Public Summary Document

Product:	Methylphenidate hydrochloride, extended release tablets, 18 mg, 36 mg and 54 mg, Concerta®
Sponsor:	Janssen-Cilag Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission requested a Section 85 listing on the Pharmaceutical Benefits Scheme (PBS) for methylphenidate hydrochloride extended release tablet (Concerta) as an Authority required benefit for the treatment of attention deficit hyperactivity disorder in children and adolescents aged 6-18 years who require continuous coverage over 12 hours.

2. Background

The Pharmaceutical Benefits Advisory Committee (PBAC) had not previously considered a submission for this formulation of methylphenidate hydrochloride.

3. Registration Status

The sponsor received TGA approval on 1 September 2003 for the marketing of methylphenidate hydrochloride extended release tablet in Australia for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6-18 years.

4. Listing Requested and PBAC's View

Authority required

For the treatment of ADHD in children and adolescents aged 6-18 years who require continuous coverage over 12 hours. Prescription use must be in accordance with State and Territory law.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

An extended release formulation of methylphenidate hydrochloride will assist in compliance with therapy for ADHD which is a key determinant of symptom control.

6. Comparator

The submission nominated methylphenidate hydrochloride immediate release tablet (MPH IR) as the main comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The scientific basis of comparison consisted of three randomised, double-blind, registration trials comparing MPH-CR with both placebo and MPH-IR. In addition, one pragmatic randomised open-label trial comparing MPH-CR with MPH-IR over an 8 week period was also included. The patient population in these trials were children aged 6-12 years diagnosed with attention deficit disorder (ADHD). Three further supportive trials and two systematic reviews were also provided.

Six of these trials were published at the time of submission, and one subsequently (Steele, 2006), as follows:

Trial/ First author	Protocol/Publication title	Publication citation
HEAD-TO-HEAD TRIALS COMPARING MPH-CR AND MPH-IR		
Double-blind trials		
Swanson et al	Comparison of the efficacy and safety of OROS methylphenidate HCL with methylphenidate three times daily and placebo in children with ADHD.	Paediatric Research 2000; 47:34A.
Pelham et al	Once a day Concerta methylphenidate versus three-time-daily methylphenidate in laboratory and natural settings.	Pediatrics 2001; 107(6):E105.
Wolraich ML	Randomised controlled trial of OROS methylphenidate once a day in children with attention deficit/hyperactivity disorder.	Pediatrics 2001; 108(4):883-92.
Open label trials		
Steele et al	A randomised, controlled, effectiveness trial of OROS-methylphenidate compared to usual care with immediate release methylphenidate in attention deficit-hyperactivity disorder.	Can J Clin Pharmacol 2006; 13(1); e50-e62
Supportive evidence		
Lopez et al.	Comparative efficacy of two once daily methylphenidate formulations (Ritalin® LA and Concerta® and placebo in children with attention deficit hyperactivity disorder across the school day.	Paediatric Drugs 2003; 5(8): 545-55.
Stein et al.	A dose-response study of OROS® methylphenidate in children with attention-deficit/hyperactivity disorder.	Pediatrics 2003; 112(5):e404-e413.
Swanson et al	A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study).	Pediatrics 2004; 113(3):e206-e216.

8. Results of Trials

The IOWA Conners rating scale, inattention/overactivity (I/O) sub-scale was the primary outcome used in the three double-blind registration trials. The results of these registration trials did not demonstrate a statistically significant difference between MPH-CR and MPH-IR in the primary endpoint.

In contrast, the results of the randomised but open-label trial indicated a statistically significantly difference in proportion of patients achieving remission favouring MPH-CR. Remission was defined as a patient achieving a score of less than or equal to 1 on every item of the list of 18 items of the SNAP-IV rating scale.

There was no statistically significant difference between MPH-CR and MPH-IR in terms of the incidence of any adverse events. None of the trials reported the occurrence of any serious adverse events. However, two of the trials recruited known methylphenidate responders and excluded patients with significant adverse experiences with the drug.

For PBAC's view of these results, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that extended release methylphenidate was significantly more effective than immediate release methylphenidate and had similar or less toxicity. The PBAC considered that superiority in effectiveness had not been adequately demonstrated by the data presented.

10. Economic Analysis

A preliminary economic evaluation was presented.

A modelled economic evaluation was presented also presented. This evaluation presented a cost-utility analysis and included the long term effectiveness as well as drug costs and medical interventions. The base case modelled incremental cost per responder was < $1,500.

For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost per year to the PBS was estimated to be approximately $10 million in Year 5. The PBAC noted these figures were likely to be underestimates.

12. Recommendation and Reasons

The PBAC noted that results of the three double-blind registration trials compared with MPH-immediate release indicated no statistically significant difference in any of the outcomes measured.

In contrast, results of the pragmatic, randomised, open-label trial indicated a statistically significantly difference in proportion of patients achieving remission favouring MPH-CR. The Committee was advised that for some more severely affected patients, compliance with a three times daily regimen was problematic. Furthermore, exposure to peaks and troughs with the immediate release preparation could be unnerving for some children. The sponsor argued that the open label trial was a randomised trial that assessed the advantage of a once per day formulation in terms of patient compliance and clinical outcomes, under usual practice conditions. The main outcome measure was remission, defined as a score $\underline{<}$1 on every item of the first 18-items of the SNAP-IV rating scale.

However, as none of the double blind, randomised trials showed a statistically significant difference between MPH-CR and MPH-IR, the PBAC had residual uncertainty that the results of the open trial were due to real differences in the effect of the drug or because the trial design was unable to minimise observer bias in the measurement of subjective outcomes. The PBAC considered the open trial could have been more been informative had a third arm been added with MPH-CR and a placebo lunchtime dose (and possibly a third placebo dose).

Although the PBAC accepted that it is likely that there will be a benefit of improved compliance with a once a day formulation and it could represent an advantage in terms of avoiding stigmatisation and diversion, these benefits had not been adequately demonstrated in the submission. A further advantage that a once a day treatment is more convenient than a three times a day treatment, was also accepted.

Although the PBAC accepted there may be some additional benefit with the controlled release formulation, the extent of this benefit was unclear. As the PBAC did not accept the

extent of benefit claimed in the submission based upon the results of the open label study, the results of the economic evaluations were not considered reliable. The PBAC also noted a number of other uncertainties about the economic model.

The PBAC thus rejected the submission because of uncertain extent of clinical benefit over the comparator and uncertain cost-effectiveness.

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

It is important to note that design and conduct of registration trials ensures a high level of compliance with medication. Thus, the full benefits of a once-a-day versus multiple daily dosing on compliance and patient outcomes may not be demonstrated. While Janssen-Cilag accepts that non-blinding does result in some potential for bias, the fact that the Steele et al (2006) study was a well conducted, randomised controlled study provides a reasonable method of assessing patients outcomes resulting from once-a-day therapy. Janssen-Cilag is continuing to work with the PBAC to determine the impact of trial design and other factors on health outcomes for children with ADHD.