PUBLIC SUMMARY DOCUMENT
Product: Methylphenidate hydrochloride, Tablets, 18 mg, 27 mg, 36 mg, and 54 mg,(extended release) Concerta®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application
Extend the current Authority Required listing to include use in patients diagnosed with attention deficit hyperactivity disorder (ADHD) after the age of 18 years.

2. Background
At the March 2006 meeting, the PBAC rejected a submission seeking Section 85 listing 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 on a basis of uncertain extent of clinical benefit over the comparator and uncertain and unacceptable cost-effectiveness at the price proposed of about six times the comparator.

At the November 2006 meeting, the PBAC recommended listing Concerta® as an Authority Required Benefit for the treatment of ADHD in children and adolescents aged between 6-18 years inclusive who meet certain criteria, on a cost effectiveness basis over immediate release methylphenidate at the new price proposed. Listing was effective on 1 April 2007.

At the July 2009 meeting, the PBAC recommended the listing of methylphenidate hydrochloride extended release tablets and modified release capsules be modified to allow continued treatment of attention deficit hyperactivity disorder beyond the age of 18 years in patients who were diagnosed between the ages of 6 and 18 years consistent with the advice of the Paediatric Medicines Advisory Group.

3. Registration Status
Methylphenidate hydrochloride extended released tablets were TGA registered on 3 September 2003 for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6-18 years.

The current TGA registration for methylphenidate hydrochloride extended released tablets is for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years.

Use in infants and children: Methylphenidate hydrochloride should not be used in patients under 6 years of age.

4. Listing Requested and PBAC's View
Note
Care must be taken to comply with the provisions of State/Territory law when prescribing methylphenidate hydrochloride.

Note

Continuing Therapy Only:
For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Authority required
Treatment of attention deficit hyperactivity disorder (ADHD) in a patient aged 6 or above who has demonstrated a response to immediate release methylphenidate hydrochloride with no emergence of serious adverse events, and who requires continuous coverage over 12 hours.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Attention deficit hyperactivity disorder (ADHD) is defined as a persistent pattern of inattention and/or hyperactive and impulsive behaviour that is more frequent and severe than is typically seen at a given stage of development. Symptoms are usually present from early childhood, they tend to become particularly problematic when the child starts school and they may remain troublesome across the lifespan. The symptoms of ADHD are associated with impairment in educational, social and emotional function.

Adults with ADHD have difficulties with education, progressing at work, family interactions, social activities and are at higher risk of workplace accidents, adverse driving outcomes, criminal activity and incarceration.

The submission proposed that extended release methylphenidate (Concerta®) would provide an alternative PBS-subsidised treatment option for adults diagnosed with ADHD.

6. Comparator

The submission nominated extended release methylphenidate when used in patients diagnosed with ADHD aged 18 years or less as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented four randomised trials comparing methylphenidate (ER) with placebo in 1,267 patients with ADHD. Trial 02-159 and Trial 3014, as pivotal evidence, used a flexible dosing model, leading to an individualised dose of methylphenidate for each subject which is most likely to occur in clinical practice. Trial 3002 and Trial 3013, as supportive evidence, were dose-response trials in which patients were randomised to a specific dose of methylphenidate (18 mg, 36 mg and 72 mg in Trial 3002; 54 mg and 72 mg in Trial 3013), which did not reflect usual clinical practice.

Based on these studies, the submission presented an unpublished post-hoc analysis comparing the effectiveness of methylphenidate (ER) in patients diagnosed after the age of 18 with its effectiveness in patients diagnosed before or at the age of 18. The PBAC noted that the subgroup of patients diagnosed before or at the age of 18 years was small across all four trials, representing approximately 10-30% of the total study populations. This made any comparison to placebo or to patients diagnosed after the age of 18 years uncertain.

The PBAC noted that the patients enrolled in each of the trials were not entirely representative of those for whom listing was sought as:

1) they were not required to have demonstrated a response to immediate release methylphenidate with no emergence of serious adverse events, and
2) they did not necessarily require continuous coverage over 12 hours.

In addition, 53% patients enrolled in Trial 02-159 did not have a diagnosis of ADHD before entering the trial. These patients were diagnosed upon trial entry (i.e., at age 18 or greater) and were classified into age at diagnosis groups (≤18 years or >18 years) based upon their age at entry into the trial. Given the inclusion criteria of this particular trial, it was not clear whether these patients would be representative of those for whom listing is sought, or whether they would have been diagnosed earlier in the Australian setting.

