

Public Summary Document

Product: Ropinirole, tablets, 0.25 mg, 0.5 mg and 2 mg, Repreve®
Sponsor: GlaxoSmithKline Pty Ltd
Date of PBAC Consideration: March 2006

1. Purpose of Application

This application sought an Authority required listing on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients suffering with severe primary restless legs syndrome (RLS).

2. Background

Although the PBAC had not previously considered an application for ropinirole for the treatment in severe primary restless legs syndrome, the Committee had recommended the listing of ropinirole (Requip®) as an Authority required benefit for the treatment of Parkinson's disease at its December 1997 meeting. However, ropinirole (Requip) was never listed in the PBS schedule, as the sponsor, SmithKline Beecham Pty Ltd, decided not to proceed with listing.

3. Registration Status

Repreve is TGA registered for marketing in Australia for the 'treatment of primary restless legs syndrome, including the reduction of associated periodic limb movement and episodes of nocturnal arousal.'

4. Listing Requested and PBAC's View

The submission requested an authority required listing for the treatment of severe primary restless legs syndrome in patients who score greater than or equal to 21 on the International Restless Legs Severity Scale (IRLS) and who manifest the four diagnostic criteria below:

International Restless Legs Syndrome Study Group (IRLSSG) Diagnostic criteria:

- a desire to move the limbs usually associated with paraesthesias or dysaesthesias
- motor restlessness (during wakefulness does the patient move the limbs in an attempt to relieve the discomfort)
- symptoms worse or exclusively present at rest with at least partial and temporal relief by activity
- symptoms worse in the evening or night

Ropinirole is not PBS subsidised for secondary restless legs syndrome (renal failure, iron deficiency anaemia or pregnancy) or Parkinson's disease.

See the PBAC Recommendations and Reasons for PBAC's View.

5. Clinical Place for the Proposed Therapy

Restless legs syndrome (RLS) is an internationally recognised neurological disorder. The disease is recognised in two forms: primary (or idiopathic) and secondary. Between 60% and 80% of RLS patients fall within the primary disease category.

Restless legs syndrome is a condition in which a sense of uneasiness, restlessness and itching often accompanied by twitching and pain is felt in the legs and sometimes arms when sitting or lying down, especially in bed at night.

Ropinirole is currently the only TGA-approved pharmacological agent for the treatment of RLS in Australia.

6. Comparator

The submission nominated placebo as the main comparator providing data to demonstrate that the majority of severe primary RLS patients are currently untreated.

The PBAC considered that while a large number of patients with clinically significant restless legs syndrome are not on treatment this does not justify the assumption that placebo be the only comparator. Cabergoline and levodopa could also be comparators.

See the PBAC Recommendations and Reasons for more information.

7. Clinical Trials

The submission presented data from four key studies (study 190, 191, 194, and 249) and three supportive studies (study 188, 192, and 243).

All seven studies were published at the time of the submission as follows:

Trial/First author	Protocol/Publication title	Publication citation
188/ Karrasch J	A study of the maintained efficacy and safety of ropinirole versus placebo in the long term treatment of restless legs syndrome (RLS)	Sleep 2004; 27 Abstr. Suppl.:A294 Abs no. 658.
190/ Trenkwalder C	A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of ropinirole in patients suffering from restless legs syndrome (RLS).	Journal of Neurology, Neurosurgery and Psychiatry 2004;75: 92-97.
191/ Allen RP	A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy, safety and tolerability of ropinirole in subjects with restless legs syndrome (RLS) suffering from periodic leg movements of sleep (PLMS)	Mov. Disorder 2004; 19 Suppl. 9:S430 Abs no. 1261. Sleep 2004; 27 (5): 907-914.
192/ Dreykluft T	A 52 week open-label extension study of the long term safety of ropinirole in subjects suffering from restless legs syndrome (RLS)	Mov. Disorder 2004; 9:S430-S431; Abs no. 1262
194/ Walters AS	A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of ropinirole in patients suffering from restless legs syndrome (RLS)	Mov. Disorder 2004; 19(2): 1414-1423.
243/Dreykluft T	A 52 week open-label extension study of the long term safety of ropinirole in subjects suffering from restless legs syndrome (RLS)	Mov. Disorder 2004; 9:S430-S431; Abs no. 1262.
249/ Bogan R	A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of ropinirole in patients suffering from restless legs syndrome (RLS)	Neurology 2005; 64(6 Suppl.1):A27 Abs no. S04.002.

The submission also presented the results of a post-hoc meta-analysis of the proportions of “responders” to ropinirole and placebo in the sub-group of patients with severe RLS (score of greater than or equal to 21 on the IRLS severity scale) from the four key studies. Patients with severe disease are those targeted by the proposed PBS listing restriction. This analysis had not been published at the time of submission.

The submission relied upon the REST General Population study (epidemiology study involving 16,202 adults, conducted in the USA and five European countries) to estimate the prevalence of RLS in Australia.

