

PUBLIC SUMMARY DOCUMENT

Product: RISPERIDONE, tablets, 1 mg, 2 mg, 3 mg and 4 mg; oral disintegrating tablets, 1 mg and 2 mg, Quicklet[®]; oral solution, 1 mg per mL, Risperdal[®]

Sponsor: Janssen-Cilag Pty Ltd

Date of PBAC Consideration: November 2005

1. Purpose of Application

This submission sought Pharmaceutical Benefits Scheme (PBS) listing for risperidone as adjunctive therapy to mood stabilisers for the treatment of an episode of acute mania for the treatment of bipolar I disorder.

2. Background

Risperidone has not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC) for the treatment of bipolar 1 disorder.

3. Registration Status

The Therapeutic Goods Administration (TGA) has approved risperidone for treatment of the following indications:

- schizophrenia and related psychoses;
- acute mania associated with bipolar I disorder;
- behavioural disturbances in dementia;
- conduct and other disruptive disorders in children (over 5 years), adolescents and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent; and
- behavioural disorders associated with autism in children and adolescents.

4. Listing Requested and PBAC's View

The sponsor requested the following listing:

Authority required

Adjunctive therapy to mood stabilisers for the treatment of an episode of acute mania associated with bipolar I disorder.

For consistency with the TGA-approved indication, the PBAC considered it appropriate to include a reference to the duration of treatment (up to six months) in the restriction wording.

5. Clinical Place for the Proposed Therapy

Adjunctive therapy with antipsychotic medication for bipolar I disorder is used in two common situations:

- 1) Concurrent commencement with a 'mood stabiliser' to control disruptive behaviour and allow adequate time for the mood stabiliser to achieve maximal effect; and
- 2) As an option for augmentation of the mood stabiliser when the patient does not respond adequately to that mood stabiliser alone.

6. Comparator

The submission nominated olanzapine as the most appropriate comparator. This comparator was accepted by the PBAC.

7. Clinical Trials

The submission provided an indirect comparison between risperidone (two randomised trials of three weeks duration), and olanzapine (one randomised trial of six weeks duration) using placebo as the common reference. The trials included patients with current manic or mixed episodes associated with bipolar I disorder on lithium, sodium valproate or carbamazepine. As supportive evidence, the submission also included two placebo-controlled trials of risperidone monotherapy.

All three comparative randomised trials were published at the time of the submission as follows:

Trial/first author	Title	Publication citation
Sachs GS, et al.	Combination of a mood stabiliser with risperidone or haloperidol for the treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety.	<i>Am J Psychiatr</i> 2002; 159(7):1146-54.
Yatham LN, et al.	Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial.	<i>Br J Psychiatr</i> 2003; 182:141-7.
Tohen M, et al.	Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy.	<i>Arch Gen Psychiatr</i> 2002; 59(1):62-9.

8. Results of Trials

The primary outcome in the clinical trials was the mean reduction in Young Mania Rating Scale (YMRS) from baseline, and the secondary outcome was the proportion of patients achieving $\geq 50\%$ reduction in mean YMRS. The PBAC noted the indirect comparison showed no difference in efficacy between the two drugs.

The PBAC considered the responder analysis in which patients had to achieve a $\geq 50\%$ reduction from baseline in YMRS score to be a more useful basis to compare risperidone and olanzapine. The PBAC noted the indirect comparison showed no difference between the two drugs.

There were no apparent differences between treatment and control arms regarding severe adverse events or adverse events leading to withdrawal from the trial. The discontinuation rates in both the risperidone and olanzapine trials were substantial, 74% and 64% respectively. Rates of treatment discontinuation due to intolerable side effects were lower with risperidone (10%) than olanzapine (18%).

9. Clinical Claim

The submission claimed that the efficacy of risperidone was no worse than olanzapine in this particular patient population.

For the PBAC's view see Recommendations and Reasons.

10. Economic Analysis

A cost-minimisation analysis was presented based on drug costs for an episode of acute mania. This approach was considered valid by the PBAC.

11. Estimated PBS Usage and Financial Implications

The submission estimated the listing of risperidone for the treatment of patients with bipolar I disorder would be expected to be associated with a net saving to the PBS, as usage would be at the expense of the more costly drug, olanzapine.

The submission predicted the estimated financial savings would climb to < \$1 million in Year 4 of listing.

The likely number of patients per year was estimated to be approximately 5,000 in Year 4. The PBAC noted that it was difficult to predict usage of risperidone as this estimate depended on the uptake of risperidone in place of olanzapine, and duration of treatment.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis after concluding that the indirect comparison indicated that risperidone was no worse than olanzapine in the treatment of bipolar 1 disorder. The equi-effective doses are risperidone 3.75 mg per day and olanzapine 10.4 mg per day.

Recommendation

RISPERIDONE, tablets, 1 mg, 2 mg, 3 mg and 4 mg; oral disintegrating tablets, 1 mg and 2 mg; oral solution, 1 mg per mL, 100 mL.

Restriction: Authority required

Adjunctive therapy to mood stabilisers for up to six months, of an episode of acute mania associated with bipolar 1 disorder.

Maximum quantity 60 (1 mg, 2 mg, 3 mg, and 4 mg, tablets) / 56 (1 mg and 2 mg, disintegrating tablets) / 1 (1 mg per mL, 100mL oral solution)

Repeats: 5 (all strengths)

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor welcomes this decision by the PBAC to provide access to an additional treatment option for people experiencing an episode of acute mania associated with bipolar I disorder.