PUBLIC SUMMARY DOCUMENT
Product: Levodopa with carbidopa monohydrate, intestinal gel, 20 mg – 5 mg (base) per mL, 100 mL, Duodopa®
Sponsor: Solvay Pharmaceuticals
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) PBS listing for initial treatment commenced in a hospital based Movement Disorder Clinic for patients with advanced Parkinson disease with severe disabling motor fluctuations not adequately controlled by oral therapy.

The submission also sought a Section 85 authority required PBS listing for continuing treatment for patients commenced in a hospital based Movement Disorder Clinic.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

At the March 2008 meeting, the PBAC rejected a submission seeking a Section 100 Highly Specialised Drug listing for treatment by a neurologist of patients with advanced Parkinson disease with severe disabling motor fluctuations not adequately controlled by oral therapy on the basis of the unacceptably high and uncertain incremental cost effectiveness ratio for levodopa with carbidopa gel compared to standard medical management.

3. Registration Status

Duodopa was TGA registered on 27 February 2008 for the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised oral treatment. A positive clinical response to Duodopa administered via a temporary nasoduodenal tube should be confirmed before a permanent percutaneous endoscopic gastrostomy (PEG) tube is inserted.

4. Listing Requested and PBAC's View

Section 100 Public and Private Hospital Authority Required
Initial treatment, commenced in a hospital based Movement Disorder clinic specialising in the treatment of advanced Parkinson disease with Duodopa

Patients should have adequate cognitive function to manage administration with a portable continuous infusion pump.
NOTE:
Specialist Movement Disorder clinics are required to have the following facilities for the provision of specialised clinical support of advanced Parkinson's patients:

(a) a Neurologist or Geriatrician experienced in the management of advanced Parkinson's Disease
(b) a Parkinson's Disease Specialist nurse;
(c) a Gastroenterologist experienced in PEG-J insertion and hospital facility equipped for this procedure
(d) 24 hour access by patients to medical advice

(e) a hospital pharmacy with adequate cold chain storage

Section 85 - Authority Required
Continuation of treatment with Duodopa intestinal gel commenced in a hospital based specialised Movement Disorder clinic.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Parkinson disease (PD) is a chronic, progressive neurological disease. PD causes the neurons in the substantia nigra cells to die, leading to a lack of dopamine in the brain, especially in the basal ganglia. This results in loss of the ability to control normal body movements, with varying degrees of loss of muscular control.

Patients with advanced PD experience daily changes in symptoms, medication side effects that limit treatment and the loss of independence in activities of daily living.

Duodopa would provide a treatment for advanced idiopathic PD in patients who no longer respond to oral treatment.

6. Comparator

The submission nominated standard medical management and deep brain stimulation as the main comparators. The PBAC considered this was appropriate.

7. Clinical Trials

The March 2008 submission presented results from two randomised trials (NPP-001-02 (DIREQT) and NPP-001-99) and five non-randomised studies (NPP-001-92, NPP-002-02, DAPHNE, Antonini and Odin/Eggert). No new clinical evidence for Duodopa was provided in this submission.

New data on the clinical effectiveness of deep brain stimulation (DBS) were included.

For the published direct randomised trials see the March 2008 PSD. For the non-randomised trials and DBS trials published at the time of March 2009 submission see below:

Nonrandomised studies		
Trial NPP-001-92 Nilsson et al Nilsson et al.	Long-term intraduodenal infusion of a water based levodopa-carbidopa dispersion in very advanced Parkinson's disease. Duodenal levodopa infusion in Parkinson's disease – long-term experience.	Acta Neurologica Scandinavica 1998; Vol 97 (3): 175-83. Acta Neurologica Scandinavica 2001; Vol 104(6): 343-8.
Antonini study	Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome.	Movement Disorders 2007; 22(6): 1-5.
Odin / Eggert study	Kongressreport, 5th German Parkinsons Congress. Besserung von motorischen und night-motorischen Symptonen.	Neurologie & Rehabilitation 2007, 2.
Deep Brain Stimulation trials – direct randomised trials/systematic reviews		

Deuschl 2006	A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease	N Engl J Med 2006; 355:896-908.
Schupbach 2006	Neurosurgery at an earlier stage of Parkinson disease	Neurology 2007; 68:267–271
Deep Brain Stimulation systematic reviews and reports		
Hamani 2005	Bilateral subthalamic nucleus stimulation for Parkinson's disease. A systematic review of clinical literature.	Neurosurgery 2005. 56(6):1313-1324
Kleiner-Fisman 2006	Subthalamic Nucleus Deep Brain Stimulation: Summary and Meta-Analysis of Outcomes	Movement Disorders Vol. 21, Suppl. 14, 2006, pp. S290–S304
Temel 2006	Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: A systematic review	Parkinsonism and Related Disorders 12 (2006) 265–272

8. Results of Trials

The key results presented for levodopa-carbidopa were unchanged from the previous submission – see March 2008 PSD.

