

PUBLIC SUMMARY DOCUMENT

Product: Levodopa with Carbidopa, intestinal gel, 20 mg–5 mg per mL, Duodopa[®]

Sponsor: Solvay Pharmaceuticals

Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) Public and Private Hospital Authority Required listing for the treatment by a neurologist for patients with advanced Parkinson's disease with severe disabling motor fluctuations not adequately controlled by oral therapy.

2. Background

This formulation and method of administration had not previously been considered by the PBAC. Levodopa with carbidopa in a tablet formulation has been listed for many years.

3. Registration status

Duodopa was granted Orphan Drug status on 18 April 2006 and was registered by the TGA on the 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. Requested Listing and PBAC's view

Section 100 (Highly Specialised Drug)

Public and Private Hospital Authority required

Treatment by a neurologist for patients with advanced Parkinson's disease with severe disabling motor fluctuations not adequately controlled by oral therapy.

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

For the PBAC's view, see Recommendation and Reasons.

5. Clinical place for the proposed therapy

Duodopa would provide a novel treatment for advanced idiopathic Parkinson's disease in patients not adequately controlled by oral therapy

6. Comparator

The submission nominated standard medical management, defined as a mix of suboptimal oral medication (including oral levodopa and carbidopa) and continuous subcutaneous apomorphine infusion.

For PBAC's comments see Recommendations and Reasons.

7. Clinical Trials

The submission presented two randomised cross-over trials comparing levodopa-carbidopa intestinal gel with conventional medication in patients with advanced idiopathic levodopa-responsive Parkinson's Disease (PD), with severe motor fluctuations

in spite of individually optimised conventional treatment. A comparison of the trial interventions is shown in the table below.

Interventions compared by the direct randomised trials

Trial	Treatment	Dosage regimen	Duration of treatment	Duration of follow-up
Trial NPP-001-02	Group 1 (CM→D)	3 weeks of conventional PD medication ^a followed by 3 weeks of Duodopa ^b or vice versa Individually optimised dosage of Duodopa (26-196mg/hr; 456-3556mg/day; 20-200mg morning bolus) and conventional medication	Maximum of 6 weeks	6 weeks
	Group 2 (D→CM)			
Trial NPP-001-99	Group 1 (CM→D)	3 weeks of conventional PD medication ^c followed by 3 weeks of Duodopa ^b Individually optimised dosage of Duodopa (46-116mg/hr) and conventional medication	Maximum of 6 weeks	6 weeks
	Group 2 (D→CM)			

Notes: CM=conventional medication; D=Duodopa

^a Conventional PD medication included levodopa, apomorphine, amantadine and dopamine agonists such as ropinirole.

^b Duodopa was administered via a nasoduodenal catheter only.

^c Oral carbidopa/levodopa (Sinemet[®])

The following table lists the trials as published at the time of submission.

Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Trial NPP-001-99	Nyholm et al. Optimising levodopa pharmacokinetics: intestinal infusion versus oral sustained release tablets.	<i>Clinical Neuropharmacology</i> 2003; Vol 26 (3):156-163
	Westin J, Nyholm D, Groth T et al. Outcome prediction of enteral levodopa/carbidopa infusion in advanced Parkinson's disease.	<i>Parkinsonism and Related Disorders</i> 2006; Vol 12: 509-513
Trial NPP-001-02	Nyholm et al. Duodenal levodopa infusion monotherapy vs. oral polypharmacy in advanced Parkinson disease.	<i>Neurology</i> 2005; Vol 64: 216-223

Trial NPP-00102 was open for the patient and the investigator. Two independent and blinded observers evaluated the video recordings. However, the electronic diaries, Unified Parkinson's Disease Rating Scale (UPDRS), the Parkinson's Disease Questionnaire (PDQ) and the fifteen-dimensional measure of health-related quality of life (15D) used unblinded assessments. Blinding was not used in trial NPP-001-99.

8. Results of trials

The primary outcome in trial NPP-001-02 was the between-treatment difference in the percentage of video recordings during which the Treatment Response Scale (TRS) was in the range -1 to +1 (defined interval of normal).

