PUBLIC SUMMARY DOCUMENT
Product: Pramipexole hydrochloride, tablet, 125 micrograms and 250 micrograms, Sifrol®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission requested an extension of the current Restricted Benefit listing to include the treatment of severe idiopathic Restless Legs Syndrome (RLS).

2. Background

At its March 1999 meeting the PBAC recommended the listing of pramipexole hydrochloride tablets 125 micrograms, 250 micrograms and 1 mg for the treatment of Parkinson Disease as adjunctive therapy in combination with levodopa-decarboxylase inhibitor combinations on a cost-minimisation compared with bromocriptine. Listing took place on 1 June 2008.

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 because of uncertain clinical benefit and uncertain cost-effectiveness. The PBAC agreed that the selection of cabergoline as the comparator in preference to levodopa was not fully justified in the submission. The PBAC considered this to be a major impediment to the cost-minimisation approach taken by the sponsor for the submission and provided no basis to establish the cost-effectiveness of pramipexole. (See also Public Summary Document in November 2006).

At the July 2007 meeting, the PBAC again rejected an application for pramipexole for treatment of severe, idiopathic RLS in patients who meet certain criteria because of high and uncertain cost-effectiveness. The PBAC noted the requested listing was for severe RLS with an International Restless Legs Syndrome Rating Scale (IRLSRS) score of greater than or equal to 21, compared with greater than or equal to 15 in the previous submission. The nominated comparators were levodopa/benserazide and placebo, which were considered appropriate. Overall, the PBAC considered that the primary evidence supported the conclusion that pramipexole is no worse than levodopa/benserazide in terms of clinical effectiveness and toxicity, but did not justify the claim of overall superiority. (See also Public Summary Document at July 07).

3. Registration Status

Pramipexole was first registered by the TGA on 20 April 1999 for the treatment of the signs and symptoms of Parkinson Disease. An application to extend the registered indications to include the symptomatic treatment of primary restless legs syndrome was approved on 10 August 2006.

4. Listing Requested and PBAC's View

CAUTION

Episodes of sudden onset of sleep without warning, during activity, have been reported with this drug.

Restricted Benefit

Treatment 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 (IRLSRS) 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; and
- The urge to move or unpleasant sensations begins or worsens during periods of rest of 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.

NOTE:
Pramipexole is not PBS subsidised for Restless Legs Syndrome secondary to other causes.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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.

Dopamine agonists are considered first-line medications for RLS but are not currently listed on the PBS for this indication. Pramipexole is a non-ergot dopamine agonist and may provide an alternative treatment option for RLS.

6. Comparator

The submission nominated levodopa with benserazide as the main comparator. This is as previously agreed by the PBAC.

7. Clinical Trials

The basis of the submission was a double-blind, randomised, cross-over trial comparing pramipexole versus levodopa with benserazide (Trial 518). This trial was not published at the time of the submission.

No changes had been made to the trial data presented in the previous submission.

8. Results of Trials

The primary outcome measure for Trial 518 was change from baseline in Periodic Limb Movement Index (PLMI). There were no statistically significant differences between pramipexole and levodopa with benserazide treatment in PLMI in both the intention-to-treat (ITT) and per-protocol (PP) populations. The submission did not present results for the severe sub-population for the primary outcome. The PBAC had previously noted that there were no statistically significant differences between pramipexole and levodopa with benserazide in any of the secondary outcomes. (Refer to the July 2007 Pramipexole PSD).

The PBAC agreed with the submission's claim that pramipexole was non-inferior in terms of comparative effectiveness with levodopa/benserazide in patients with moderate to severe RLS.

No new toxicity data were presented in the re-submission. The PBAC agreed with the submission's claim that pramipexole was non-inferior in terms of comparative safety over levodopa/benserazide in patients with moderate to severe RLS.

9. Clinical Claim

The submission described pramipexole as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over levodopa/benserazide. The re-submission did not present evidence whether this claim also applied to the sub-group of patients with severe RLS. Based on the supporting data, the PBAC accepted that pramipexole was non-inferior for patients with moderate to severe RLS.

10. Economic Analysis

The submission presented a cost minimisation analysis. The PBAC accepted pramipexole 490 microgram and levodopa with benserazide 192 mg/48 mg to be equi-effective for the purposes of this listing.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year (accounting for market share) was estimated by the submission to be in the range of 10,000 – 50,000, while the financial cost per year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated by the submission to be < $10 million in Year 5. The PBAC considered this to be uncertain.

12. Recommendation and Reasons

The PBAC recommended the listing of pramipexole on the Pharmaceutical Benefits Scheme as a Section 85 Restricted Benefit item for the treatment of severe idiopathic (primary) restless legs syndrome on a cost-minimisation basis with levodopa with benserazide. The equi-effective doses for the purposes of this listing were pramipexole 490 micrograms and levodopa with benserazide 192/48 mg. The restriction appropriately limited treatment to patients who met the all diagnostic criteria and whose pre-treatment score on the International Restless Legs Rating Scale (IRLRS) was equal to or greater than 21.

The PBAC agreed with the submission's claim that pramipexole was non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over levodopa/ benserazide in patients with moderate to severe RLS.

The Committee, although agreeing with the ESC and the DUSC that utilisation in this indication was highly uncertain as there was likely to be usage beyond the restriction, noted that the pre-PBAC response reiterated the sponsor's conviction that the submission's estimates were reasonable.

The PBAC noted Boehringer Ingelheim's commitment to promoting the quality use of pramipexole in this indication through its planned educational activities and also requested that the National Prescribing Service consider providing independent educational material on idiopathic restless legs, its diagnosis and severity ratings as well as on the use of pramipexole as a treatment option.

Recommendation
PRAMIPEXOLE, tablet 125 micrograms, 250 micrograms, Sifrol®

Restriction:
CAUTION:
Episodes of sudden onset of sleep without warning, during activity, have been reported with this drug.

Restricted Benefit:
Treatment of severe primary Restless Legs Syndrome in a patient who manifests all four diagnostic criteria below and whose baseline International Restless Legs Syndrome Rating Scale (IRLSRS) score is greater than or equal to 21 points prior to initiation of pramipexole.

The date and IRLSRS score must be documented in the patient's medical records at the time pramipexole treatment is initiated.

The diagnostic criteria for Restless Legs Syndrome are:
(a) An urge to move the legs usually accompanied or caused by unpleasant sensations in the legs; and
(b) The urge to move or unpleasant sensations begins or worsens during periods of rest of inactivity such as lying or sitting; and
(c) 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
(d) 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.

Pramipexole is not PBS subsidised for Restless Legs Syndrome secondary to other causes.

NOTE:
No applications for increased maximum quantities and/or repeats will be authorised.

Maximum quantity:	30	(125 micrograms)
	100	(250 micrograms)
Number of repeats:	2	(both strengths)

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 welcomes the PBAC decision to approve pramipexole for patients with severe primary RLS satisfying the above criteria.