The table below details the published trials and associated reports presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Trial 02-159 (2007)	A placebo-controlled, double-blind, parallel-group, dose-titration study to evaluate the efficacy and safety of Concerta in adults with attention deficit hyperactivity disorder at doses of 36mg, 54mg, 72mg, 90mg or 108mg per day.	Clinical study report 02-159
Trial 3014 (2011)	Adult study / OROS methylphenidate hydrochloride (HCL) (OROS MPH) in adults with attention deficit hyperactivity disorder (ADHD).	Clinical Study Report ATT-3014
Trial 3002 (2007)	A multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the safety and efficacy of prolonged release OROS methylphenidate (18, 36 and 72mg/day), with open-label extension, in adults with attention deficit hyperactivity disorder.	Clinical study report 42603ATT3002
Medori R, et al. 2008	A randomized, placebo-controlled trial of three fixed dosages of prolonged-released OROS methylphenidate in adults with attention-deficit/hyperactivity disorder.	Biological Psychiatry; 63: 981-989.
Buitelaar J, et al. 2011	Predictors of treatment outcome in adults with ADHD treated with OROS® methylphenidate.	Progress in Neuro-Psychopharmcology and Biological Psychiatry; 35(2): 554-560.
Trial 3013 (2009)	A multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the safety and efficacy of prolonged release OROS methylphenidate (54 and 72 mg/day) in adults with attention deficit hyperactivity disorder.	Clinical study report 42603ATT3013

8. Results of Trials

The submission presented the primary outcomes of ADHD Investigator Symptom Rating Scale (AISRS) from of the pivotal trials (02-159 and 3014)

Both Trials 02-159 and 3014 demonstrated that methylphenidate (ER) was statistically significantly more efficacious than placebo in reducing the AISRS score from baseline in the overall population.

The subgroup analyses for Trials 02-159 and Trial 3014 showed that in the group of subjects with age at diagnosis >18 years, subjects treated with methylphenidate had a significantly greater decrease in AISRS score, compared with subjects treated with placebo. The non-significant results in the <18 years at age of diagnosis subgroup should be interpreted noting the small number of patients in this subgroup in both trials, with resulting reduction in power to detect a difference. In particular, the <18 years subgroup in Trial 02-159 included only 26 patients (comprising only 12% of the total trial population).

The submission also presented the results of the primary outcome of Conners'Adult ADHD Rating Scale (CAARS) total score from the supportive trials 3002 and 3013.

Both Trials 3002 and 3013 demonstrated that methylphenidate (ER) was more efficacious than placebo in reducing the CAARS score from baseline in the overall population, although the evidence in favour of methylphenidate was not statistically significant for the 54 mg group in Trial 3013. Trial 3002 and Trial 3012 were powered based on a clinically meaningful expected improvement between methylphenidate (ER) and placebo of 6 points. The estimates of treatment effect in the 72 mg arms of Trial 3002 and 3013 were 6.1 and 5.3 respectively. Hence, the improvement in CAARS appeared to meet the clinically meaningful treatment difference threshold only for the 72 mg arm of Trial 3002, but not for the other treatment arms of Trial 3002 and not for Trial 3013. The subgroup analysis showed that treatment with methylphenidate was consistently significantly associated with greater mean change in CAARS score than placebo in patients diagnosed with ADHD after 18 years for all doses of methylphenidate except the 18 mg in Trial 3002 and 54 mg in Trial 3013.

Methylphenidate (ER) is already PBS-subsidised for use in adults who were diagnosed with ADHD between the ages of 6-18 years. The adverse events reported in the trials and in the extended assessment of comparative harms are consistent with those described in the Australian Product Information for methylphenidate (ER).

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described methylphenidate (ER) in adults with ADHD diagnosed aged >18 years as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over methylphenidate (ER) in adults with ADHD diagnosed ≤18years. The PBAC considered that this claim was inadequately supported.

10. Economic Analysis

The submission stated that the eligible population who would receive Concerta under the proposed restriction would have already responded to immediate release methylphenidate, and as such, the patients accessing Concerta under the PBS will be methylphenidate responders with tolerable side effects.

The submission's economic approach was based on the assumption that if the effectiveness (as assessed by the AISRS and CAARS) of methylphenidate (ER) is the same in adults

regardless of whether they were diagnosed before or after 18 years of age, then the cost-effectiveness will also be the same. This assumption was not considered reasonable, as the potential for benefits in patients diagnosed as children, may differ from that in patients diagnosed as adults. Therefore, considering only the AISRS and CAARS scores in the adult populations may not reflect all benefits that would be considered in the determination of cost-effectiveness for the diagnosed <18 years population.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated per year was estimated in the submission to be less than 10,000 in Year 5 at an estimated net cost to the PBS of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered that while the proposed PBS restriction may be reasonable, there were a number of uncertainties in defining the proposed PBS population. The PBAC considered the approach to the comparator proposed in the submission i.e. methylphenidate extended release (ER) used in patients diagnosed with attention deficit hyperactivity disorder (ADHD) aged 18 years or less, was not consistent with the PBAC Guidelines as it was not the treatment most likely to be replaced in practice. The comparative clinical evidence presented in the submission had limited applicability to the proposed PBS population. The PBAC considered that the effect of treatment in patients diagnosed at an age greater than 18 years compared to those diagnosed at or before 18 years of age is unclear, and it is unknown whether the same clinical benefit and safety would be observed with treatment in these two patient groups. The PBAC further noted that patients enrolled in trials 02-159 and 3014 were not required to have demonstrated a response to methylphenidate IR without emergence of serious adverse effects, which would be the characteristics defining the requested PBS population.

