PUBLIC SUMMARY DOCUMENT
Product: Rotigotine, transdermal patch, 4.5 mg (releasing approximately 2 mg per 24 hours), 9.0 mg (releasing approximately 4 mg per 24 hours), 13.5 mg (releasing approximately 6 mg per 24 hours), 18.0 mg (releasing approximately 8 mg per 24 hours), Neupro®.
Sponsor: UCB Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application
The submission sought an unrestricted listing for use as monotherapy or in combination with levodopa for the treatment of idiopathic Parkinson's disease (PD) from early stage to advanced disease.

2. Background
This was the first time rotigotine had been considered by the PBAC.

3. Registration Status
Rotigotine patches were registered by the TGA on 22 November 2007 and are indicated as monotherapy, or in combination with levodopa, for the treatment of idiopathic Parkinson's disease from early stage to advanced disease.

4. Listing Requested and PBAC's View
The submission requested an unrestricted listing. However, the PBAC noted the sponsor had indicated a willingness to accept a 'restricted benefit' listing if rotigotine were recommended for listing.

5. Clinical Place for the Proposed Therapy
The rotigotine transdermal patch would provide access to a non-ergot dopamine agonist as a transdermal patch for patients with Parkinson's disease.

6. Comparator
The submission nominated cabergoline as the appropriate main comparator.

The PBAC accepted this as an appropriate comparator, but considered a comparison with levodopa in early Parkinson's disease should also have been presented.

See Recommendation and Reasons for PBAC's view.

7. Clinical Trials
The submission presented five randomised, double-blind, placebo controlled trials comparing rotigotine in varying doses with placebo (three in early PD and two in PD with motor fluctuations) and three randomised, double-blind, placebo controlled trials comparing cabergoline with placebo in patients with PD with motor fluctuations.

Details of the trials published at the time of the submission are presented in the table below.

Trial/First author	Protocol title	Publication citation
Common reference: placebo		
Rotigotine		
SP506 Blindauer K et al, 2003 Morgan JC et al, 2006	A controlled trial of rotigotine monotherapy in early Parkinson's disease. Rotigotine for the treatment of Parkinson's disease.	*Arch Neurol* 2003; 60(12): 1721–1728 Expert Review of Neurotherapeutics. *2006;6(9):1275-82*
SP512 Jankovic J et al, 2007 Watts RL, et al, 2007	Transdermal rotigotine: Double-blind, placebo-controlled trial in Parkinson disease. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease.	*Arch Neurol* 2007; 64(5): 676–682 *Neurology* 2007; 68(4): 272–276
SP513 Giladi N et al, 2007	Rotigotine transdermal patch in early Parkinson's disease: A randomized double-blind, controlled study versus placebo and ropinirole	Movement Disorders*. Available from: http://www3.interscience.wiley.com/journal/76507419/home*
SP515 Poewe WH et al, 2007	Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial.	*Lancet Neurol* 2007; 6(6): 513–520
SP650 LeWitt PA et al, 2007	Advanced Parkinson's disease treated with rotigotine transdermal system.	*Neurology* 2007; 68:1262–1267
Cabergoline		
Ahlskog 1996	Adjunctive cabergoline therapy of Parkinson's disease: Comparison with placebo and assessment of dose responses and duration of effect.	*Clin Neuropharmacol* 1996; 19(3): 202–212
Hutton 1996	Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. Visual contrast sensitivity in Parkinson's disease is worsened with cabergoline treatment.	*Neurology* 1996; 46(4): 1062–1065 *Parkinsonism Relat Disord* 1999; 5: 87–91
Steiger 1996	Double-blind study of the activity and tolerability of cabergoline versus placebo in parkinsonians with motor fluctuations.	*J Neurol* 1996; 243: 68–72

8. Results of Trials

ROTIGOTINE TRIALS – PRIMARY OUTCOMES IN EARLY PD

The primary outcome in the early PD rotigotine trials was the change in the sum of the Unified Parkinson's Disease Rating Scale (UPDRS) Activities of Daily Living (ADL) and motor scores and the proportion of patients achieving at least a 20% of reduction in sum of UPDRS ADL and motor subscales from baseline to end of maintenance phase. The results demonstrate that patients with early PD, treated with rotigotine, have a statistically significantly reduced sum of UPDRS ADL and motor subscales and a statistically significantly greater proportion of patients treated with rotigotine achieved at least a 20%

reduction in sum of UPDRS ADL and motor subscales, from baseline to end of maintenance phase, compared with those treated with placebo. Some heterogeneity between the trials was noted. The results are presented in the tables below.

