PUBLIC SUMMARY DOCUMENT

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

Sponsor: Boehringer Ingelheim Pty Limited

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought an authority required listing for use in moderate to very severe, idiopathic Restless Legs Syndrome (RLS) in patients who meet certain criteria.

2. Background

This drug had not previously been considered by the PBAC for the restless legs syndrome indication.

3. Registration Status

Pramipexole was registered by the TGA on 10 August 2006 for the symptomatic treatment of primary restless legs syndrome (RLS).

4. Listing Requested and PBAC's View

Authority required

Pramipexole is indicated for use in moderate to very severe, idiopathic Restless Legs Syndrome (RLS).

Severity must be established through the use of the International Restless Legs Syndrome Rating Scale (RLSRS). Patients with a baseline score greater than 15 points are eligible for PBS subsidy. The baseline RLSRS score must be included on the Authority form.

Secondary causes of RLS - including iron deficiency, neurological lesions, pregnancy, uraemia or drug-induced RLS - must be excluded prior to initiation of therapy with pramipexole.

See Recommendation and Reasons for the PBAC's view.

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.

RLS is a chronic disorder for which there is currently no cure and management is aimed at symptom relief. Dopamine agonists are considered first-line medications for RLS but are not currently listed on the PBS for this indication. The currently available dopamine agonists on the PBS are ergoline-derived, and may be associated with significant ergot-related side effects, including pericarditis and retroperitoneal or pleural fibrosis.

Pramipexole is a non-ergot dopamine agonist that is indicated for the symptomatic treatment of primary RLS and for Parkinson's disease. It does not have the associated adverse effects of the ergoline- derived dopamine agonists.

6. Comparator

The submission nominated cabergoline as the main comparator. Cabergoline is not approved by the TGA for RLS but is used 'off label'. The submission also nominated ropinirole as a comparator since it was considered by the PBAC at its March 2006 meeting.

The PBAC did not agree that cabergoline was the appropriate comparator. *See Recommendations and Reasons.*

7. Clinical Trials

The submission presented an indirect comparison of three randomised control trials (RCTs) which compare pramipexole with placebo for 3 to 12 weeks duration against:
- cabergoline versus placebo (1 RCT); or
- ropinirole versus placebo (6 RCTs).

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

Pramipexole versus placebo

Trial/First author	Protocol title	Publication citation
Winkelmann J et al (2005)	Pramipexole is efficacious and safe in treating RLS patients results of a 12 weeks placebo controlled fixed dose study.	Sleep Medicine 6 (Suppl. 2): S74

Carbergoline versus placebo

Trial/First author	Protocol title	Publication citation
Stiasny-Kolster et al (2004)	Effective cabergoline treatment in idiopathic restless legs syndrome.	Neurology 63 (12): 2272-2279
Stiasny-Kolster K et al (2002)	Cabergoline in restless legs syndrome (RLS) - a double-blind placebo-controlled multi-center dose-finding trial.	European journal of neurology 9 (Suppl. 2): 50

Ropinirole versus placebo:

Trial/First author	Protocol title	Publication citation
Trial 190; Trenkwalder C et al (2004)	Ropinirole in the treatment of restless legs syndrome: Results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries.	Journal of Neurology, Neurosurgery & Psychiatry 75 (1): 92-97
Trial 191; Allen R et al (2004)	Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome.	Sleep 27 (5): 907-914
Trial 194; Walters AS et al (2004)	Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: A 12-week, double-blind, randomized, parallel-group, placebo-controlled study.	Movement Disorders 19 (12): 1414-1423
Trial 249; Bogan et al (2006)	Ropinirole in the treatment of patients with restless legs syndrome: A US based randomized, double-blind,	Mayo Clinic Proceedings 81 (1): 17-27

Trial/First author	Protocol title	Publication citation
	placebo-controlled clinical trial.	

8. Results of Trials

The results of the key trials are summarised in the table below.

Outcome	Treatment effect WMD (95% CI)			
Change in RLSRS score from baseline	**PPX vs. PBO**	**CBG vs. PBO**	**Indirect estimate of effect**	**p-value**
	-6.35 (-8.72, -3.97)[a]	-10.85 (-15.14, -6.56)[b]	4.5 (-0.40, 9.40)	0.072
		ROP vs. PBO		
		-3.02 (-4.08, -1.96)[c]	-3.33 (-5.93, -0.73)	0.012

WMD = weighted mean difference, PPX = pramipexole, PBO = placebo, CBG = cabergoline, ROP = ropinirole, RLSRS = restless leg syndrome rating scale (also referred to IRLS, International Restless Legs Syndrome Severity Scale in the ropinirole trials)

[a] estimate derived from meta-analysis using 3 week data Trial 515, 6 week data Trial 520 and 12 week data Trial 543.

[b] 5 week data from Stiasny-Kolster 2004

[c] estimate derived from meta-analysis of week 12 data from 4 of the 6 trials

Through the direct comparison, the data suggested that pramipexole is more effective than placebo and through the indirect comparisons, no more effective than cabergoline or ropinirole.

See Recommendation and Reasons for the PBAC's view.

9. Clinical Claim

The submission described pramipexole as being no worse than cabergoline or ropinirole in terms of effectiveness and toxicity.

The PBAC considered that the submission's claim of non-inferiority against cabergoline was not reasonable and that the data presented were unable to substantiate non-inferiority of pramipexole compared to cabergoline.

See Recommendation and Reasons for the PBAC's view

10. Economic Analysis

A preliminary economic evaluation was presented using a cost-minimisation approach which compared pramipexole and cabergoline. The resources included were drug costs.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients to be in the range 10,000 – 50,000 in Year 4. The financial cost/year to the PBS minus any savings in use of other drugs was estimated to be in the range $10 – 30 million in Year 4.

The PBAC considered these to be likely under-estimates in the submission due to uncertain estimates of RLS diagnosis and market share along with a likelihood of leakage beyond the indication.

12. Recommendation and Reasons

The PBAC considered that the selection of cabergoline as the comparator in preference to levodopa is not fully justified in the submission. Cabergoline is listed as a Restricted Benefit for Parkinson's disease and separately, as a Restricted Benefit for the prevention of the onset of lactation in the period immediately after child birth for medical reasons. In contrast, levodopa is PBS listed as an unrestricted benefit and is used in the treatment of restless leg syndrome (RLS). In addition, even if cabergoline were to be accepted as the therapy most likely to be used in clinical practice, its cost-effectiveness in the treatment of restless legs syndrome has not been established for the purpose of PBS subsidisation. The PBAC considered this to be a major impediment to the cost-minimisation approach taken by the sponsor for this submission and provided no basis to establish the cost-effectiveness of pramipexole.

The Committee noted that the outcome measures are not comparable across the trials presented in the submission, because the endpoints are measured at different time points within drugs and across drugs. For example, the three pramipexole trials have endpoints at 3, 6 and 12 weeks. The only available evidence for cabergoline treatment of RLS has outcomes measured at 5 weeks. Furthermore, the RLSR score is the only endpoint that is available to compare the efficacy of pramipexole to the main comparator cabergoline.

The PBAC considered that the submission's claim of non-inferiority against cabergoline is not reasonable. The PBAC therefore considered that the data presented were unable to substantiate non-inferiority of pramipexole compared to cabergoline.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and the resulting 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

Boehringer Ingelheim is considering the PBAC decision in detail and whether it is possible to prepare a resubmission for pramipexole for the treatment of RLS.