PUBLIC SUMMARY DOCUMENT

Product: Pramipexole hydrochloride, tablet, 125 micrograms and 250 micrograms, Sifrol®

Sponsor: Boehringer Ingelheim Pty Limited

Date of PBAC Consideration: July 2007

1. Purpose of Application

The resubmission sought an authority required listing for treatment of severe, idiopathic Restless Legs Syndrome (RLS) in patients who meet certain criteria.

2. Background

At the November 2006 meeting, the PBAC rejected an application for pramipexole for use in moderate to very severe, idiopathic RLS in patients who meet certain criteria on the basis of uncertain clinical benefit and the resulting uncertain cost-effectiveness.
(See also Public Summary Document for November 2006).

3. Registration Status

Pramipexole is TGA registered for:

- the treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa.
- the symptomatic treatment of idiopathic Restless Legs Syndrome.

4. Listing Requested and PBAC's View

Authority required

CAUTION: Episodes of sudden sleep without warning, during activity, have been reported with this drug.
Initial treatment, by an appropriate medical specialist, of severe idiopathic Restless Legs Syndrome (RLS) in a patient who manifests all four diagnostic criteria below and who has a baseline International Restless Legs Syndrome Rating Scale (IRLS) score of greater than or equal to 21 points.

-an urge to move the legs usually accompanied or caused by unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs); and

-the urge to move or unpleasant sensations begins or worsens during periods of rest or inactivity such as lying or sitting; and

-the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and

-the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur during the evening or night.

The baseline IRLS score must be included on the Authority form.
Note: pramipexole is not PBS subsidised for Parkinson's disease nor restless legs syndrome secondary to other causes.

First application for continuing treatment in a patient with severe idiopathic Restless Legs Syndrome (RLS) who has demonstrated a decrease in International Restless Legs Syndrome Rating Scale score of at least 30% from baseline.

Second and subsequent applications for continuing treatment in a patient with severe idiopathic Restless Legs Syndrome (RLS) who has previously been issued with an authority prescription for pramipexole.

The PBAC noted the resubmission requested a listing for severe Restless Legs Syndrome (RLS) with an International Restless Legs Syndrome Rating Scale (IRLSRS) score of greater than or equal to 21, compared with the previous submission which requested a listing for moderate to severe RLS with an IRLSRS score of greater than or equal to 15.

5. Clinical Place for the Proposed Therapy

Restless Legs Syndrome (RLS) is a neurological disorder characterised by unpleasant sensations in the legs and an irresistible urge to move the legs to relieve the discomfort. Symptoms worsen during the evening and during periods of inactivity or relaxation. As a result, RLS can lead to profound disruption of sleep with associated daytime drowsiness, fatigue, and disruption of normal functioning and quality of life.

Pramipexole is a non-ergot dopamine agonist that is indicated for RLS.

6. Comparator

The nominated comparators were levodopa/benserazide and placebo, as requested by the PBAC following the previous submission. This was considered to be appropriate, and the comparison with levodopa/benserazide was considered to be the more informative analysis.

7. Clinical Trials

The re-submission presented six randomised comparative trials of pramipexole versus placebo and one direct randomised trial of pramipexole versus levodopa with benserazide.

The trials that had been published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Trial 515 Partinen et al 2006	Efficacy and safety of pramipexole in idiopathic restless legs syndrome: a polysomnographic dose-finding study - the PRELUDE study.	Sleep Medicine 7 (5), 407-417
Trial 543 Winkelman JW et al 2006	Efficacy and safety of pramipexole in restless legs syndrome.	Neurology. 67(6):1034-9
Trial 546 Trenkwalder C et al 2006	Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome.	Movement Disorders 21 (9) , 1404-1410
Montplaisir et al 1999	Restless legs syndrome improved by pramipexole: a double-blind randomized trial.	Neurology 52 (5) , 938-943

The PBAC noted that the trial participants were not representative of the requested PBS listing in that the trials' inclusion criterion for RLS was an IRLSR score of greater than15.

8. Results of Trials

Comparative effectiveness

In a double-blind, randomised, cross-over trial comparing pramipexole versus levodopa/benserazide, the periodic limb movement index (PLMI) was the primary outcome measure. There were no statistically significant differences between pramipexole and levodopa/benserazide treatment in PLMI in both the intention-to-treat (ITT) and per-protocol (PP) population. The submission did not present results for the severe subpopulation for the

primary outcome. There were no statistically significantly differences between pramipexole and levodopa/benserazide in any of the secondary outcomes.

The re-submission's superiority claim over levodopa/benserazide was based on a post-hoc analysis for the severe to very severe subpopulation (IRLSR total score >21 in both treatment periods of the cross over design) of the per protocol population. Significantly more patients in the pramipexole group than in the levodopa/benserazide group achieved a reduction from baseline IRLSRS in line with that specified in the proposed PBS listing restriction. However the number of patients in both groups was small. The ITT results for the IRLSRS outcome were not presented.

