

PUBLIC SUMMARY DOCUMENT

Product: Pramipexole hydrochloride, tablet, 125 micrograms, 250 micrograms and 1 mg, Sifrol[®]

Sponsor: Boehringer Ingelheim Pty Limited

Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought to amend the Restricted benefit listing (effective 1 June 2008) for Parkinson disease (PD) and requested the removal of the requirement to be used with levodopa- decarboxylase inhibitor combinations, which would allow use as monotherapy (early disease) or in combination with levodopa (advanced disease).

2. Background

At the March 1999 meeting, the PBAC recommended an authority required listing for 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 the basis of cost-minimisation compared with bromocriptine.

At the December 1999 meeting, the PBAC recommended changing the authority required listing for pramipexole to a restricted benefit and to require that a caution note be included in the listing: CAUTION: Episodes of sudden onset of sleep without warning, during activity, have been reported with this drug.

Listing was effective from 1 June 2008.

3. Registration Status

Pramipexole was TGA registered on 20 April 1999 for:

- the treatment of signs and symptoms of idiopathic Parkinson disease in advanced states of the disease (in combination with levodopa).

An extension to the registration was granted on 14 June 2002 to include the treatment of signs and symptoms of idiopathic Parkinson disease as monotherapy or in combination with levodopa. Pramipexole is also registered for the symptomatic treatment of primary Restless Legs Syndrome.

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

Parkinson disease.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Parkinson disease is a progressively disabling neurodegenerative disorder manifested clinically by bradykinesia (slow movement), tremor, rigidity and postural instability caused by loss of pigmented neurons in the brainstem. In addition to the progressive motor disability, there are many disabling non-motor manifestations including dementia, depression

and autonomic instability. Pramipexole is a non-ergot dopamine agonist therapy for the treatment of Parkinson disease.

6. Comparator

The submission nominated cabergoline as the main comparator. Cabergoline is an ergot dopamine agonist that has a restricted benefit listing for Parkinson disease. Carbergoline is the most commonly used ergot dopamine agonist on the PBS.

The PBAC accepted that cabergoline is a reasonable comparator.

For PBAC's view see Recommendations and Reasons.

7. Clinical Trials

The submission presented an indirect analysis of one trial comparing pramipexole with carbidopa-levodopa (CALM-PD) and one trial comparing cabergoline with carbidopa-levodopa (PKDS009) in patients with early Parkinson disease. The common comparator was carbidopa-levodopa.

The key trials (and associated reports) published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Pramipexole		
CALM-PD	Randomised, double-blind trial comparing the safety and efficacy of pramipexole and carbidopa-levodopa in patients with early PD.	BI Trial Report – Parallel Group, Double-Blind Comparison Study of Pramipexole and Carbidopa-Levodopa in the Treatment of Parkinson Disease.
Holloway 2004	Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4–year randomized controlled trial.	BI Trial Report – Parallel Group, double-blind comparison study of pramipexole and carbidopa-levodopa in the treatment of Parkinson disease. Archives of Neurology, 2004, Vol 61 p 1044-1053, 2004.
Parkinson Study Group 2000	Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group.	Parkinson Study Group et al, JAMA, 2000, Vol 284 p 1931-1938, 2000.
Cabergoline		
Bracco 2004	The long-acting dopamine receptor agonist cabergoline in early Parkinson disease: final results of a 5-year, double blind, levodopa-controlled study.	Bracco et al, CNS Drugs, Vol 18 p 733-746, 2004.
Rinne 1998	Early treatment of Parkinson disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial.	Drugs, Vol 55 Suppl 1 p 23-30, 1998.
Rinne 1997	Cabergoline in the treatment of early Parkinson disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa.	Neurology, Vol 48 p 363-368, 1997.
Meta-analysis		
Inzelberg 2003	Cabergoline, Pramipexole and Ropinirole used as Monotherapy in Early Parkinson disease: An Evidence-based Comparison.	Drugs & Aging, Vol 20 p 847-855, 2003.

Abbreviations: PD, Parkinson disease; RCT, randomised controlled trial

8. Results of Trials

The risk of developing motor complications, the primary outcome of the CALM - PD trial, showed a statistically significant reduction with pramipexole compared with carbidopa-levodopa. However there was no significant difference between the two treatments in regards

to some of the secondary outcomes such as patients experiencing “on-off” fluctuations and “off” period dystonias. In addition, the risk of experiencing freezing, a secondary outcome, was increased with pramipexole compared with carbidopa-levodopa. Patients treated with carbidopa-levodopa reported a statistically significant greater improvement in disease symptoms than patients treated with pramipexole (change in Unified Parkinson Disease Rating Scale (UPDRS) scores from baseline, a secondary outcome).

