

## 5.03 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 of submission

- 1.1 The Category 2 submission requested General Schedule and Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listings for the treatment of advanced Parkinson’s disease (PD) with severe disabling motor fluctuations not adequately controlled by oral therapy.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus levodopa/carbidopa intestinal gel (LCIG).

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the 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-foscarnidopa (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 1-1, p30 of the submission.

Abbreviations: CSCI = continuous subcutaneous infusion; FosLD/FosCD = foslevodopa/foscarnidopa; LCIG = levodopa carbidopa intestinal gel; MDS = Movement Disorder Society; PD = Parkinson’s disease; PDQ = Parkinson’s disease questionnaire; UPDRS = unified Parkinson’s disease rating scale

### 2 Background

#### Registration status

- 2.1 Foslevodopa/foscarnidopa (FosLD/FosCD) was submitted under the Therapeutic Goods Administration (TGA)/Pharmaceutical Benefits Advisory Committee (PBAC) parallel process.
- 2.2 FosLD/FosCD is to be administered with the Vyafuser pump and ancillary devices:
- Vyafuser pump (legal manufacturer: Phillips-Medisize, ARTG registration sponsored by Emergo)
  - Syringe (legal manufacturer and ARTG registration sponsored by: B Braun)

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- Neria Guard Infusion set (legal manufacturer and ARTG registration sponsored by: ConvaTec)
- Vial adapter (legal manufacturer: West Pharma; ARTG registration sponsored by: Emergo).

2.3 Consideration of FosLD/FosCD by the PBAC was initially requested for the July 2023 meeting. Consideration was deferred after receiving advice that a regulatory decision would be made once the Vyafuser pump device had been assessed for registration.

2.4 The Vyafuser pump device was included in the ARTG on 22 February 2024, and FosLD/FosCD was TGA registered on 1 March 2024.

### 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FOSLEVODOPA/FOSCARBIDOPA					
Foslevodopa foscarnidopa; 2400 mg/10 mL and 120 mg/10 mL continuous subcutaneous infusion; 7 vials	S100 HSD Public \$5,768.00 published price \$ effective price  S100 HSD Private \$5,815.82 published price \$ effective price  General Schedule \$5,929.30 published price \$ effective price	4	28	5	Vyalev®
Foslevodopa foscarnidopa; 2400 mg/10 mL and 120 mg/10 mL continuous subcutaneous infusion; 7 vials	S100 HSD Public \$11,536.00 published price \$ effective price  S100 HSD Private \$11,583.82 published price \$ effective price  General Schedule \$11,697.30 published price \$ effective price	8	56	5	Vyalev®

Note: The dispensed prices were corrected during the preparation of the ESC Advice using the correct PBS mark-ups and fees.

<b>Category / Program:</b> General Schedule/Section 100
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
<b>Severity:</b> Advanced
<b>Condition:</b> Parkinson's disease
<b>Indication:</b> Advanced Parkinson's disease not adequately controlled by oral therapy
<b>Treatment Phase:</b> Initial and continuing
<b>Clinical criteria:</b>
Patient must have severe disabling motor fluctuations not adequately controlled by oral therapy

<p><b>Treatment criteria:</b></p> <p>Must be commenced by a specialist physician OR Must be commenced by a physician who has consulted a specialist physician with expertise in the management of Parkinson's Disease</p>
<p><b>Prescribing Instructions: Note:</b> Maintenance Therapy ONLY Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