ANCOVA results for change in sum of UPDRS ADL and motor subscales from baseline to the end of the maintenance phase in the early PD rotigotine trials

Trial	Rotigotine		Placebo		Weighted Mean Difference (95% CI)
	n (%)	Mean (SD)	n (%)	Mean (SD)	
SP512	177 (97.8)	–3.98 (9.41)	96 (100)	1.31(9.37)	**–5.29 (–7.62, –2.96)**
SP513	213 (99.1)	–6.83 (9.62)	117 (98.3)	–2.33 (9.54)	**–4.50 (–6.66, –2.34)**
Meta-analysis: Rotigotine-Early PD Chi-square (Q) for heterogeneity=0.24 p=0.63; I^2 statistic=0%					**-4.86 (-6.45, -3.28)**

CI=confidence interval; SD=standard deviation; n=number of participants reporting data;
Bolded typography indicates statistically significant differences between treatment groups;
UPDRS ADL – Unified Parkinson's Disease Rating Scale Activities Daily Living;
ANCOVA- Analysis of Covariance model.

Number of patients achieving at least a 20% reduction in sum of UPDRS ADL and motor subscales from baseline to end of maintenance phase (dichotomous data) comparing trial medication with placebo in the early PD rotigotine trials

Trial	Rotigotine		Placebo		Relative risk (95% CI)
	n (%)	Number of responders	n (%)	Number of responders	
SP506	254 (95.8)	123	62 (96.9)	18	**1.67 (1.11, 2.51)**
SP512[a]	177 (97.8)	84	96 (100)	18	**2.53 (1.62, 3.95)**
SP513[a]	213 (99.1)	110	117 (98.3)	35	**1.73 (1.27, 2.35)**
Meta-analysis: Rotigotine-Early PD Chi-square (Q) for heterogeneity=2.37 p=0.31; I^2 statistic=15.5%					**1.88 (1.48, 2.38)**

CI=confidence interval; SD=standard deviation; n=number of participants reporting data;
Bolded typography indicates statistically significant differences between treatment groups;
[a] primary outcome

ROTIGOTINE TRIALS – PRIMARY OUTCOMES IN ADVANCED PD

The primary outcome in the advanced PD rotigotine trials was the change in absolute time "off" in hours and the proportion of patients achieving at least a 30% reduction in absolute time 'off' in hours, from baseline to end of maintenance phase. The results for these outcomes are presented in the following tables.

ANCOVA results for change in absolute time 'off' in hours from baseline to end of maintenance phase (continuous data) in the advanced PD rotigotine trials

Trial	Rotigotine		Placebo		Weighted Mean Difference (95% CI)
	n (%)	Change from baseline mean (SD)	n (%)	Change from baseline mean (SD)	
SP515	201 (100)	-2.46 (2.89)	100 (100)	-0.88 (2.9)	**-1.58 (-2.27, -0.89)**
SP650	222 (96.1)	-2.41 (3.37)	119 (99.2)	-0.90 (3.27)	**-1.51 (-2.05, -0.77)**
Meta-analysis: Rotigotine – Advanced PD Chi-square (Q) for heterogeneity=0.02 p=0.89; I^2 statistic=0%					**-1.55 (-2.05, -1.04)**

CI=confidence interval; SD=standard deviation; n=number of participants reporting data;
Bolded typography indicates statistically significant differences between treatment groups.

Number of patients achieving at least a 30% reduction in absolute time 'off' in hours from baseline to the end of the maintenance phase (dichotomous data) comparing trial medication with placebo in the advanced PD rotigotine trials

Trial	Rotigotine		Placebo		Relative risk (95% CI)
	n (%)	Number of responders	n (%)	Number of responders	
SP515	201 (100)	120	100 (100)	35	**1.71 (1.28, 2.28)**
SP650	222 (96.1)	124	119 (99.2)	41	**1.62 (1.29, 2.13)**
Meta-analysis: Rotigotine – Advanced PD Chi-square (Q) for heterogeneity=0.06 p=0.80; I^2 statistic =0%					**1.66 (1.36, 2.03)**

CI=confidence interval; SD=standard deviation; n=number of participants reporting data;
Bolded typography indicates statistically significant differences between treatment groups.

The results demonstrated that patients with advanced PD, treated with rotigotine, have a statistically significant reduction in absolute time 'off' in hours and a statistically significantly greater proportion of patients treated with rotigotine achieved at least a 30% reduction in absolute time 'off' in hours, from baseline to end of maintenance phase, compared with those treated with placebo.

INDIRECT COMPARISON OF ROTIGOTINE WITH CABERGOLINE

The results of all the indirect comparisons (all rotigotine trials, only the advanced PD rotigotine trials and only rotigotine trial SP515) demonstrated that there was no significant difference in UPDRS ADL subscale scores at the end of the maintenance phase between rotigotine and cabergoline with a weighted mean difference (WMD) (95% CI) of 0.60 (-1.86, 3.06); 0.11 (-2.54, 2.76) and -0.1 (-2.98, 2.78), respectively.

