

**7.06 FOSLEVODOPA with FOSCARBIDOPA,  
Solution for subcutaneous infusion foslevodopa  
2400 mg with foscarnidopa 120 mg in 10 mL,  
Vyalev<sup>®</sup>,  
ABBVIE PTY LTD.**

**1 Purpose and summary of changes**

- 1.1 The early re-entry resubmission sought to address the issues raised by the PBAC at its May 2024 intracycle meeting, when it did not recommend the listing of foslevodopa with foscarnidopa (FosLD/FosCD) for the treatment of advanced Parkinson's disease (PD) with severe disabling motor fluctuations not adequately controlled by oral therapy.
- 1.2 The re-submission remained based on a claim of non-inferior comparative effectiveness and safety versus levodopa/carbidopa intestinal gel (LCIG) (unchanged from previous submission). A summary of the issues raised by the PBAC and how the re-submission addresses them is presented in the table below.

**Table 1: Summary of key matters to be addressed**

Matter of concern	Response	Addressed?
<p>The PBAC considered further data and analyses were required to address concerns regarding the impact of discontinuations in the pivotal FosLD/FosCD trial (M15-736) on both the estimated efficacy for FosLD/FosCD and the indirect comparison with LCIG (paras 7.1, 7.8, 7.9, 7.15).</p>	<p>The re-submission presented additional clinical evidence and analyses to support the clinical claim of non-inferior comparative effectiveness to LCIG, including sensitivity analyses accounting for treatment discontinuation and missing data.</p> <p>The re-submission also presented additional clinical evidence to support the claim of non-inferior comparative safety to LCIG.</p>	<p>Yes.</p>
<p>Based on the CMA presented in the submission, the PBAC considered the cost of FosLD/FosCD per patient was likely to be higher than that of LCIG, due to: (a) the initiation cost of FosLD/FosCD being underestimated; (b) the cost for the surgical insertion of PEG-J tubes for LCIG being likely overestimated; (c) the duration of the CMA being too short; (d) a lack of clarity as to whether additional FosLD/FosCD doses were accounted for; and (e) not including costs associated with managing adverse events (para 7.11, 7.15).</p>	<p>The revised CMA in the re-submission explored issues a-e (noted left) raised by the PBAC, and stated that accounting for these results in an effective price of \$ [redacted] per 7-pack, representing a reduction of [redacted]% on the effective AEMP proposed in the original submission (\$ [redacted] per 7-pack), based on a CMA duration of 4.13 years.</p>	<p>Yes.</p>
<p>The PBAC noted the financial estimates assumed a different discontinuation rate for FosLD/FosCD than for LCIG (para 7.13). The PBAC considered revised financial estimates should incorporate a revised CMA price for FosLD/FosCD and potentially revised treatment persistence (para 7.15).</p>	<p>The revised financial estimates accounted for the revised cost-minimised price of FosLD/FosCD and assumed treatment persistence of 85% for both FosLD/FosCD and LCIG.</p>	<p>Yes.</p>
<p>The PBAC considered that given the uncertain use of FosLD/FosCD in practice and the magnitude of differences in costs between oral therapies and later stage treatments like apomorphine and LCIG that a Risk Sharing Arrangement would be required to mitigate the risk of substantially higher use than predicted, and the level of rebate would need to be higher than the [redacted]% currently in place for LCIG (para 7.14).</p>	<p>The re-submission proposed a Risk Sharing Arrangement (RSA) structure where FosLD/FosCD would join the existing RSA for LCIG (and potentially also LECIG (recommended by the PBAC in July 2024)), with an increase in the caps to account for additional use associated with FosLD/FosCD, and a proposed rebate level of [redacted]%.</p>	<p>Yes, however the proposed rebate [redacted]</p>

Source: Based on information in the foslevodopa/foscarbidopa Public Summary Document, May 2024 intracycle meeting, (relevant paragraphs referenced) and Section 1.1 of the re-submission

Abbreviations: FosLD/FosCD = foslevodopa with foscarbidopa; LCIG = levodopa/carbidopa intestinal gel; CMA = cost minimisation approach; PEG-J = percutaneous endoscopic gastrojejunostomy; RSA = risk sharing arrangement; AEMP = approved ex-manufacturer price; LECIG = levodopa/entacapone/carbidopa intestinal gel; CSR = clinical study report.

1.3 The changes to the comparative clinical evidence, economic analysis and utilisation/financial estimates are discussed further within the relevant sections below.

## 2 Background

- 2.1 FosLD/FosCD was TGA registered on 1 March 2024 ‘for the treatment of advanced idiopathic Parkinson’s disease with severe motor fluctuations despite optimised alternative pharmacological treatment’; the associated Vyafuser pump device was included in the ARTG on 22 February 2024.
- 2.2 The PICO from the previous submission is presented below (unchanged in the re-submission).

**Table 2: Key components of the clinical issue addressed by the re-submission**

Component	Description
Population	Patients with advanced Parkinson’s disease with severe disabling motor fluctuations not adequately controlled by oral therapy.
Intervention	24-hour continuous subcutaneous infusion of foslevodopa-foscarbidopa (FosLD/FosCD) (2400 mg levodopa-4-monophosphate and 120 mg carbidopa-4-monophosphate in 10 mL vials).
Comparator	16-hour continuous infusion of levodopa-carbidopa intestinal gel (LCIG) (2000 mg levodopa and 500 mg carbidopa monohydrate solution in 100 mL cassettes).
Outcomes	Disease activity endpoints: change in mean number of “On” hours without troublesome dyskinesia, change in mean number of “Off” hours per day, change in MDS-UPDRS Part II score. Patient reported outcome: Change in PDQ-39 score.
Clinical claim	In patients with advanced PD with severe disabling motor fluctuations not adequately controlled by oral therapy, FosLD/FosCD CSCI is non-inferior to LCIG in terms of efficacy and safety.

