Expert peer review on application for inclusion of risperidone

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes ✓  No  (if no, please provide reference and information)

Although the study is mentioned, there is perhaps insufficient attention paid to the results from the CATIE study (Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RSE, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. New England Journal of Medicine 2005; 353: 1209-1223).

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
Risperidone has broadly similar efficacy to the other second-generation, atypical antipsychotics, but is associated with fewer extrapyramidal adverse effects that the first-generation, typical agents.

c. Please provide any additional relevant information with reference

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes ✓  No  (if no, please provide reference and information)

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
Risperidone is associated with fewer general movement disorders than are the typical antipsychotic medications, but is associated with more weight gain. In comparison to other atypical antipsychotics, risperidone is associated with significant increase in prolactin and also with marginally more extrapyramidal side effects. Weight gain in patients treated with risperidone is less than in clozapine, olanzapine and sertindole, but more than in amisulpride.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
a. Have all relevant data on cost and availability provided
   Yes ✓  No  (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
The costs of generic risperidone have fallen dramatically in recent years, making this an affordable option in addition to the existing first-generation agents. Chlorpromazine oral solid dosage forms are still very inexpensive (median $0.0148/100mg tab-cap), while haloperidol (median $0.0446/1.5mg tab-cap) is now marginally more expensive than risperidone (median $0.0339/2mg tab-cap) on a per tablet basis.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

Yes, a large number of generic manufacturers is now available.

4. **Assessment of public health need**
   
a. Please provide the public health need for this product (1-2 sentences)

The public health need for antipsychotic medicines is justified by the global burden of disease. Given the proportion of patients who do not respond to or cannot tolerate first-line typical antipsychotics, the need for a second-line option is supported.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Risperidone is included as one of many atypical agents that may be considered, according to:


The WHO Department of Mental Health and Substance Abuse endorses the algorithms for the treatment of schizophrenia issued by the Collegium Internationale Neuro-Psychopharmacologicum (http://www.ipap.org/schiz/). In addition, the desirability of being able to access an alternative to the first-generation agents was mentioned in the Mental Health Gap Action Programme Intervention Guide published by WHO in 2010.

5. **Are there special requirements for use or training needed for safe/effective use?**

If yes, please provide details in 1-2 sentences

Skills in the diagnosis and management of mental health conditions with psychotic elements is needed.

6. **Is the proposed product registered by a stringent regulatory authority?**

   Yes ✓   No

7. **Any other comments**
8. What is your recommendation to the committee (please provide the rationale)

This application needs to be considered in the light of the competing application for the addition of clozapine, another second-generation or atypical antipsychotic. Although clozapine has been available for longer, it has the major disadvantage of a unique haematological adverse effect profile. Risperidone has in the past been far more expensive than the first-generation agents, but is increasingly available in generic versions and at far more affordable prices. Although risperidone is associated with a different set of potential adverse effects, it represents a better option for addition to the WHO Model EML than clozapine, in order to meet the clearly demonstrated need for an alternative to the listed first-generation antipsychotics. Given the results of the CATIE study (Lieberman JA et al. N Engl J Med 2005;353:1209-23), which showed high rates of treatment discontinuation for all antipsychotics (on average, 74% before 18 months), the need to retain the older, first-generation antipsychotics is clearer than might previously have been believed. Although the CATIE study included perphenazine, it is recommended that the existing first-generation agents be retained on the List. Risperidone is available in a large number of dosage forms, including depot injectable versions which are more costly. The proposal from the Young Professionals Chronic Disease Network (YPCDN) recommends listing the oral tablets containing 0.25 mg, 0.5 mg, 1 mg, 2mg, 3 mg, 4 mg, and 6 mg, for the Adult (Core) List only. The proposal from the Mount Sinai School of Medicine Program in Global Mental Health recommends including the 0.25 mg, 1 mg, and 2 mg oral tablets on the Core List and the 1 mg/mL oral solution and 25mg long-acting depot intramuscular injection on the Complementary List. However, the public health importance of an antipsychotic for children has not been demonstrated and there are insufficient benefits to justify the inclusion of an atypical injectable at this time. It is recommended, therefore, that the addition of risperidone oral solid dosage forms (in the 0.25 mg, 1 mg, and 2 mg strengths) be approved. Consideration should be given to including risperidone on the complementary list, as some additional skills (if not equipment) are necessary to diagnose and manage this set of mental health conditions. Although the efficacy and safety of the atypical antipsychotics, apart from clozapine, are broadly comparable, generic availability varies considerably. It is therefore recommended that risperidone be listed as a single molecule, without the square box symbol.