The submission also presented the IRLSRS results for the randomised comparative trials of pramipexole versus placebo. As previously the data suggested pramipexole is more effective than placebo *(see also November 2006 Public Summary Document)*.

Based on trial results provided the PBAC noted that in the severe patients subgroup a response of ≥30% change from baseline in IRLSRS produced a higher mean utility gain than a ≥50% change from baseline in IRLSRS. This suggested that the relationship between IRLSRS and utility is weak.

Comparative toxicity

Based on new toxicity data presented from the listed trials, the PBAC noted the greater rates of adverse events relating to pramipexole as compared with levodopa/benserazide with the main concern being nausea and other gastrointestinal adverse events while levodopa/benserazide was associated with more nervous system adverse events.

9. Clinical Claim

The re-submission described pramipexole as having significant advantages in effectiveness and similar or less toxicity than placebo.

The re-submission described pramipexole as having significant advantages in effectiveness and similar or less toxicity than levodopa with benserazide.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a modelled economic evaluation. The base case economic evaluation was a stepped economic evaluation. The types of economic evaluation presented were a cost-effectiveness analysis and cost-utility analysis for a comparison of pramipexole versus placebo and pramipexole versus levodopa/benserazide.

The submission estimated the incremental cost-effectiveness ratio (ICER) to fall in the range $15,000 - $45,000 when comparing pramipexole versus levodopa/benserazide.

The PBAC was concerned about the validity of the economic models - *see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The likely number of packs/year was estimated by the submission to be within the range 100,000 – 200,000 in Year 5.

The financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the evidence from the six randomised comparative trials of pramipexole versus placebo supported superiority of pramipexole over placebo in terms of effectiveness on various measures in separate trials and in the meta-analysis, but that it has greater toxicity, in particular nausea.

The PBAC considered that the evidence presented to support the claim that pramipexole has a therapeutic advantage over levodopa/benserazide, was weak. The primary outcome in the only head to head comparative trial presented was the periodic limb movement index. The PBAC noted that this trial found no statistically significant difference between pramipexole and levodopa/benserazide for this outcome for either the intention-to-treat or per-protocol analyses. The IRLSRS was a secondary outcome of this and only the per-protocol results for the IRLSRS were provided, rather than the ITT results. The PBAC noted that these results were not statistically significant for the overall population and were only marginally significant for the severe subgroup.

Furthermore, the PBAC noted that other secondary outcomes were not statistically significant different between pramipexole and levodopa/benserazide. Overall, the statistical significance and clinical significance of the treatment effects observed were considered to be questionable, particularly in view of the high placebo response associated with RLS.

The PBAC noted the greater rates of adverse events relating to pramipexole as compared with levodopa/benserazide with the main concern being nausea and other gastrointestinal adverse events while levodopa/benserazide was associated with more nervous system adverse events.

Overall, the PBAC agreed that the primary evidence supports the conclusion that pramipexole is no worse than levodopa/benserazide, in terms of clinical effectiveness and toxicity, but does not justify the claim of overall superiority.

The PBAC was concerned about the validity of the assumptions used in the economic models, in particular whether the methodology used to derive the utilities was appropriate. The relationship between utility change and baseline disease severity (via IRLSRS), and partial-response and response were assessed using regression analyses. This is based on a weak relationship between baseline (SF-6D derived) utility, baseline IRLS score and utility gain and change in IRLS score. Of note was the absence of a statistically significance difference between the change in unadjusted utility in pramipexole in comparison to placebo across the whole patient population.

The PBAC agreed that the reported utility gain in severe patients may not be statistically robust. Analyses were not performed adjusting for potential confounding factors and the modelled relationship between RLS severity and patient utility, and change in IRLSRS and utility gain appeared weak.

Overall, while the PBAC accepted that there is a relationship between utility gain and response to treatment, the strength of this relationship remains highly uncertain. Although the PBAC acknowledged that the continuation rule included in the proposed restriction sought to address this concern, uncertainty regarding the clinical relevance of a 30 per cent reduction in IRLSRS remained.

The PBAC also had a number of other concerns with the economic model, which biased the model in favour of pramipexole.

Although the base case incremental cost-effectiveness ratio was in the range usually considered to represent acceptable cost-effectiveness by the PBAC, the PBAC concluded that the analysis was not valid because the Committee did not accept the superiority of pramipexole over levodopa/benserazide.

The PBAC noted that the prevalence rate in the re-submission was likely to be an underestimate. With a potential higher awareness of RLS if pramipexole were to be subsidised, a higher uptake of pramipexole could be expected, thereby increasing the cost to PBS. The PBAC noted the sponsor acknowledged this uncertainty and proposed a risk-sharing agreement.

Overall, the PBAC acknowledged the need for therapeutic options for RLS, but considered that the evidence presented failed to support superiority of pramipexole over levodopa/benserazide in terms of clinical effectiveness. This resulted in uncertain cost-effectiveness that was considered to be unacceptably high, and the submission was therefore rejected.

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

The sponsor does not wish to make any comments on the PBAC decision.