Source: Table 1, FosLD/FosCD Public Summary Document, May 2024 intracycle meeting

## 3 Requested listing

- 3.1 The re-submission did not present a proposed restriction. At its May 2024 intracycle meeting, the PBAC generally accepted the proposed restrictions, including dual listing in Section 100 - Highly Specialised Drugs Program (Public and Private Hospitals) and on the General Schedule. The PBAC also considered the restriction for FosLD/FosCD should include (a) an administrative note requiring patients to have adequate cognitive function to be able to manage administration with a portable continuous infusion pump; and (b) for the listing with a maximum quantity of 8 packs to include a criterion that the patient must require continuous administration or a total daily dose of more than 2,400 mg of foslevodopa per day. These changes have been included in the restriction proposed below, along with other minor changes to the proposed restriction noted in italics.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FOSLEVODOPA + FOSCARBIDOPA					
Foslevodopa 2.4 g/10 mL + foscarbidopa 120 mg/10 mL injection, 7 x 10 mL vials	NEW HSD (Public) NEW HSD (Private) New S.85	4	28	5	Vyalev
<b>Restriction Summary [new1] / Treatment of Concept: [new2]</b>					
<b>Category / Program:</b>					

Public Summary Document – November 2024 PBAC Meeting

Section 100 – Highly Specialised Drugs Program (public and private hospitals) GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code2]	
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Severity:</b> Advanced
	<b>Condition:</b> Parkinson disease
	<b>Indication:</b> Advanced Parkinson disease
	<b>Treatment criteria:</b>
	Treatment must have been commenced by a specialist physician OR Treatment must have been commenced by a physician who has consulted a specialist physician with expertise in the management of Parkinson's Disease
	<b>Clinical criteria:</b>
	Patient must have severe disabling motor fluctuations not adequately controlled by oral therapy,
	<b>Administrative Advice:</b> Patients should have adequate cognitive function to manage administration with a portable continuous infusion pump.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FOSLEVODOPA + FOSCARBIDOPA					
Foslevodopa 2.4 g/10 mL + foscarnidopa 120 mg/10 mL injection, 7 x 10 mL vials	NEW HSD (Public) NEW HSD (Private) New S.85	8	56	5	Vyalev

**Restriction Summary [new1] / Treatment of Concept: [new2]**

<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (public and private hospitals) GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code2]	
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Severity:</b> Advanced
	<b>Condition:</b> Parkinson disease
	<b>Indication:</b> Advanced Parkinson disease
	<b>Treatment criteria:</b>
	Treatment must have been commenced by a specialist physician OR Treatment must have been commenced by a physician who has consulted a specialist physician with expertise in the management of Parkinson's Disease
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have severe disabling motor fluctuations not adequately controlled by oral therapy
	<b>AND</b>
	<b>Clinical criteria:</b>

	<i>Patient must require continuous administration of foslevodopa without an overnight break OR Patient must require a total daily dose of more than 2,400 mg of foslevodopa.</i>
	<b>Administrative Advice:</b> <i>Patients should have adequate cognitive function to manage administration with a portable continuous infusion pump.</i>

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## **4 Comparator**

- 4.1 No change from previous submission. The PBAC previously considered LCIG to be an appropriate comparator (paragraph 7.7, FosLD/FosCD Public Summary Document [PSD], May 2024 intracycle meeting).

## **5 Consideration of the evidence**

### ***Sponsor hearing***

- 5.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history and epidemiology of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee’s questions.

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from individuals (3) and organisations (Parkinson’s Australia and National Parkinson’s Alliance) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with FosLD/FosCD including the possibility for out of hospital administration, and improved quality of life. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Clinical trials***

- 5.3 In the original submission, the comparative clinical evidence was based on an anchored indirect treatment comparison of FosLD/FosCD and LCIG informed by one randomised controlled trial of FosLD/FosCD versus oral levodopa/carbidopa (LD/CD) (M15-736; N=141) and one randomised controlled trial of LCIG versus oral LD/CD (Olanow 2015; N=71). In its consideration in May 2024, the PBAC noted the high drop-out rates in M15-736, as well as other concerns including apparent unblinding of participants and differing results for the common comparator arm (oral LD/CD) between the two trials (paragraph 7.8, FosLD/FosCD PSD, May 2024 intracycle meeting). The PBAC considered a claim of non-inferior comparative effectiveness was uncertain for these reasons, although may be supported. The Committee considered a re-submission should include further detail on baseline characteristics for patients who dropped out versus completed the trial for both the FosLD/FosCD and oral LD/CD groups [in M15-736], and additional sensitivity analyses that look at the impact of

using alternative ways to handle the missing data (paragraph 7.9, FosLD/FosCD PSD, May 2024 intracycle meeting).

5.4 The re-submission presented a summary of baseline characteristics from M15-736, stratified by completed/discontinued status (see Table 3 below).