A statistically significant difference in the percentage time in the 'normal' motor state (percentage of video recordings in the range -1 to +1 of the TRS) during the 6-week treatment period was observed between levodopa-carbidopa intestinal gel and conventional medication in trials NPP-001-02 and NPP-001-99. The results showed that subjects spent more time in the 'on' motor state on levodopa-carbidopa intestinal gel. This difference in trial NPP-001-02 was statistically significant ($p < 0.01$) in favour of levodopa-carbidopa intestinal gel, in both the intention to treat (ITT) and per protocol (PP) populations using various analyses and reliability test. However, when the results of the two groups are compared separately for Trial NPP-001-02, there was a significant difference at the 0.05 level in favour of levodopa-carbidopa intestinal gel in patients who received 3 weeks of treatment with conventional medication and a subsequent 3 weeks of treatment with levodopa-carbidopa intestinal gel (Group 1). When the sequence of treatments was reversed (3 weeks of levodopa-carbidopa intestinal gel followed by 3 weeks of conventional medication, Group 2), there were no significant differences at the 0.05 level in the amount of time spent in the "normal" motor state for patients enrolled in Trial NP-001-02. For patients enrolled in trial NPP-001-99, a significant difference at the 0.05 level in the amount of time spent in the "normal" motor state was observed regardless of the sequence of treatments. However the assessment in this trial was unblinded and thus subject to observer bias.

Trial NPP-001-02 showed a statistically significant difference ($p < 0.01$) in favour of levodopa-carbidopa intestinal gel for the primary endpoint percentage of video recordings in the range -1 to +1 of the TRS.

The primary outcome in trial NPP-001-99 was mean levels and variability (variance, coefficient of variation) in plasma levodopa concentrations.

The variance in plasma levodopa concentrations was significantly less during levodopa-carbidopa intestinal gel treatment. In addition, daily within-patient plasma levodopa coefficients of variation were significantly lower during levodopa-carbidopa intestinal gel treatment. The results show that intraduodenal administration of levodopa-carbidopa intestinal gel is accompanied by decreased variability in plasma levodopa, measured as variance and coefficient of variation.

No statistically significant difference in mean plasma levodopa during the 6-week treatment period was observed between levodopa-carbidopa intestinal gel and conventional medication in trial NPP-001-99.

Quality of life measures used in NPP-011-02 included electronic diary, PDQ-39 (Parkinson's disease questionnaire), and 15-D (a 15 item Quality of Life instrument).

A statistically significant difference in the PDQ-39 summary indices during the 6-week treatment period was observed between levodopa-carbidopa intestinal gel and conventional medication in trial NPP-001-02. Levodopa-carbidopa intestinal gel was also significantly better than conventional therapy in regard to 7 of the 8 dimensions of the PDQ-39 (excluding 'Social Support').

Analysis of the electronic diary showed levodopa-carbidopa intestinal gel was significantly better than conventional therapy in relation to responses to the morning question regarding ability to turn in bed, and the morning and daytime questions

regarding difficulty walking, having been “off”, difficulty with chores and satisfaction with functioning.

A statistically significant difference in quality of life as measured by 15D results during the 6-week treatment period was observed between levodopa-carbidopa intestinal gel and conventional medication in trial NPP-001-02.

The key adverse events results are summarised in the table below:

Summary of adverse events in the direct randomised trials

Trial ID	Duodopa n /N (%)	Conventional medication n /N (%)	RR ^b (95% CI)
Trial NPP-001-02^a			
Adverse events	17/22 ^a (77.3)	16/21 (76.2)	1.01 (0.73, 1.41)
Treatment-related adverse events	11/22 ^a (50.0)	8/21 (38.1)	1.31 (0.66, 2.61)
Serious adverse events	2/24 (8.3)	1/21 (4.8)	1.75 (0.17, 17.95)
Number discontinued due to AEs	3/24 (12.5)	0/21 (0.0)	6.16 (0.34, 112.77)
Number died	0	0	
Trial NPP-001-99			
Adverse events	10/12 (83.3)	15/16 (93.8)	0.89 (0.67, 1.18)
Treatment-related adverse events	9/12 (75.0)	13/16 (81.3)	0.92 (0.62, 1.38)
Serious adverse events	1/12 (8.3)	0/16 (0)	3.92 (0.17, 88.67)
Number discontinued due to AEs	0	0	
Number died	0	0	

^a The study report for the pivotal trial NPP-001-02 used a denominator of 24 patients when calculating AE rates for the Duodopa treatment period. However, only 22 patients actually received Duodopa, 2 patients withdrew after the start of the Duodopa treatment period but before receiving any medication.

^b Calculated during the evaluation.

The extended assessment of comparative harms was based on the Periodic Safety Update Report for the period 21 January 2007 to 20 July 2007. An estimated 600 patients were exposed to Duodopa during the period covered by this report. During the reference period a total of 59 serious and unlisted non-serious ADR-reports from healthcare professionals were received, 55 (93%) of which were regarded as serious.

Of major concern to the PBAC is that adverse events related to the pump and/or tubing may be substantial. The open-label NPP-002-02 trial which followed-up 65 patients from 1991 to 2002 reported that tube dislocation occurred in 65.5% and tube occlusion in 37.9% of patients. The Pre-Sub-Committee Response acknowledged that the delivery of Duodopa is associated with more adverse events than the comparators, but claimed that that new tubing is now used that is less prone to dislocation.