The submission also presented some comparative data of DBS versus standard care. The results of the two trials (Deuschl 2006, Schupbach 2006) are presented below. Their primary outcomes were PD Questionnaire (PDQ-39) scores; the Unified PD Rating Scale (UPDRS-III) scores were also used as outcomes in one trial (Deuschl 2006). Comparisons with the PDQ-39 and UPDRS-III results reported in levodopa-carbidopa trial NPP-001-02 (secondary outcomes) are also presented below.

Results of the Parkinson's disease Questionnaire (PDQ-39) summary index primary outcome measure for the DBS randomised trials

Treatment	Baseline	Endpoint	Δ Baseline to endpoint (SD)	WMD (95% CI)
NP-001-02: Endpoint = 6 weeks, Mean (SD)				
Duodopa	n =18 38.4 (12.1)	n =18 26.5 (9.4)	-11.9 (10.5)	**-9.5 (-14.83, -4.17)**
CM		n =18 36.0 (11.8)	-2.4 (4.8)	
Deuschl et al (2006): Endpoint = 6 months, Mean (SD)				
Surgery	n =78 41.8 (13.9)	n = 71 31.8 (16.3)	**-9.5 (15.3)**	**-9.3 (-13.69, -4.91)**
CM	n =78 39.6 (16.0)	n = 73 40.2 (14.4)	-0.2 (11.2)	
Schupbach et al (2006): Endpoint = 18 months, Median (range)				
Surgery	n = 10 35.4 (24.4-51.5)	n = 10 28.9 (5.7-53.1)	-6.5 (NR)	**NA**
CM	n = 10 37.9 (23.4-53.1)	n = 10 41.9 (13.5-57.3)	4 (NR)	

Statistically significant differences between groups are bolded
SD = standard deviation; CI = confidence interval; CM = conventional medication treatment;
WMD = weighted mean difference, NR = not reported

The results of the UPDRS-III outcome measure from the randomised trials are summarised below:

Results of the Unified Parkinson's Disease Rating Scale part III (UPDRS—III) (primary outcome measure for Deuschl 2006)

Treatment	Baseline	Endpoint	Δ Baseline to endpoint (SD)	WMD (95% CI)
NP-001-02: Endpoint = 6 weeks, Mean (SD)				
Duodopa	NR	NR	NR	**Mean Difference (SD)**
CM	NR	NR	NR	-6.9 (12.6)
Deuschl et al (2006): Endpoint = 6 months, Mean (SD)				
On medication				
Surgery	n =78 18.9 (9.3)	n = 71 14.6 (8.5)	**-4.0 (10.1)**	***-4.40 (-7.34, -1.46)***
CM	n =78 17.3 (9.6)	n =73 17.5 (10.6)	0.4 (7.7)	
Off medication				
Surgery	n =78 48.0 (12.3)	n =71 28.3 (14.7)	**-19.6 (15.1)**	***-20.0 (-24.14, -15.86)***
CM	n =78 46.8 (12.1)	n =72 46.0 (12.6)	-0.4 (9.5)	
Schupbach et al (2006): Endpoint = 18 months, Mean (SD)				
On medication				
Surgery	2.9 (3.0)	NR	NR	NA
CM	2.6 (2.8)	NR	NR	
Off medication				
Surgery	32.7 (13.4)	NR	69%	NA
CM	25.3 (8.7)	NR	-29%	

SD = standard deviation; CI = confidence interval; CM = conventional medication treatment;
Δ = change in, NR = not reported, NA = not applicable

A formal indirect comparison of levodopa-carbidopa and DBS was not undertaken because of differences in trial design, patient populations and the inconsistent way time-points outcomes were measured. This was appropriate.

The key adverse events results presented for levodopa-carbidopa were unchanged from the previous submission – see March 2008 PSD.

The adverse events reported for DBS in Deuschl (2006) are presented below:

Summary of number of adverse events in Deuschl et al (2006)

Deuschl *et al* (2006)	Surgery	Conventional Medication	RR (95% CI)
Serious Adverse Events	10/78	3/78	3.3 (0.95, 11.65)
Death	3	1	3.0 (0.32, 28.22)
Readmission to hospital	7	2	3.5 (0.75, 16.32)
Non-serious adverse events	77/78	96/78	NA
Mild	35	8	
Moderate	32	39	
Severe	10	49	

For PBAC's view, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that levodopa-carbidopa intestinal gel has statistically significant advantages in effectiveness over standard medical management with regards to 'on' time (treatment success), time spent in Parkinsonian health state ('off' time), and health related quality of life as measured by the 15D instrument.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

An updated modelled economic evaluation was presented. The methods used in the modelled economic evaluation were substantially unchanged from the previous submission. However updated estimates were used to generate the results.