**Table 3: Baseline demographics M15-736 by completion and discontinuation status**

Mean (SD), or n (%)	Oral LD/CD-IR + placebo infusion			M15-736 - FosLD/FosCD + placebo tablets			Total
	Completed	Discontinued	All	Completed	Discontinued	All	
<b>Demographic Characteristics</b>							
N	62	5	67	48	26	74	141
Female (%)	14 (22.6%)	4 (80%)	18 (26.9%)	15 (31.3%)	9 (34.6%)	24 (32.4%)	42 (29.8%)
Age, Years	66.4 (9.94)	69.0 (8.75)	66.6 (9.82)	64.5 (8.97)	69.6 (8.87)	66.3 (9.20)	66.4 (9.47)
White (%)	56 (90.3)	5 (100)	61 (91.0)	45 (93.8%)	25 (96.2%)	70 (94.6)	131 (92.9)
BMI (kg/m <sup>2</sup> )	27.49 (5.98)	27.23 (5.24)	27.47 (5.89)	27.76 (5.97)	24.57 (3.60)	26.61 (5.43)	27.02 (5.65)
<b>Disease Characteristics</b>							
Duration of PD, years	8.34 (5.06)	14.36 (8.0)	8.79 (5.49)	7.48 (3.99)	10.03 (4.22)	8.38 (4.22)	8.58 (4.85)
<b>Disease Activity ('On/off time' outcomes in hours per day)</b>							
"Off-time"	5.94 (1.91)	5.57 (1.70)	5.91 (1.88)	6.50 (2.06)	6.02 (2.65)	6.34 (2.27)	6.13 (2.10)
"On-time" without dyskinesia	7.51 (3.77)	7.04 (3.37)	7.47 (3.72)	7.32 (2.82)	7.05 (3.72)	7.23 (3.14)	7.35 (3.42)
"On-time" with non-troublesome dyskinesia	1.95 (2.77)	2.80 (2.56)	2.02 (2.75)	1.76 (2.40)	2.37 (2.58)	1.97 (2.46)	1.99 (2.60)
"On-time" without troublesome dyskinesia	9.46 (2.63)	9.84 (2.80)	9.49 (2.62)	9.08 (2.33)	9.42 (2.63)	9.20 (2.43)	9.34 (2.51)
"On-time" with troublesome dyskinesia	0.60 (1.48)	0.59 (1.31)	0.60 (1.46)	0.41 (0.91)	0.56 (0.77)	0.46 (0.86)	0.53 (1.18)
MDS-UPDRS Part II score/UPDRS Part II score	13.16 (6.51)	14.60 (4.51)	13.27 (6.37)	15.19 (7.15)	15.54 (6.64)	15.31 (6.93)	14.34 (6.73)

Source: Table 1 of the re-submission

Abbreviations: LD/CD-IR = levodopa/carbidopa immediate release; FosLD/FosCD = foslevodopa/foscarbidopa; SD = standard deviation; BMI = body mass index; PD = Parkinson disease; MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale.

5.5 The re-submission stated the baseline demographics were comparable from both a patient and disease perspective, and argued the data supports the position in the original submission that the missing data for patients who discontinued was assumed to be missing at random. The re-submission also stated that due to the sample size, there was insufficient power to test statistical significance between groups. While a formal statistical test was not feasible, the baseline characteristics for those who

completed or discontinued the trial appeared to be generally comparable, however it was observed that in both the oral LD/CD and the FosLD/FosCD arms, the mean baseline disease duration appeared to be numerically longer in discontinuers than in those who completed the study, noting however for oral LD/CD the number of discontinuers was small (n=5) and the standard deviation (8.0 years) was large. The pre-PBAC response stated that while the time since diagnosis is numerically higher amongst discontinuers than continuers (10.03 years versus 7.48 years) that this variance is not statistically significant. The pre-PBAC response further stated that disease duration alone is not a treatment effect modifier, as confirmed by results of the subgroup analyses on the primary effect endpoints, which indicated that there was no treatment-by-subgroup interaction for duration of PD < 10 years versus duration of PD ≥ 10 years.

### Comparative effectiveness

5.6 The re-submission stated the handling of missing values and sensitivity analysis conducted on the primary efficacy endpoints to account for missing data were specified in the M15-736 statistical analysis plan, with the main analysis handling missing data using mixed-model repeat measurement (MMRM). The re-submission presented analyses using the MMRM method, as well as two sensitivity analyses using an analysis of covariance (ANCOVA) and a jump-to-reference analytical approach, which were drawn from the M15-736 Clinical Study Report (CSR). A summary of the results based on these approaches for the primary outcome of average daily ‘on time’ without troublesome dyskinesia is presented in the table below.