9. Clinical claim

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

For PBAC's views see Recommendations and Reasons.

10. Economic analysis

A cost-effectiveness approach was adopted and a modelled economic evaluation was presented.

The modelled economic evaluation took a societal perspective and included disutilities to carers in the base case. The model also included an incremental gain in carer utility associated with patients' improvement in Hoehn & Yahr status (the Hoehn and Yahr scale is a five stage disability scale used in Parkinson's disease). The key factors driving the results were the probability of transitioning to a nursing home and the probability of improvement in Hoehn and Yahr status.

The base case incremental cost per extra QALY gained (including care burden) compared to standard medical management was between \$45,000 and \$75,000. The submission estimated that this cost would rise to between \$130,000 and \$150,000 when carer burden was excluded.

The PBAC was advised of several issues of economic uncertainty associated with the model.

For the PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients per year would be well below 2,000, as the product is an orphan drug, as designated by TGA and suitable only for a small sub-group of the possible total population. The total cost per year was estimated to be between \$10 to 30 million.

12. Recommendations and Reasons

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

The place of levodopa with carbidopa intestinal gel (Duodopa) was confirmed during the hearing as being a last line treatment for Parkinson's disease that would replace such therapies as continuous subcutaneous apomorphine infusion, suboptimal oral treatment or deep brain stimulation (DBS). The PBAC considered it was not appropriate that DBS had been excluded from the mix of comparators in the submission and also noted that the trial populations excluded patients with dementia or cognitive impairment who would be eligible for PBS-subsidised treatment under the sponsor's proposed listing.

The PBAC accepted 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 the Parkinsonism health state ('off' time), and health related quality of life as measured by the 15D instrument. However, there was uncertainty associated with the clinical importance of the trial results as the two randomised trials presented were small, and, in the larger trial with 12 participants in each treatment group, there were five treatment withdrawals. An additional area of concern to the Committee was that the use of electronic diaries, the UPDRS, PDQ and 15D were all unblinded, and there were no long term efficacy or safety data. The Committee also noted

that the 15D is a less preferred instrument than other instruments (it is well documented to have poor correlation with other multi-attribute utility instruments).

Of major concern to the PBAC was that adverse events related to the pump and/or tubing may be substantial. The open-label NPP-002-02 trial which followed-up 65 patients from 1991 to 2002 reported that tube dislocation occurred in 65.5% and tube occlusion in 37.9% of patients. The Pre-Sub-Committee Response acknowledged that the delivery of Duodopa is associated with more adverse events than the comparators, but claimed that that new tubing is now used that is less prone to dislocation. However, no evidence for this statement was provided, and the PBAC was advised that percutaneous endoscopic gastrostomy into the duodenum is generally not as successful as into the stomach.

The PBAC was advised of several areas of uncertainty associated with the modelled economic evaluation presented which calculated an incremental cost per extra QALY gained of between \$45,000 to \$75,000 compared to standard medical management. Furthermore this QALY included a cost for 'carer burden' and the incremental cost effectiveness ratio excluding carer utilities was between \$105,000 and \$200,000. Although the PBAC acknowledged that there is a significant carer burden related to the cost of care with Parkinson's disease and carer disutility, it considered carer utilities should have been incorporated in a sensitivity analysis, distinct from the base case.

The PBAC also commented on the high cost of the drug in this presentation, and the potential for wastage due to storage requirements.

The PBAC therefore rejected the submission on the basis of the unacceptably high and uncertain incremental cost effectiveness ratio for levodopa with carbidopa gel compared to standard medical management.

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

Solvay will work with the PBAC to address the key issues identified in the Duodopa PBAC submission in order to make this orphan drug available for Advanced Parkinson's Disease patients. Duodopa has been granted Orphan Drug Status by the TGA and by definition, it is suitable only for a small number of Parkinson's disease patients, hence the overall paucity in the availability of clinical data. Solvay is disappointed that the Highly Specialised Drugs Working Party did not consider that Duodopa and its innovative mode of delivery met the highly specialised drug criteria. The higher rate of device complications reported in earlier trials has been addressed by Solvay with significant product development and changes implemented over the last 10 years. Many issues with

the earlier systems including leakage, PEG/PEJ dislocation and occlusion has been addressed and ongoing market acceptance testing results show reductions in complication events over time. Solvay strongly believes that the base case cost effectiveness analysis should include all the costs associated with Parkinson disease (including carer burden). It should be noted, like all orphan drugs, there are very little economies of scale, hence the commercial viability of drugs is often marginal. Given the lack of therapeutic options available for advanced PD, Solvay believes there is a strong argument to make Duodopa available on the PBS.