The results of all the indirect comparisons (all rotigotine trials, only the advanced PD rotigotine trials and only rotigotine trial SP515) demonstrated that there was no significant difference in UPDRS motor subscale scores at the end of the maintenance phase between rotigotine and cabergoline.

Analysis of change in UPDRS ADL subscale scores from baseline to the end of the maintenance phase demonstrated that patients treated with rotigotine in the early and advanced stages of PD and those treated with cabergoline in the advanced PD have statistically significantly greater reductions in UPDRS ADL scores from baseline to the end of the maintenance phase, compared with those treated with placebo.

Based on trial data rotigotine and cabergoline have similar adverse event profiles in terms of dopaminergic effects including nausea, dizziness, somnolence and hallucinations. Rotigotine is associated with increased application site reactions compared with placebo. Cabergoline is associated with fibrotic serosal reactions including valvulopathy.

9. Clinical Claim

The submission claimed that based on the clinical evidence presented rotigotine is therapeutically non-inferior to cabergoline, but has fewer serious safety issues.

For the PBAC's views see Recommendation and Reasons.

10. Economic Analysis

The equi-effective doses of rotigotine 7.6 mg daily and cabergoline 3.42 mg daily used in the cost-minimisation analysis were considered a likely underestimate favouring rotigotine. The

mean daily dose (8.8 mg) using only the optimal dose trials which correspond with the dosage regimens proposed in the submission, trials SP513 and SP515, was considered more appropriate.

For the PBAC's views see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The estimated financial cost per year to the PBS was less than $10 million in Year 5. The PBAC considered that this was a likely underestimate.

12. Recommendation and Reasons

The PBAC noted the sponsor had indicated its willingness to accept a restricted benefit listing if rotigotine were recommended for listing.

The PBAC accepted that cabergoline, as a dopamine receptor agonist, is an appropriate comparator in advanced Parkinson's disease (PD), noting also that cabergoline has a small but valuable place as first line treatment in early PD. However, the PBAC considered a comparison versus levodopa in early PD should also have been presented. The Pre-PBAC response had reiterated the opinion that there is a growing international trend towards using dopamine agonists as first line therapy for PD, however, other comments made to the PBAC, coupled with the high PBS usage of levodopa, indicated this was not current Australian clinical practice.

The PBAC considered that although no significant differences between rotigotine and cabergoline were observed in any of the indirect comparisons presented, the dose of cabergoline used in the trials may have represented sub-therapeutic doses of cabergoline (up to 5 mg per day was used in the trials, however the TGA-approved PI recommends use of up to 6 mg). The PBAC noted studies of the relative bioavailability of rotigotine found differences in bioavailability varying from <1% (abdomen versus hip) to 41% (shoulder versus thigh) depending on the application site. Therefore, the dose of rotigotine delivered (and the subsequently effectiveness of rotigotine) may vary from day to day depending on the application site.

With respect to safety, the claim that rotigotine has fewer serious safety issues compared to cabergoline was not considered to be demonstrated to the extent claimed in the submission. The therapeutic claims are based on an indirect comparison of five rotigotine and three cabergoline randomised controlled trials using placebo as a common comparator. No direct comparison was provided. Therefore, although there are probably fewer serious safety issues with rotigotine than with cabergoline, the absolute magnitude of this benefit is unclear. The data presented were considered equivocal and incomplete**,** as important adverse effects about which only incomplete information is currently available include the relative incidence of sleep attacks, ophthalmological adverse reactions and fibrosis.

The equi-effective doses of rotigotine 7.6 mg daily and cabergoline 3.42 mg daily used in the cost-minimisation analysis were considered a likely underestimate favouring rotigotine. The mean daily dose (8.8 mg) using only the optimal dose trials which correspond with the dosage regimens proposed in the submission, trials SP513 and SP515, was considered more appropriate.

The monitoring costs for cabergoline were also considered to be an over-estimate as there is a discrepancy between the monitoring recommended by the Movement Disorder Society of Australia (MDSA) and the PI, and some assessments would be performed by the treating neurologist incurring few, if any, extra consultations.

The PBAC also noted advice that the estimation of likely numbers of patients eligible for rotigotine treatment should have taken into account the substitution of levodopa with rotigotine. The submission should have also taken into account the likely numbers of patients who are not currently receiving dopamine agonists that may be eligible for rotigotine treatment.

The PBAC rejected the application on the grounds that a comparison should also have been made against levodopa and a decarboxylase inhibitor in early Parkinson's disease, the claim of superior safety profile over cabergoline had not been substantiated, and because the claimed cost offsets for monitoring the safety of cabergoline were unacceptable.

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 looks forward to working with the PBAC to clarify the decision and progress these matters towards successful resolution.