**Table 4: Results of analyses for methods of handling missing data**

	Oral LD/CD-IR (n=66)		FosLD/FosCD (n=73)	
<b>Average Daily ‘On time’ without troublesome dyskinesia</b>				
<b>Base case/Primary analysis</b>				
	<b>N = 67</b>		<b>N = 73</b>	
	<b>Baseline</b>	<b>Change</b>	<b>Baseline</b>	<b>Change</b>
<b>Mean (SD)</b>	9.49 (2.62)	0.80 (3.36)	9.20 (2.42)	2.39 (3.67)
<b>Within group change</b>				
MRMM	$p = 0.0574$		$p \leq 0.001$	
<b>Treatment difference</b>		<b>LS Mean of difference (95% CI)</b>		
MMRM (Change to day 85)		1.75 (0.46, 3.05), $p = 0.0083$		
<b>Sensitivity analyses</b>				
	<b>N = 66</b>		<b>N = 73</b>	
	<b>Baseline</b>	<b>Change</b>	<b>Baseline</b>	<b>Change</b>
<b>Mean (SD)</b>	9.46 (2.63)	0.80 (3.36)	9.20 (2.42)	2.39 (3.67)
<b>Within group change</b>				
ANCOVA	$p = 0.0580$		$p \leq 0.001$	
<b>Treatment difference (SAP base case)</b>		<b>LS Mean of difference (95% CI)</b>		
ANCOVA (Last available value imputation)		1.53 (0.36, 2.71), $p = 0.0111$		
Jump-to-reference (Change to Day 85)		1.14 (NR), $p = 0.0093$		

Source: Based on Table 2 of the re-submission, with data from Table 14.2\_2.1, Table 14.2\_2.4 and Table 14.2\_2.5 of the M15-736 CSR. Abbreviations: LD/CD-IR = levodopa/carbidopa immediate release; FosLD/FosCD = foslevodopa/foscarbidopa; SD = standard deviation; ANCOVA = analysis of covariance; MRMM = mixed-model effect model repeat measurements; LS = least squares; SAP = statistical analysis plan.

- 5.7 The re-submission stated that for the sensitivity analyses:
- The ANCOVA analysis used last available value to impute the missing 12-week data; and
  - The jump-to-reference analysis assumed data for the control group was missing at random, but not missing at random for the active treatment group.
- 5.8 The re-submission claimed the results of the sensitivity analyses are consistent with the results of the primary efficacy analysis.
- 5.9 The re-submission argued therefore that, given the above information for patient baseline characteristics and handling of missing data, the results of the indirect treatment comparison presented in the original submission were valid.

### Comparative harms

- 5.10 The re-submission presented additional long-term safety data from the Summary of Clinical Safety (Attachment 5 to the re-submission), to reinforce the outcomes from the M15-736 study and to further support the claim that FosLD/FosCD is non-inferior to LCIG. A summary of adverse events of interest over time is presented in the table below.

**Table 5: First occurrence of AEs that occurred in ≥ 10% of subjects by 90 day-time intervals: Open label analysis set**

Preferred term	Number of Subjects with First Event During Time Interval/Number of Subjects at Risk for First Event During Time Interval (%)					
	Days 1 to 90 N = 347	Days 91 to 180 N = 270	Days 181 to 270 N = 237	Days 271 to 360 N = 214	After Day 540 N = 118	At Any Time N = 347
Any AE	310/347 (89.3)	9/30 (30.0)	3/18 (16.7)	1/15 (6.7)	1/4 (25.0)	325/347 (93.7)
Fall	30/347 (8.6)	12/244 (4.9)	7/202 (3.5)	8/179 (4.5)	9/87 (10.3)	72/347 (20.7)
Hallucination	42/347 (12.1)	7/243 (2.9)	2/207 (1.0)	2/188 (1.1)	5/99 (5.1)	65/347 (18.7)
Infusion site reaction	30/347 (8.6)	5/251 (2.0)	2/218 (0.9)	2/197 (1.0)	0/106	39/347 (11.2)

Source: Table 4 of the re-submission. The open label analysis set includes data from three studies (M15-741, M15-737 and M20-098). Abbreviations: AE = adverse event; N = number of subjects who received FosLD/FosCD during the time interval

- 5.11 The re-submission stated no new safety concerns were identified in the longer-term data in the open label studies and noted the occurrence of AEs within the longer-term data was predominantly within the first 12 weeks of treatment (out to ~day 90 in the above analysis).

### Clinical claim

- 5.12 The re-submission argued that the information presented in the sections above supports the claim in the original submission of non-inferior comparative effectiveness and safety of FosLD/FosCD and LCIG.
- 5.13 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 5.14 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

- 5.15 The re-submission presented a revised cost-minimisation approach (CMA) that explored the five main issues the PBAC identified as needing to be addressed, including:
- The initiation cost of FosLD/FosCD being underestimated;
  - The cost of surgical insertion of PEG-J tubes for LCIG likely being overestimated;
  - The duration of the CMA being too short;
  - A lack of clarity if additional FosLD/FosCD doses were accounted for; and
  - The CMA not including costs associated with managing adverse events.
- 5.16 The equi-effective doses for the cost-minimisation approach (CMA) were 1.32 vials of FosLD/FosCD and 1.10 cassettes of LCIG per day. This was unchanged from the previous submission, which the evaluation had considered appeared to be reasonable (paragraph 6.42, FosLD/FosCD PSD, May 2024 intracycle meeting). The re-submission stated that in relation to whether additional FosLD/FosCD doses were accounted for, that as there was no additional dosing in the pivotal trial that additional dosing was not accounted for in the CMA.
- 5.17 With respect to the initiation costs for FosLD/FosCD, the re-submission adjusted the MBS items to include increased fees associated with specialist attendances for initiation and subsequent visits and altered the initiation costs based on an assumption that 2.04% of FosLD/FosCD patients would be initiated in an inpatient setting (PBS data January 2023-December 2023). The input for this component of the CMA increased from \$108.96 in the original submission to \$709.08 in the re-submission. The changes to these inputs in the CMA are contrasted with the values in the original submission in the table below.

