

# NEW DRUG EVALUATION

No. 57

June 2003

## RISPERIDONE DEPOT

Risperidone is the first atypical antipsychotic to become available as a long-acting intramuscular injection for the treatment of schizophrenia. Available data on its use is limited but it appears to be as effective as oral risperidone in controlling positive and negative symptoms. It has not been compared to conventional depot injections and is significantly more expensive. Its place in treatment is currently unclear.

### *What is it?*

Risperdal Consta<sup>®</sup>, (Janssen Cilag) is a long-acting intramuscular risperidone injection. It is the first atypical antipsychotic to be available as a depot formulation and is licensed for the treatment of schizophrenia.

### *Dosage and Administration*

The recommended dose is 25-50 mg intramuscularly every 2 weeks. In patients who have not previously used the drug, oral risperidone should be used initially to assess tolerability. Treatment should be supplemented with oral risperidone for the first 3 weeks as therapeutic levels are not reached within this time.<sup>1</sup>

Risperidone is presented as vials of dry powder (25 mg, 37.5 mg or 50 mg) which require suspension before injection. Syringes containing the aqueous-based solvent for reconstitution plus needles for administration are provided. The entire pack should be stored in the refrigerator. The product can be stored at temperatures not exceeding 25°C for up to 7 days prior to administration.

### *How effective is it?*

Published evidence for risperidone depot is limited to abstracts and poster presentations.<sup>2,3,4</sup>

In a 12-week placebo-controlled, double-blind study, 400 patients were randomised to receive either risperidone depot 25 mg, 50 mg, 75 mg or placebo every two weeks.<sup>2</sup> The primary efficacy measure was the change in PANSS<sup>a</sup> total score. Risperidone depot significantly improved PANSS total scores compared with placebo ( $p=0.002$  for 25 mg and  $p<0.001$  for 50 mg and 75 mg doses).  $\geq 20\%$  reduction in PANSS total score occurred in 47%, 48% and 39% of patients receiving 25 mg, 50 mg and 75 mg respectively compared with 17% for placebo ( $p<0.001$  for all doses).<sup>2</sup> Improvements on the CGI<sup>b</sup> severity and change

scales, a secondary outcome measure, were also significantly greater for risperidone than for placebo ( $p<0.05$ ).

A second double-blind study enrolled 801 patients.<sup>3</sup> After 8 weeks patients on a stable dose of oral risperidone ( $n=640$ ) were randomised to risperidone depot (25, 50 or 75 mg every two weeks) and placebo tablets or to risperidone tablets (2, 4, or 6 mg) and placebo injection. After a further 12 weeks intramuscular and oral administration of risperidone were shown to be equally effective in reducing symptoms with similar improvements in PANSS total scores and CGI severity scores in both groups.<sup>3</sup>

Data from a non-blinded open study, which enrolled clinically stable patients ( $n=725$ ) and switched them to risperidone depot, suggests that efficacy with risperidone depot is maintained for up to one year.<sup>4</sup> The authors also conclude that these patients may experience substantial benefits by switching with improved PANSS scores at endpoint compared with baseline.<sup>4,5</sup> However in the absence of a specifically designed comparative randomised controlled trial (RCT) these claims cannot be substantiated.

There are no RCTs comparing risperidone depot with conventional antipsychotics (depot or oral) or with any other atypical agent.

### *How safe is it?*

In the placebo-controlled study the incidence of spontaneously reported extrapyramidal disorders was 3%, 4% and 8% respectively for placebo, risperidone 25 and 50 mg groups.<sup>2</sup> There were no significant changes in the Extrapyramidal Symptom Rating Scale (ESRS) scores during the study.

In the switch study the incidence of adverse effects and discontinuation rates due to adverse events were similar

with depot and oral risperidone (61% vs 59% and 5.6% vs 4.7% respectively).<sup>3</sup> There were no significant differences in ESRS scores between the two groups.

In the open label study, the following adverse events were reported by more than 10% of patients: headache, anxiety, psychosis, insomnia, depression, hyperkinesia and rhinitis. The most frequently reported extrapyramidal side effects were hyperkinesia in 13%, 12% and 12% of those receiving 25 mg, 50 mg and 75 mg respectively; extrapyramidal disorder in 6%, 7% and 8%; and tremor in 7%, 4% and 4%. The incidence of tardive dyskinesia was 0.7% over one year.<sup>4</sup>

The SPC lists weight gain (2.7 kg after one year at 50 mg), depression and fatigue as common side effects.<sup>1</sup>

#### What other options are there?

No other atypical antipsychotic is currently available as a depot injection. Five conventional antipsychotics are available as depot injections; flupenthixol, fluphenazine,

haloperidol, pipotiazine and zuclopenthixol.