8. Results of Trials

The published results for mean change in the total IRLS score for ropinirole compared with placebo from the four key trials are summarised in the table below:

Mean change from baseline in IRLS scale score in the total trial population

Trial	Study 190		Study 191		Study 194		Study 249	
	Rop	Plac	Rop	Plac	Rop	Plac	Rop	Plac
Group								
N analysed	146	138	32	33	131	135	187	193
Mean change in IRLS scale total score at Week 12 LOCF								
Adjusted mean change	-3.0		-1.2		-2.5		-3.7	
95% CI	-5.0, -1.0		-5.1, 2.9		-4.6, -0.4		-5.4, -2.0	

LOCF = last observation carried forward

The post-hoc meta-analysis of the proportions of responders to ropinirole and placebo in the sub-group of patients with severe RLS in the four key studies demonstrated that significantly more patients in the ropinirole group achieved a “response” to treatment than in the placebo group.

In the four key trials there were significantly higher numbers of adverse events in the ropinirole group compared to placebo, but the numbers of serious adverse events and events leading to withdrawal were the same. The results of long-term safety studies generally confirmed the safety of ropinirole observed in the 12-week trials in regard to most common adverse events, but augmentation was a commonly reported adverse event (>1/100; <1/10).

For the PBAC view of these results, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that ropinirole is ‘significantly more effective than the placebo and has similar or less toxicity’. The PBAC considered there to be uncertainty about the extent of clinical benefit, as described below (*see Recommendations and Reasons*).

10. Economic Analysis

The submission presented a trial based preliminary economic evaluation. The choice of the cost-effectiveness approach was considered valid.

A modelled economic evaluation was also presented.

The submission claimed that the base-case incremental cost-effectiveness of ropinirole compared to placebo was between \$15,000 - \$45,000 per quality adjusted life year (QALY) in patients with severe primary RLS.

The choice of the cost-utility approach was considered valid, however the PBAC had a number of concerns with the economic modelling (*see Recommendations and Reasons*).

11. Estimated PBS Usage and Financial Implications

The expected cost to the government was predicted by the submission to be < \$10 million in year 4 of listing, provided cost off-sets from the drugs replaced by ropinirole were realised. The PBAC considered this was an underestimate as the potential for usage outside the requested restriction for severe RLS and the increased diagnosis and prescribing due to the availability of a dedicated medication had not been factored into the submission's estimate.

12. Recommendation and Reasons

The PBAC noted the focus of the hearing was on issues relating to the diagnosis of restless legs syndrome (RLS), the use of the International Restless Legs severity questionnaire (IRLS), and the role of levodopa in treatment.

Although the potential for usage beyond the restriction is high, the Committee considered that the tightened restriction proposed in the Pre-Sub-Committee response would help address this. The PBAC considered the inclusion of the IRLS scale in the restriction as proposed by the sponsor would help address this issue and noted the reassurance at the hearing that the scale was not subject to copyright. The PBAC acknowledged the attempt to restrict use to the targeted population, despite the subjective nature of the IRLS scale, but considered that it may be appropriate for the restriction to incorporate a continuation rule.

The PBAC noted that restless legs syndrome is currently under-treated and available treatments are not commonly used. The PBAC considered that while a large number of patients with clinically significant restless legs syndrome are not on treatment this does not justify the submission's assumption that placebo be the only comparator. According to the submitted expert opinion, cabergoline is the most commonly used agent to treat symptomatic and restless legs syndrome. Dopamine agonists such as levodopa may be appropriate as they are the closest pharmacological analogues listed without restriction. The clinician at the hearing also confirmed that in the patients proposed, a dopamine agonist is used in current practice. However the PBAC agreed that the use of levodopa and cabergoline in RLS are limited by treatment associated side effects, including, for levodopa: augmentation, and for cabergoline: mitral valvulopathy with long term use.

The PBAC remained concerned about the size of the treatment effect, particularly in view of the high placebo response rate.

There were some concerns that results of Study 249 are markedly different from those of the other three key trials and that these results may have inappropriately influenced the outcome of the meta-analysis. A sensitivity analysis of the economic model using the results from Study 249 would have been informative.

Members noted that toxicity is higher with ropinirole than with placebo, and that although most side effects are transitory, a significant proportion of patients may reduce their dose of ropinirole in response. The effect of this dose reduction on the efficacy of ropinirole was unclear.

The Committee had a number of concerns with respect of the economic model, including one about the questionnaire used to elucidate utilities that the PBAC considered likely to have biased all utility weights. The incremental cost effectiveness ratio (ICER) was highly sensitive to small changes in utility.

The PBAC therefore rejected the submission because of uncertainty about the extent of clinical benefit and the resulting uncertainty about the 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

GlaxoSmithKline Australia continues to be concerned that there are no registered therapeutic medicines listed on the PBS for the treatment of patients suffering with severe primary restless legs syndrome. GlaxoSmithKline believes that it would have been appropriate to list Repreve[®] for the above indication as supported by the application submitted, and every effort was made to address the PBAC's concerns. GlaxoSmithKline have sought further clarity around the PBAC's recommendation and have decided not to resubmit at this stage.