**Table 6: Derivation of the FosLD/FosCD initiation cost for the CMA**

Component	Description	Initial submission	Revised early re-entry
<b>Outpatient inputs</b>			
Clinic visits during optimisation	Average number of visits for dose titration	2.4	2.4
Clinic visit (initiation)	Clinic visit cost to initiate FosLD/FosCD	\$45.40 (MBS item 105)	\$305.15 (MBS item 132)
Clinic visit (subsequent)	Subsequent clinic visit cost	\$45.40 (MBS item 105)	\$87.30 (MBS item 116)
<b>Initiation costs</b>		<b>\$108.96</b>	<b>\$427.37</b>
<b>Inpatient inputs</b>			
Percentage of FosLD/FosCD patients initiated in hospital		N/A	2.04%
Minor small and large bowel interventions, minor complexity (DRG G05B)			<b>\$14,244</b>
<b>Weighted FosLD/FosCD initiation cost for the CMA</b>			
Out of hospital initiation	[A] = (97.96% x \$427.37)	N/A	\$418.66
In hospital initiation cost	[B] = (2.04% x \$14,244)		\$290.34
<b>Weighted FosLD/FosCD cost</b>	[A] + [B]		<b>\$709.08</b>

Source: Compiled by the Secretariat from Tables 7 and 9 of the submission, with supporting data from Tables 6 and 8.

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; MBS = Medicare Benefits Schedule; DRG = Disease Related Groups; CMA = cost minimisation approach.

- 5.18 To address the issue of the LCIG initiation cost being too high, the re-submission assumed that all LCIG initiations will only be based on the G05B (Minor Small and Large Bowel Interventions, Minor Complexity) Disease Related Group (DRG) cost of \$14,244 per initiation event. This represents a reduction of 12% from the original submission cost of \$16,942, which was based on a weighted estimate of use of the G05B and G05A (Minor Small and Large Bowel Interventions, Major complexity) DRGs.
- 5.19 To address the issue of the CMA period being too short, the re-submission increased the duration of treatment to 4.13 years (up from 2 years in the original submission), which it stated is in line with LCIG treatment in the PBAC 10% Sample.
- 5.20 To address the occurrence and costs of AEs associated with FosLD/FosCD, the re-submission used data on hallucinations, falls and associated injuries, infusion site reactions, infusion site infections as well as intestinal tube and stoma complications to estimate these costs. The re-submission calculated, but did not include AE costs for LCIG, which it stated was a conservative approach. The derivation of AE costs for FosLD/FosCD and LCIG are presented in the table below.

**Table 7: Cost of Adverse Event management**

Events, n (%)	M15-736		Olanow 2014		Unit cost	Reference
	FosLD/FosCD	Oral LD/CD	LCIG	Oral LD/CD		
N	74	67	37	34		
TEAE of special interest						
Hallucinations	11 (14.9)	2 (3.0)	1 (2.7)	1 (2.9)	\$87.30	MBS item 116
Falls and associated injuries	13 (17.6)	17 (25)	4 (10.8)	4 (11.8)	\$7,680.00	Section 3 Workbook <sup>a</sup>
Infusion site infection	21 (28.4)	2 (3.0)	4 (10.8)	8 (23.5)	\$87.30	MBS item 116
Infusion site reaction	46 (62.2)	5 (7.5)	NR	NR	\$87.30	MBS item 116
Intestinal tube complication	0	0	14(37.8%)	12(35%)	\$567.63	Minor surgical non-admitted patient weights (10.03)
Stoma complication	0	0	15(40.5%)	15(44%)	\$4,599.85	DRG G11B <sup>b</sup>
<b>Expected costs per patient associated with management of AE</b>	<b>\$1,443.87</b>		<b>\$2,934.35</b> (Not included in CMA)			

Source: Table 11 of the re-submission

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; LD/CD = levodopa/carbidopa; LCIG = levodopa/carbidopa intestinal gel; TEAE = treatment-emergent adverse event; MBS = Medicare Benefits Schedule; AE = adverse event; CMA = cost minimisation approach; NR = not reported; DRG = Disease Related Group

<sup>a</sup> Cost of falls worksheet of Attachment 1 to the re-submission (Section 3 Workbook). Cost estimate from Hendrie et al 2014: Health system costs of falls in Western Australia

<sup>b</sup> DRG G11B - Minor anal and stomal interventions, minor complexity - G11B - NHDC COST WEIGHTS FOR AR-DRG VERSION 10.0 Round 24

- 5.21 The re-submission further argued that some of these proposed costs, such as the costs of falls and associated injuries, were likely to be higher than proposed in the re-submission, although the re-submission did not provide support for this assertion. During preparation of the Overview, it was noted that the Hendrie et al 2014 publication stated that the average total health system cost per fall injury episode in Western Australia was a lower cost of \$6,700.
- 5.22 Accounting for these changes, the cost-minimised effective price for FosLD/FosCD was \$| per unit, with an effective AEMP of \$| per 7 pack of vials. This represents a |% price reduction compared to the original submission. A stepped summary of the CMA is presented in the table below.