Depot preparations are used for maintenance therapy especially where compliance may be unreliable. Conventional depots may give rise to a higher incidence of extrapyramidal reactions than the equivalent oral preparations.

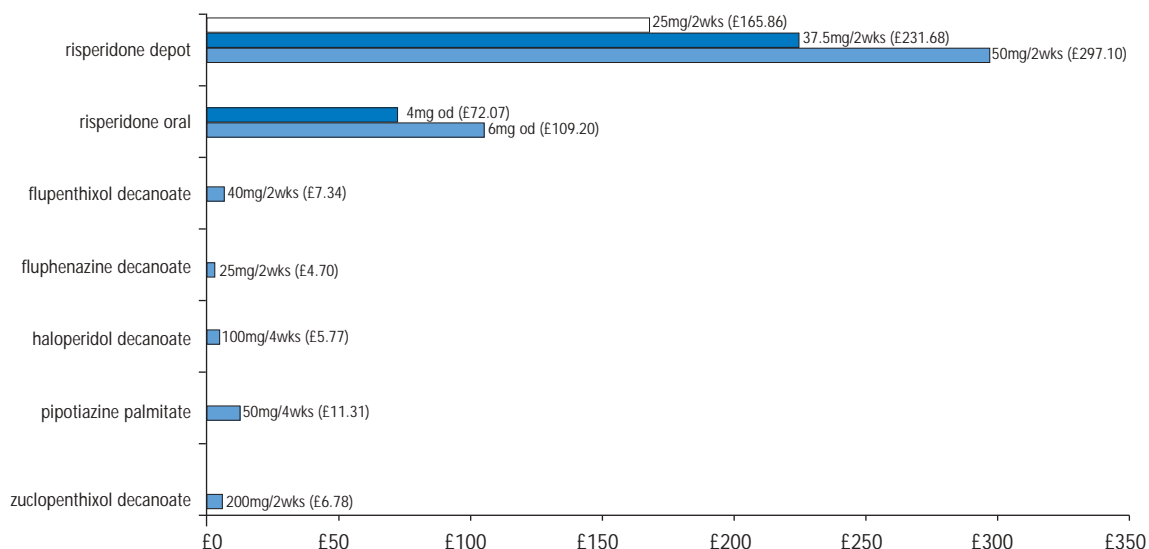
#### When should it be used?

The National Institute for Clinical Excellence has published an appraisal on the use of atypical antipsychotic drugs in June 2002<sup>6</sup> and more recently a guideline for the management of schizophrenia in primary and secondary care in December 2002.<sup>7</sup> Both documents were published before the availability of risperidone depot.

Published data on the efficacy and safety of risperidone depot are limited and there are no robust comparative data with conventional depot formulations. Its place in therapy is therefore unclear.

#### How much does it cost?

##### Cost for 4 week's treatment (prices from MIMS/Drug Tariff April 2003)



NB doses of conventional depot antipsychotics shown are listed as approximately equivalent in the BNF

#### REFERENCES

- Janssen-Cilag Ltd. Risperdal Consta SPC. December 2002.
- Kane J et al. Efficacy and safety of Risperdal Consta, a long-acting injection risperidone formulation. Poster presented at the American College of Neuropsychopharmacology Conference. December 2001. (Abs)
- Chue P et al. Efficacy and safety of long-acting risperidone microspheres and risperidone oral tablets. Poster presented at the 11th Biennial Workshop on Schizophrenia, Davos, Switzerland. March 2002. (Abs)
- Fleischhacker WW et al. Long-term safety and efficacy of Risperdal Consta, a long-acting injection formulation of risperidone. Poster presented at the American College of Neuropsychopharmacology Conference. December 2001. (Abs)
- Lasser R et al. Does constant therapy infer optimal efficacy in schizophrenia? Moving to an advanced pharmacotherapeutic option. Poster presented at the American College of Neuropsychopharmacology Conference, Puerto Rico. December 2002. (Abs)
- National Institute for Clinical Excellence. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. Technology Appraisal Guidance No. 43. June 2002. (R)
- National Institute for Clinical Excellence. Core interventions in the treatment and management of schizophrenia in primary and secondary care. Clinical Guideline 1. December 2002. (R)

KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A- abstract, E-editorial

**NHS Northern and Yorkshire  
Regional Drug and Therapeutics Centre  
Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH  
Tel: 0191 232 1525 Fax 0191 261 9359 E-mail: nyrdtc.di@ncl.ac.uk  
www.nyrdtc.nhs.uk**