugs such as paliperidone should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

## What other options are there?

NICE has recommended atypical antipsychotics (amisulpiride, olanzapine, quetiapine, risperidone or zotepine) as one of the

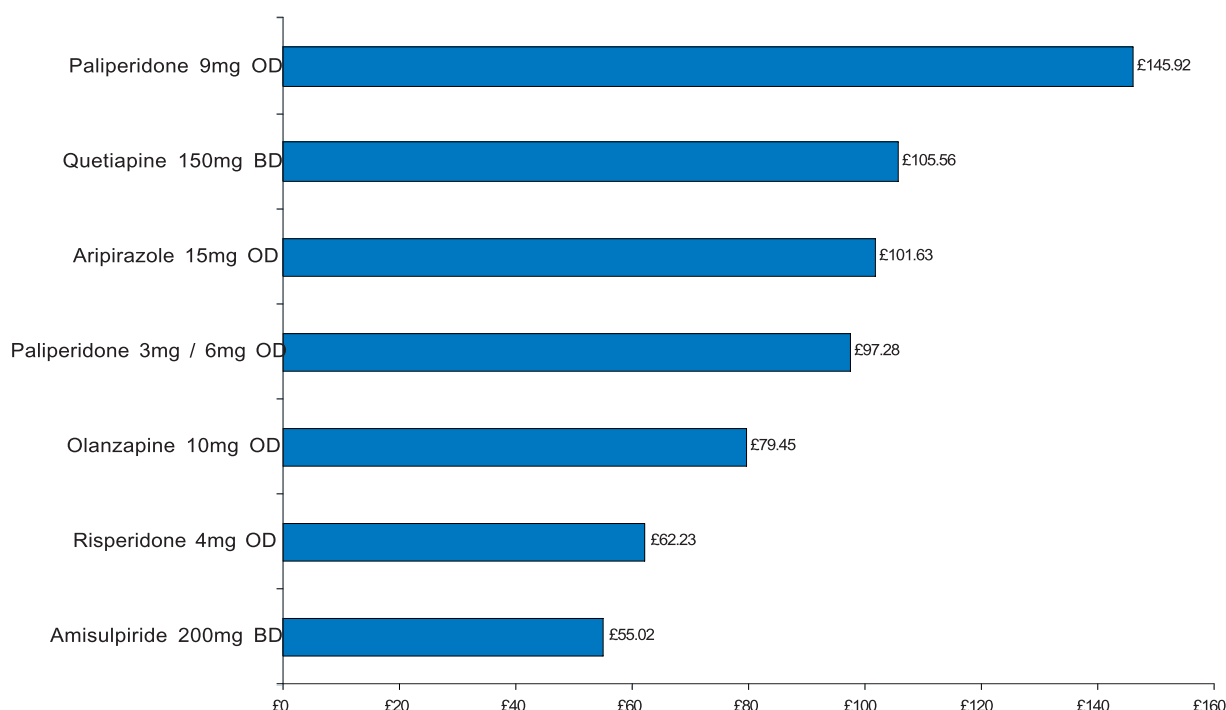
first-line treatment options in newly diagnosed schizophrenia;<sup>8</sup> they are also recommended where a traditional antipsychotic is causing unacceptable side effects, and for those in relapse who have previously experienced unsatisfactory management or unacceptable side effects with traditional drugs. NICE advises that the choice of antipsychotic should be made jointly by the individual and the clinician, and when this is not possible, an atypical antipsychotic should be considered the option of choice. Where more than one agent is considered appropriate the least costly agent should be chosen.<sup>8</sup> Individuals with treatment-resistant schizophrenia should be prescribed clozapine.

## When should it be used?

There are limited comparative data with other less costly atypical agents. Those that are available do not demonstrate consistent advantages. Fully published, long-term data are currently lacking. Paliperidone should not be used routinely in preference to adequate trials of more established atypical antipsychotics.

## How much does it cost?

Cost of 28 days treatment (Drug Tariff/eMIMS February 2008)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. Average daily quantity (ADQ) is used where available.

## REFERENCES

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KEY Abs – abstract, G - guideline, RCT - randomised controlled trial.

## Regional Drug and Therapeutics Centre

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH

Tel: 0191 232 1525 Fax 0191 260 6192

E-mail: [nrdtc.di@ncl.ac.uk](mailto:nrdtc.di@ncl.ac.uk) Website: [www.nrdtc.nhs.uk](http://www.nrdtc.nhs.uk)

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