**Table 8: Stepped cost-minimisation approach for FosLD/FosCD and LCIG**

Row	Parameter	Input	Source / calculation
	<b>LCIG</b>		
A	Ex-manufacturer price per unit	\$█	Confidential effective pricing
B	Units per day	1.10	Olanow 2014
C	Units per year on treatment	401.8	B*365.25
D	Cost per year	\$█	A*C
E	Duration of treatment	4.13	Paragraph 5.19
F	Total drug costs	\$█	D*E
G	Initiation cost	\$14,243.69	Paragraph 5.18
H	Total cost per course of treatment	\$█	F+G
	<b>FosLD/FosCD</b>		
I	Total cost per course of treatment	\$█	H
J	Initiation cost	\$709.08	Table 6
K	Adverse event treatment costs	\$1,443.87	Table 7
L	Total drug costs	\$█	I-(J+K)
M	Duration of treatment	4.13	=E (same as LCIG)
N	Cost per year	\$█	L/M
O	Units per day	1.32	M15-736, CSR
P	Units per year on treatment	482.1	O*365.25
Q	Ex-manufacturer price per unit	\$█	N/P
	<b>Price reduction vs initial PBAC submission</b>	-█%	\$█ / \$█
	<b>Cost reduction per course vs initial PBAC submission over 4.13 years</b>	-\$█	CMA Workbook

Source: Adapted from Table 12 of the re-submission

5.23 Sensitivity analyses on the CMA prepared by the Secretariat are detailed in the table below.

**Table 9: Sensitivity analyses on the cost-minimisation approach for FosLD/FosCD and LCIG**

Parameter	Input	Ex-manufacturer price per unit	AEMP	Price reduction vs initial PBAC submission	Cost reduction per course vs initial PBAC submission
Base case in re-submission		\$█	\$█	-█%	-\$█ over 4.13 years
Duration of treatment (base case 4.13 years)	5 years	\$█	\$█	-█%	-\$█ over 5 years
	3.5 years	\$█	\$█	-█%	-\$█ over 3.5 years
Unit cost of falls and associated injuries (base case \$7,680)	\$6,700 <sup>a</sup>	\$█	\$█	-█%	-\$█ over 4.13 years
	\$4,800 <sup>b</sup>	\$█	\$█	-█%	-\$█ over 4.13 years
Initiation cost (base case \$14,243.69)	\$10,000	\$█	\$█	-█%	-\$█ over 4.13 years
	\$18,000	\$█	\$█	-█%	-\$█ over 4.13 years

<sup>a</sup> Average total health system cost per fall injury episode (p369 Hendie et al 2014)

<sup>b</sup> Total health system cost per fall injury episode in the 65 to 69-year age group (p369 Hendie et al 2014)

Source: Compiled by the Secretariat using Section 3 CMA Workbook

### Drug cost/patient/year

5.24 Using the proposed effective ex-manufacturer price (\$█ per unit), the drug cost/patient/year was estimated to be \$█ (\$█ x 1.32 x 365.25) for FosLD/FosCD and \$█ (\$█ x 1.1 x 365.25) for LCIG. After accounting for the price of FosLD/FosCD proposed based on the revised CMA, the annual cost of FosLD/FosCD remained more expensive than LCIG based on drug costs only, although the incremental difference has reduced

by \$█ per year (down from an annual FosLD/FosCD cost of \$█ in the previous submission).

**Table 10: Drug cost/patient/year**

	FosLD/FosCD			LCIG		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean number of vials <sup>a</sup>	1.32	1.32	1.32	1.10	1.10	1.10
Mean duration	62.4 days <sup>b</sup>	1,508.5 days <sup>c</sup>	1,607.1 days <sup>d</sup>	82.3 days <sup>b</sup>	1,508.5 days <sup>c</sup>	1,607.1 days <sup>d</sup>
Cost/patient per 28-day cycle <sup>e</sup>	\$█	\$█	\$█	\$█	\$█	\$█
Cost/patient/course	\$█	\$█	\$█	\$█	\$█	\$█

Source: compiled by the Secretariat.

<sup>a</sup> Average number of vials and cassettes trial dose/duration used for the calculation unchanged from the original submission (Table 12 of the original submission)

<sup>b</sup> Mean duration unchanged from previous submission (Table 12 of the original submission)

<sup>c</sup> Based on a treatment duration of 4.13 years utilised in the CMA.

<sup>d</sup> Calculated by applying treatment continuation of 85% (average treatment of 4.4 years per patient).

<sup>e</sup> Based on a cost per unit of \$█ for FosLD/FosCD and \$█ for LCIG (without adjustment for mean number of vials).

### Estimated PBS usage & financial implications

5.25 The re-submission presented revised utilisation and financial estimates based on the revised cost-minimised price (discussed above) and aligning treatment persistence assumptions for both FosLD/FosCD and LCIG based on that for LCIG on PBS 10% sample data (with treatment persistence assumed to be 85% for both therapies over the duration of the estimates). The original submission annual persistence inputs differed between FosLD/FosCD and LCIG, with 65% in year 1 and 89% in subsequent years for FosLD/FosCD patients and 85% for LCIG.

5.26 Revised financial estimates accounting for this change and the revised cost-minimised price of FosLD/FosCD are presented in the table below.

