PUBLIC SUMMARY DOCUMENT

Product: Risperidone, tablet, 500 microgram, 1 mg, 2 mg, oral solution 1 mg per mL, Risperdal®, oral disintegrating tablet, 500 microgram, 1 mg, 2 mg, Risperdal®Quicklet®

Sponsor: Janssen-Cilag Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought an Authority Required PBS listing for the treatment of severe behavioural disturbances in children and adolescents with autism.

2. Background

This drug had not previously been considered by the PBAC for the treatment of severe behavioural disturbances in children and adolescents with autism.

3. Registration Status

Risperidone is TGA approved for the following indications:

- for the treatment of schizophrenia and related psychoses.
- for the short term treatment of acute mania associated with bipolar 1 disorder.
- for the treatment of behavioural disturbances in dementia.
- for the treatment of conduct and other disruptive disorders in children (over 5 years), adolescents and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviours (eg aggression, impulsivity and self-injurious behaviours) are prominent.
- for the treatment of behavioural disorders associated with autism in children and adolescents.

4. Listing Requested and PBAC's View

Authority required
Treatment by or under the supervision of a paediatrician or psychiatrist for severe behavioural disturbances in children and adolescents with autism. Behaviour disturbances are characterised by severe aggression and injuries to self or others where non-pharmacological methods have been unsuccessful.

The diagnosis of autism must be made based on the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) or ICD-10 international classification of mental and behavioural disorders.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Autism is characterised by impairment in social interaction and communication, restricted repetitive and stereotyped behaviour.

Risperidone is indicated for specific behavioural symptoms when they significantly impact on the child's function and the daily life of the child and family, to improve the child's symptoms such that the child is able to respond optimally to standard non-drug interventions.

6. Comparator

The submission nominated placebo (no pharmacological therapy) as the main comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented one randomised comparative trial comparing risperidone and placebo in children or adolescents with severe behavioural disturbances associated with autism (RUPP Autism Network 2002 and 2005); and one randomised comparative trial comparing risperidone and placebo in children aged 5-12 years of age with disruptive behavioural symptoms associated with autism and other pervasive developmental disorders (Shea et al 2004).

These trials had been published at the time of submission, as follows:

Trial/First author	Publication title	Publication citation
McCracken JT et al (RUPP Autism Network 2002)	Risperidone in children with autism and serious behavioral problems.	The New England Journal of Medicine, 2002; 347(5): 314-321
RUPP Autism Network 2005	Risperidone treatment of autistic disorder: longer term benefits and blinded discontinuation after 6 months.	American Journal of Psychiatry, 2005: 162(7): 1361-1369
Shea S et al 2004	Risperidone in the treatment of disruptive behavioural symptoms in children with autistic and other pervasive developmental disorders.	Pediatrics, 2004; 114(5): 634-641

8. Results of Trials

Efficacy in the trials was assessed using the Aberrant Behaviour Checklist (ABC) and the Change in Clinical Global Impression measurement tool (CGI-C).

The ABC assessed a change in behaviour related to treatment in subjects with developmental disabilities. There were five sub-scales in the checklist: irritability; lethargy and social withdrawal; stereotypic behaviour; hyperactivity/ non compliance; and inappropriate speech. The ABC was completed by the subject's parent or primary caregiver under guidance of the investigator.

The CGI-C assessed the change of the subject's condition compared with baseline and was measured on a seven point scale: ranging from very much improved to very much worse. The CGI-C was completed by an independent clinician.

The results from RUPP Autism Network 2002 (baseline to week 8) showed there was a statistically significant difference in ABC irritability sub-scale score and CGI-C favouring risperidone in the trial's primary analysis of change in irritability scores.

During the 8-week discontinuation phase (RUPP Autism Network 2005), 62.5% of children who had received a minimum of 24 weeks treatment with risperidone relapsed when risperidone treatment was withdrawn compared with 12.5% of patients who continued risperidone treatment.

The results of Shea et al 2004 showed that risperidone produced a statistically greater reduction in ABC irritability sub-scale score versus placebo and there was a statistically significant greater proportion of CGI-C responders in the risperidone arm versus placebo. 30% of subjects had a pervasive developmental disorder other than autism.

The most common adverse events reported in the risperidone arm (n = 49) of RUPP Autism Network 2002 were: increased appetite (73%), fatigue (59%) and drowsiness (49%). Weekly assessment with the Abnormal Involuntary Movement Scale and the Simpson-Angus scale showed no extrapyramidal symptoms in either group. Parents or caretakers reported 5 neurologic side effects: tremors, dyskinesia, rigidity, akathisia, and difficulty swallowing.

9. Clinical Claim

The PBAC accepted the submission's claim that risperidone has significant advantages in effectiveness over placebo but was associated with more toxicity.

10. Economic Analysis

The submission presented a cost-effectiveness approach based on drug costs and effectiveness measured by the proportion of responders. This approach was considered valid by the PBAC.

The submission estimated that the trial-based incremental cost per responder would be < $15,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 4 of listing the likely number of patients would be < 10,000 and the financial cost to the PBS would be < $10 million.

12. Recommendation and Reasons

The PBAC recommended listing for severe behavioural disturbances in a child or adolescent with autism on a cost-effectiveness basis compared with placebo. The PBAC further recommended that the listing restriction specify that treatment take place under the supervision of a paediatrician or psychiatrist; that non-pharmacological measures are continued during treatment; that the diagnosis of autism is made according to the DSM-IV or ICD10 criteria; and that the number of repeats is limited to two.

In making this recommendation the Committee accepted that the statically significant differences in the ABC irritability sub-scale score and the CGC-C favouring risperidone in the key trial (RUPP Autism Network 2002 and 2005) represent a clinically meaningful improvement in behaviours in the severely affected children and adolescents with autism targeted by the restriction. The Committee noted that risperidone treatment is associated with a high rate of somnolence and weight gain but as the median treatment duration is likely to be short these side effects were of lesser concern.

The PBAC recommended the 20-day safety net rule should not apply.

Recommendation
RISPERIDONE, tablet, 500 microgram, 1 mg, 2 mg, oral solution 1 mg per mL, Risperdal®, oral disintegrating tablet, 500 microgram, 1 mg, 2 mg

Restriction:	Authority required Treatment under the supervision of a paediatrician or psychiatrist, in combination with non-pharmacological measures, of severe behavioural disturbances in a child or adolescent aged less than 18 years with autism. Behaviour disturbances are defined as severe aggression and injuries to self or others where non-pharmacological methods alone have been unsuccessful. The diagnosis of autism must be made based on the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) or ICD-10 international classification of mental and behavioural disorders.
Maximum Quantity:	60 / 56 (tablets/orally disintegrating tablets) / 1 (oral solution)
Repeats:	2

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 the first pharmacological treatment for children and adolescents with autism experiencing behavioural disturbances. Risperidone treatment can provide a significant positive influence on the child's function and thus favourably impact the daily life of the child, their family and carers.