The results of the indirect comparison of pramipexole with cabergoline showed only weak evidence in support of the non-inferiority claim made in the submission.

There was no significant difference in the number of total adverse events or the number of serious adverse events for either pramipexole or cabergoline compared with carbidopa-levodopa. However, the submission highlighted the risk of fibrotic complications, including cardiac valvulopathy, pericarditis and retroperitoneal or pleural fibrosis associated with cabergoline in the extended assessment of comparative harms.

For PBAC’s comments on these results, see Recommendations and Reasons.

9. Clinical Claim

The submission described pramipexole as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over cabergoline.

For PBAC’s view, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis, based on the currently approved prices for pramipexole and cabergoline, and the average daily doses used in the trials.

The submission presented a supportive cost-analysis for monitoring patients receiving treatment with cabergoline. The submission estimated that the substitution of cabergoline with pramipexole would represent an annual cost saving per patient.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year to be less than 10,000 patients in Year 5 at a financial cost/year to the PBS of less than \$10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted the submission nominated cabergoline, an ergot dopamine agonist, as the main comparator. The PBAC accepted that cabergoline is a reasonable comparator, however consistent with its recent consideration of rotigotine, the Committee also considered that levodopa with a decarboxylase inhibitor is an appropriate additional comparator for pramipexole in the treatment of patients with early Parkinson disease. This reflects the current situation where some neurologists favour using dopamine agonists early in Parkinson disease, whereas other neurologists prefer to begin therapy with a levodopa product and taking into account that a proportion of this latter group may be persuaded to switch to a non-ergot dopamine agonist such as pramipexole.

The Committee noted the submission presented an indirect analysis of one trial comparing pramipexole with carbidopa-levodopa (CALM-PD) and one trial comparing cabergoline with carbidopa-levodopa (PKDS009) in patients with early Parkinson disease.

The PBAC agreed that the evidence to support the claim that pramipexole was non-inferior to cabergoline was weak. First, the claim is based on an indirect comparison and suffers from all the inherent uncertainty around such comparisons. Second, the submission did not specify a non-inferiority margin, as is standard for a head-to-head non-inferiority trial. Third, the outcome considered of most relevance by PBAC, change in UPDRS motor disability scale from baseline, could not be assessed in the indirect analysis. Additionally the outcome, risk of motor complications over time, was not able to be evaluated because the definition and confirmation of motor complications differed between the trials.

The PBAC agreed that the CALM-PD study provided a good basis upon which to compare pramipexole with carbidopa-levodopa, notwithstanding that the Committee had some concern that the patients recruited into this trial did not meet the definition of early Parkinson disease, with some patients having had the disease for 7 years at study entry (mean 1.4 years). The Committee was more concerned however, that, on the outcome of most interest, the UPDRS, which is a measure of the success of treatment, patients treated with carbidopa-levodopa reported a statistically significant greater improvement in disease symptoms than patients treated with pramipexole (change in UPDRS scores from baseline).

Although, the submission described pramipexole as superior to cabergoline in terms of safety, the PBAC concluded that the safety evidence presented was insufficient to determine the superiority or equivalence between the two dopamine agonists. Pramipexole and cabergoline appear to have different safety profiles, however no significant difference was demonstrated in the number of total adverse events or the number of serious adverse events for either pramipexole or cabergoline compared with carbidopa-levodopa. Data was outlined in the submission on the risk of fibrotic (including cardiac valvulopathy) and serosal inflammatory conditions associated with cabergoline treatment, however the relative importance of episodes of somnolence associated with pramipexole treatment was not addressed.

The PBAC noted that although the submission presented a cost minimisation analysis against cabergoline, no economic analysis against levodopa-carbidopa was presented. Given the concerns the PBAC had with the indirect comparison of the two trials, there was also uncertainty regarding the equi-effective doses presented.

In summary, the PBAC rejected the request to extend the PBS-subsidy of pramipexole to include early Parkinson disease because of insufficient evidence to substantiate the claim that pramipexole is non-inferior to cabergoline or levodopa-carbidopa.

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

Boehringer Ingelheim is disappointed that pramipexole was rejected for use in patients with early Parkinson's disease and intends to work with the PBAC to facilitate listing. The sponsor has submitted a minor submission to the PBAC to seek clarity on the appropriate comparator for a resubmission. The sponsor is concerned that the only dopamine agonists currently listed to treat patients with early Parkinson's disease are the ergot dopamine agonists. These drugs are associated with significant fibrotic complications and ongoing monitoring costs.