**Table 11: Estimated use and financial implications (effective prices)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of PBS/RPBS scripts dispensed	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of FosLD/FosCD</b>						
Cost to PBS/RPBS less copayments	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>4</sup>	\$█ <sup>5</sup>	\$█ <sup>6</sup>	\$█ <sup>7</sup>
<b>Estimated financial implications for LCIG</b>						
Cost to PBS/RPBS less copayments	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>5</sup>
Net cost to MBS	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>	-\$█ <sup>8</sup>
Net cost to Australian Government	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>4</sup>	\$█ <sup>5</sup>
<b>Previous submission (May 2024)</b>						
Net cost to PBS/RPBS	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>4</sup>	\$█ <sup>5</sup>

Source: Table 14 of the re-submission, with additional information from Attachment 2 to the re-submission (Financial table workbook)

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> \$0 to < \$10 million

<sup>4</sup> \$10 million to < \$20 million

<sup>5</sup> \$20 million to < \$30 million

<sup>6</sup> \$30 million to < \$40 million

<sup>7</sup> \$40 million to < \$50 million

<sup>8</sup> net cost saving

5.27 The revised estimates show that, with the revised CMA price and updated treatment persistence estimates that the net cost to the PBS/RPBS over 6 years is \$60 million to < \$70 million (with this cost largely coming from increased utilisation by patients receiving oral therapy for Parkinson’s disease.) The net cost has reduced in Year 6 (a reduction of 3.5%), however with a net increase in expenditure over 6 years of \$0 to < \$10 million (an increase of 5.1%). The net increase over 6 years is driven by higher costs in Years 1-4 compared to the submission considered by the PBAC in May 2024, which is likely due to the increase in treatment persistence from 65% to 85% in Year 1 of the estimates, increasing the number of patients continuing treatment into Year 2 and beyond.

### Quality Use of Medicines

5.28 The re-submission provided additional information on Quality Use of Medicines (QUM) activities being undertaken by the Sponsor, including a discussion of the existing specialised nursing support program in place for LCIG and a commitment to implement a similar support program for treating clinicians and patients on the best practice use of FosLD/FosCD and its administration, with ongoing support for patients.

### Financial Management – Risk Sharing Arrangements

5.29 The re-submission proposed a revised risk sharing arrangement (RSA) that included both an increased rebate level for FosLD/FosCD of |% (compared to |% for LCIG) and an adjustment for the revised financial estimates. The re-submission argued the PBAC had considered incremental uptake from oral therapies for Parkinson's disease to be reasonable, therefore it was appropriate for the existing LCIG RSA caps to be increased to allow for this anticipated use in a larger cohort of patients.

5.30 For reference, the past 7 years of Commonwealth payments for LCIG are shown in Table 12 below.

Table 12: Commonwealth expenditure on LCIG, 2017 to 2024

Cap year	Cap threshold	Total Commonwealth payment	Cap reimbursement	% cap reached
17 - 18	\$	\$	\$	%
18 - 19	\$	\$	\$	%
19 - 20	\$	\$	\$	%
20 - 21	\$	\$	\$	%
21 - 22	\$	\$	\$	%
22 - 23	\$	\$	\$	%
23 - 24	\$	\$	\$	%

Source: compiled by the Secretariat during preparation of the submission overview

5.31 The RSA proposal included assumptions of LCIG being replaced by FosLD/FosCD, with additional expenditure for the anticipated increased use from patients switching from

oral therapies. The current RSA runs until 2026, and where a new arrangement is not re-negotiated, the cap amount of \$ (and the cap rebate of %) will continue to apply to future years. However, the re-submission extrapolated the agreed cap for LCIG from year 2026 out to the year 2031 with the cap increasing each year. The pre-PBAC response stated that a growth rate of % year-on-year (based on standard population growth in patients aged 65 years and over) is included in the current RSA for LCIG, and that a conservative annual rate of % was applied to the estimates for future years given that population growth in the age group 65 years plus has increased to 3.6% and is predicted to increase further over time (Australian Bureau of Statistics 2020)

5.32 Details of the proposed RSA caps presented in the re-submission are detailed in the table below.

**Table 13: Revised risk sharing arrangement proposal (figures in \$'000's)**

	2025	2026	2027	2028	2029	2030
LCIG cap (pre FosLD/FosCD)	\$	\$	\$	\$	\$	\$
LCIG cost offsets post FosLD/FosCD	-\$	-\$	-\$	-\$	-\$	-\$
LCIG (post FosLD/FosCD)*	\$	\$	\$	\$	\$	\$
FosLD/FosCD expenditure	\$	\$	\$	\$	\$	\$
<b>Proposed expanded cap**</b>	\$	\$4	\$	\$	\$	\$
FosLD/FosCD Share of spend	%	%	%	%	%	%

\*Accounting for cost savings due to change in listing

\*\*Expenditure cap expansion accounting for cost savings due to LCIG substitution and incremental costs due to FosLD/Fos CD

Source: Attachment 2 of the re-submission, amended by the Secretariat to cover the 6 years until 2030 (as the re-submission presented two columns labelled 2026). Note: Differences due to rounding.

5.33 The re-submission stated that based on the estimated use of LCIG versus FosLD/FosCD (Table 13) the RSA proposal results in a weighted rebate level for LCIG and FosLD/FosCD of % across the 6 years.

5.34 The re-submission also noted the PBAC recommendation for levodopa/carbidopa/entacapone intestinal gel (LCIG) at the July 2024 meeting, however stated that as it is not yet PBS listed, assumptions for LCIG have not been considered; however, the re-submission suggested current LCIG utilisation estimates are considered to be representative of the entire intestinal gel market.