The PBAC considered that methylphenidate immediate release (IR) and dexamphetamine IR are the PBS listed medicines for the proposed PBS population that are most likely to be replaced in clinical practice, and therefore these products are the appropriate comparators. The PBAC further noted that the November 2006 recommendation for the listing of methylphenidate ER for the treatment of ADHD in children and adolescents aged between 6-18 years of age was based on a comparison of methylphenidate ER and IR in the specified age group.

The PBAC noted that the pooled result of the post-hoc subgroup analysis of patients diagnosed with ADHD after 18 years of age from the pivotal trials 02-159 and 3014 was a mean difference of -5.83 (-8.02, -3.63) of the ADHD Investigator Symptom Rating Scale (AISRS) the primary outcome of the trials. The PBAC agreed with the ESC and did not accept that the clinical relevance and validity of the outcome measures used in the trials had been adequately established. The PBAC considered the AISRS and the Conners' Adult ADHD Rating Scale (CAARS) have not been well validated in the literature, and noted that the AISRS score is not publicly available. The PBAC considered that the five point difference in AISRS may not be clinically meaningful. Further, the PBAC noted that the pooled result in the subgroup diagnosed at or before 18 years of age was non-significant (-

1.29 (-6.28, 3.69)). The PBAC noted that the patient numbers in the subgroups diagnosed at or before 18 years of age in each of trials 02-159 and 3014 were small, with 26 patients (comprising only 12% of the total trial population) in trial 02-159. Therefore the comparison between the two subgroups was not informative.

The PBAC considered that the safety profile of methylphenidate in adults may be different to that in children and adolescents, including the potential for increase in the incidence of hypertension in adults as an adverse effect. The PBAC noted that although a proportion of adults with ADHD (those diagnosed at or before the age of 18) currently have access to subsidised methylphenidate ER, the proposed extension to listing would expose a greater number of adults to methylphenidate ER with potential associated risks of adverse reactions.

The PBAC considered that no evidence was presented in the submission to support the substantially higher price proposed for methylphenidate ER over methylphenidate IR in patients diagnosed after 18 years of age, and hence that the higher price was not justified. The PBAC recalled that the recommendation in November 2006 for the listing of methylphenidate ER for the treatment of ADHD in children and adolescents aged between 6-18 years of age was on a cost effectiveness basis over methylphenidate IR. Although the extent of any clinical benefit over methylphenidate IR remained uncertain, the PBAC agreed at that time that the likely improvements in compliance and in ease of administration, particularly in relation to the removal of the need for a dose of medication at school, were sufficient to justify listing. The PBAC noted that a comparison of methylphenidate ER to methylphenidate IR in patients diagnosed after 18 years of age was not presented in the submission. The PBAC considered it was unknown if the additional benefits of methylphenidate ER over methylphenidate IR would be applicable to patients diagnosed after 18 years of age and therefore any cost effectiveness of those benefits would need to be established.

The PBAC considered that the utilisation of methylphenidate ER in patients diagnosed after 18 years of age was highly uncertain and that the utilisation estimates provided in the submission and the overall costs to the PBS were likely to be substantially underestimated. The PBAC noted that switching to methylphenidate ER from those receiving private prescriptions for methylphenidate modified release (Ritalin LA®) and under co-payment prescriptions for methylphenidate IR and dexamphetamine were not accounted for in the utilisation estimates and that this is a potentially large group of patients. Further, the PBAC noted that the impact of combination therapy with methylphenidate ER and methylphenidate IR or dexamphetamine IR was considered uncertain and was not factored into the submission's estimates. The PBAC considered that the proposed extension to PBS listing of methylphenidate ER would expand the ADHD market by a much larger extent than that estimated in the submission. The PBAC also considered that the proportion of patients first diagnosed with ADHD at an age greater than 18 years was uncertain.

The PBAC hence rejected the application on the basis of uncertain efficacy and safety in the proposed PBS population and hence uncertain cost effectiveness, and high and highly uncertain cost to the PBS.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:

Reject

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

Janssen is disappointed with the PBAC's decision not to recommend CONCERTA® for PBS subsidy for the treatment of all adult patients diagnosed with ADHD.
However, Janssen notes that CONCERTA® is already available on the PBS for the treatment of ADHD in patients diagnosed between the ages of 6-18 inclusive, including adults first diagnosed between the ages of 6 – 18 years, inclusive.
As a result of this PBAC decision adults diagnosed with ADHD after 18 years are only able to access CONCERTA® via a private script.