The submission excluded the costs of the DBS from the basket of comparators in the base case. The PBAC had previously advised that DBS should be included in the basket of comparators and that carer utilities should be considered in a sensitivity analysis, rather than the base case.

The revised base case calculated during the evaluation excluding carer utilities and including DBS estimated the ICER to be in the range of $75,000 – $105,000 per QALY over ten years. This was considered likely to be an under-estimate and to be highly uncertain because the model included costs associated with DBS, but no effects of DBS were attributed.

The PBAC noted that as with the previous submission, the results of the sensitivity analyses indicated that the model was most sensitive to the estimated number of cartridges of levodopa-carbidopa intestinal gel used per patient per day, the transition probabilities associated with levodopa-carbidopa intestinal gel improvements in Hoen and Yahr Scale status, the costs of supportive care at home and nursing home costs, and the disutility for caregivers. The model is moderately sensitive to the discount rate and the use of utility values from the published literature.

The PBAC considered that several other previously raised issues regarding the economic evaluation remained unaddressed.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be well below 2,000 in Year 5 and was lower than in the previous submission.

The financial net cost per year to the PBS was estimated to be in the range of $10 – $30 million in year 5 and was lower than in the previous submission.

For PBAC's view, see Recommendations and Reasons.

12. Recommendation and Reasons

The comparator, standard medical management, which also includes deep brain stimulation (DBS), was considered appropriate by the Committee.

The PBAC noted that the clinical evidence presented was the same as that for the March 2008 PBAC meeting and included results from two randomised trials, NPP-001-02 (DIREQT) and NPP-001-99, and five non-randomised studies (NPP-001-92, NPP-002-02, DAPHNE, Antonini and Odin/Eggert). The results of two recently published randomised trials (Deuschl 2006 and Schupbach 2006) were also provided in the submission for comparison of the clinical effectiveness of DBS versus standard care. The PBAC had a number of concerns with the clinical efficacy data presented. In each of the randomised trials, NPP-001-02 and NPP-001-99, the levodopa with carbidopa gel was administered via a nasogastric tube (NG),

rather than via percutaneous endoscopic gastrostomy (PEG), which is the main feature of the Duodopa formulation, and there were still concerns regarding adverse events related to the pump and/or tubing as identified in the March 2008 PBAC Minutes. As previously, the Committee considered there was uncertainty with the clinical importance of the trial results.

The PBAC noted that the PEG administration route has a high risk of complications with insertion of the PEG tube, such as aspiration pneumonia, and that sudden cessation of the infusion (if the pump or tubing failed) could precipitate neuroleptic malignant syndrome. Based on the evidence presented the Committee considered that there are significant administration safety concerns with levodopa with carbidopa intestinal gel.

The PBAC noted that carer utilities were again incorporated into the base case for this re-submission, which was considered inappropriate and instead should have been considered in a sensitivity analysis. In addition, the PBAC considered that the safety and quality of life issues associated with PEG administration of the product should have been incorporated into the economic evaluation. The PBAC also considered that the cost of DBS should have been included in the mix of comparators in the base case of the economic evaluation. The revised base case calculated during the evaluation excluding carer utilities and including DBS estimated the ICER to be in the range of $75,000 – $105,000 per QALY over ten years. This was considered likely to be underestimated and highly uncertain as the model includes costs associated with DBS, but no effects were attributed. The Committee considered that a number of other issues previously raised with the economic evaluation for this submission remained unaddressed in the re-submission and that the cost effectiveness remained highly uncertain.

The utilisation estimates for levodopa with carbidopa intestinal gel for the treatment of advanced Parkinson disease were also considered by the PBAC to be highly uncertain. The PBAC considered that the proportion of patients with Parkinson disease who would be eligible under the proposed listing was highly uncertain as the PEG administration of the product may limit use due to concerns with the safety of PEG tube insertion and the invasive nature of the procedure.

The PBAC also noted advice from the Highly Specialised Drugs Working Party that the product did not meet all the criteria for listing under the Highly Specialised Drugs Program.

The PBAC rejected the submission for levodopa with carbidopa intestinal gel on the basis of an uncertain clinical benefit and an unacceptably high and uncertain cost effectiveness ratio.

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

Solvay will continue to work with the PBAC to address the issues identified in the Duodopa PBAC resubmission. Duodopa is an Orphan Drug with limited clinical data and is suitable for a small number of advanced Parkinson's disease patients. Solvay is disappointed that the

Highly Specialised Drugs Working Party did not accept the highly specialised drug status of Duodopa. Solvay strongly believes that, by relegating carer burden from the base case cost-effectiveness analysis to the sensitivity analysis, this devalues the importance of carers in the management of Parkinson Disease. Duodopa is reimbursed in all major European markets due to its proven benefits to patients as well as cost-effectiveness.