5.35 In an additional correspondence accompanying the submission, the Sponsor stated there are significant constraints on AbbVie's ability to accept further price reductions or , and noted there are significant costs associated with the high cost of goods (relative to proposed effective price), QUM programs and providing the drug delivery pump and ancillaries free of charge to patients.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## 6 PBAC Outcome

6.1 The PBAC recommended the S100 HSD and General Schedule listing of foslevodopa with foscarbidopa (FosLD/FosCD) for the treatment of advanced Parkinson's disease (PD) with severe disabling motor fluctuations not adequately controlled by oral

therapy. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of foslevodopa with foscarbidopa would be acceptable if it were cost-minimised to levodopa/carbidopa intestinal gel (LCIG) and included in the risk sharing arrangement (RSA) with LCIG, with revised financial caps, to contain the risk of use in a broader population.

- 6.2 The PBAC considered the equi-effective doses to be 1.32 vials of FosLD/FosCD and 1.10 cassettes of LCIG per day.
- 6.3 The PBAC considered that the re-submission had addressed the substantive outstanding issues identified at the May 2024 PBAC meeting.
- 6.4 The PBAC noted the re-submission presented additional clinical evidence and analyses to support the clinical claim of non-inferior comparative effectiveness and safety to LCIG. The Committee noted the re-submission had provided details of patient demographics at baseline in patients who completed or discontinued the trial as well as sensitivity analyses accounting for treatment discontinuation and missing data. The Committee considered that the data adequately addressed the Committee's concerns.
- 6.5 The PBAC noted the re-submission presented a respecified cost-minimisation approach with a reduced price (Table 8) and considered that this adequately addressed the Committee's concerns.
- 6.6 The PBAC noted the re-submission had presented revised utilisation and financial estimates that incorporated the reduced price proposed in the re-submission and an assumption that treatment persistence for both FosLD/FosCD and LCIG would be 85% over the duration of the estimates. The Committee considered that the revised estimates were reasonable.
- 6.7 The PBAC recalled it considered at the May 2024 meeting that given the uncertain use of FosLD/FosCD in practice and the magnitude of differences in costs between oral therapies and later stage treatments like apomorphine and LCIG that a RSA would be required to mitigate the risk of substantially higher use than predicted, and the level of rebate would need to be higher than the  $\frac{1}{2}$ % currently in place for LCIG. The PBAC noted that the re-submission had presented a revised RSA, with current subsidisation caps extrapolated based on a  $\frac{1}{2}$ % year-on-year increase to account for population growth in patients aged 65 years and over, with a proposed rebate of  $\frac{1}{2}$ % (see Table 13).  $\frac{1}{2}$ %. The Committee considered that a  $\frac{1}{2}$ % rebate for expenditure above the subsidisation caps was insufficient to address the risk to the Australian Government of the use of FosLD/FosCD in a broader population. The PBAC reiterated that a revised RSA giving effect to a significant increase in the PBS expenditure caps for LCIG and FosLD/FosCD ( $\frac{1}{2}$ % increase in Year 6 of listing as proposed in Table 13) should be accompanied by  $\frac{1}{2}$ %.
- 6.8 The PBAC advised that FosLD/FosCD should not be treated as interchangeable on an individual patient basis with any other drugs.

- 6.9 The PBAC advised that FosLD/FosCD is suitable for prescribing by nurse practitioners for maintenance therapy.
- 6.10 The PBAC recommended that the Early Supply Rule should not apply.
- 6.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because FosLD/FosCD is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over LCIG, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 6.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 7 Recommended listing

7.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
FOSLEVODOPA + FOSCARBIDOPA					
Foslevodopa 2.4 g/10 mL + foscarnidopa 120 mg/10 mL injection, 7 x 10 mL vials	NEW HSD (Public) NEW HSD (Private) New S.85	4	28	5	Vyalev
<b>Restriction Summary [new1] / Treatment of Concept: [new2]</b>					
	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (public and private hospitals) GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code2]				
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
	<b>Severity:</b> Advanced				
	<b>Condition:</b> Parkinson disease				
	<b>Indication:</b> Advanced Parkinson disease				
	<b>Treatment criteria:</b>				
	Treatment must have been commenced by a specialist physician OR Treatment must have been commenced by a physician who has consulted a specialist physician with expertise in the management of Parkinson's Disease				
	<b>Clinical criteria:</b>				
	Patient must have severe disabling motor fluctuations not adequately controlled by oral therapy,				

<b>Administrative Advice:</b> Patients should have adequate cognitive function to manage administration with a portable continuous infusion pump.
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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FOSLEVODOPA + FOSCARBIDOPA					
Foslevodopa 2.4 g/10 mL + foscarnidopa 120 mg/10 mL injection, 7 x 10 mL vials	NEW HSD (Public) NEW HSD (Private) New S.85	8	56	5	Vyalev

Restriction Summary [new1] / Treatment of Concept: [new2]	
	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (public and private hospitals) GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code2]
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Severity:</b> Advanced
	<b>Condition:</b> Parkinson disease
	<b>Indication:</b> Advanced Parkinson disease
	<b>Treatment criteria:</b>
	Treatment must have been commenced by a specialist physician OR Treatment must have been commenced by a physician who has consulted a specialist physician with expertise in the management of Parkinson's Disease
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have severe disabling motor fluctuations not adequately controlled by oral therapy
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must require continuous administration of foslevodopa without an overnight break OR Patient must require a total daily dose of more than 2,400 mg of foslevodopa.
	<b>Administrative Advice:</b> Patients should have adequate cognitive function to manage administration with a portable continuous infusion pump.

***These restrictions may be subject to further review. Should there be any changes made to the restrictions the sponsor will be informed.***

## 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the

merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.