- 3.1 The Sponsor requested a special pricing arrangement. FosCD/FosLD is a continuous, 24-hour subcutaneous infusion. The requested listing provides either 4 packs or 8 packs, allowing for 1 or 2 vials per day respectively over 28 days. With 5 repeats, the listings would permit 6 months of therapy. This is in line with the LCIG PBS listing.
- 3.2 The Sponsor in their Pre-PBAC Response stated that it was appropriate for the listing to provide an option for a maximum quantity of both 4 and 8 packs given that: i) a 4 pack was likely to be sufficient for the majority of patients and, (ii) as the product requires refrigeration, it may be difficult for some patients to store 8 packs appropriately. The PBAC considered this was reasonable.
- 3.3 The PBAC noted that the listing for a maximum quantity of 8 packs for LCIG included clinical criteria that the “Patient must require continuous administration without an overnight break; OR Patient must require a total daily dose of more than 2000 mg of levodopa” and that a statement similar to this was not included in the proposed restriction. The PBAC noted that the Sponsor stated in their Pre-PBAC Response that they would consider adding a statement requiring the need for continuous administration without an overnight break to the clinical criteria for the 8 pack of FosLD/FosCD.
- 3.4 The requested effective AEMP changed from that requested in the submission as the Pre-Sub-Committee Response (PSCR) corrected the LCIG price used in the CMA and updated the LCIG initiation costs (see paragraph 6.40 for detail). In addition, the MBS cost used for the FosLD/FosCD initiation was updated. The requested effective AEMP was further revised in the Pre-PBAC Response (see paragraph 6.46 for details).
- 3.5 The requested PBS restriction aligned with the population in the key trial, M15-736. It also aligned with the population eligible for LCIG on the PBS. To be enrolled in Study M15-736, patients must have been taking a minimum of 400 mg/day of levodopa equivalents while still experiencing more than 2.5 hours of ‘Off-time’ (time experiencing uncontrolled Parkinson’s symptoms).
- 3.6 The LCIG listing includes an administrative note that: “Patients should have adequate cognitive function to manage administration with a portable continuous infusion pump.” The ESC considered the administrative note was also appropriate for FosLD/FosCD.

- 3.7 The ESC considered that initiation is complex and should be performed in a hospital-based movement disorders clinic and is not appropriate for initiation with specialist physician advice. The Pre-PBAC Response disagreed with the ESC and noted that neither the Product Information nor clinical studies for FosLD/FosCD required initiation in a specialist hospital setting and noted additional correspondence from health care professionals and specialists in hospital-based movement disorders clinics that strongly supported the availability of FosLD/FosCD in the hospital, outpatient, and non-hospital settings. The PBAC agreed with the Sponsor and considered FosLD/FosCD was suitable for initiation beyond the hospital setting and this would be beneficial to some patients, especially those in regional and rural areas, by not needing to attend a specialist movement disorders clinic which would likely be based in a major centre.

For more detail on PBAC's view, see section 7 PBAC outcome.

## 4 Population and disease

- 4.1 Parkinson's disease (PD) is a neurodegenerative disorder that affects movements and is characterised by symptoms such as tremors, rigidity, bradykinesia, and postural instability. The underlying cause is a deficiency of dopamine from the loss of dopamine-producing cells in the substantia nigra<sup>1</sup>. In Australia, it is estimated that over 100,000 people are living with PD<sup>2</sup>. This number is expected to increase due to the ageing population.
- 4.2 Advanced Parkinson's disease develops in the later stages of PD when symptoms become more severe and may significantly impact a person's quality of life. These stages are typically characterised by motor and non-motor symptoms that may require more intensive management<sup>3</sup>. Using 10% PBS utilisation data, the submission estimated that almost 5,000 Australians are considered to have advanced PD based on their high use of levodopa.
- 4.3 The proposed intervention is FosLD/FosCD. Both compounds are prodrugs of levodopa and carbidopa, respectively. FosLD is water soluble and able to be delivered subcutaneously<sup>4</sup>. Once administered, FosLD is converted to levodopa (LD). Levodopa can cross the blood brain barrier. Once in the brain, levodopa is converted to the active neurotransmitter, dopamine. This acts to increase the concentration of dopamine in the brain and allows more dopamine to be taken up by presynaptic nerve terminals. The increased dopamine uptake by nerves replenishes neurotransmitter levels in the synapses, allowing for proper functioning<sup>5</sup>.

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<sup>1</sup> Balestrino, R. and A.H.V. Schapira, Parkinson disease. *Eur J Neurol*, 2020. 27(1): p. 27-42.

<sup>2</sup> Bivol, S., et al., Australian Parkinson's genetics study (APGS): pilot (n=1532). *BMJ Open*, 2022. 12(2): p. e052032.

<sup>3</sup> Fasano, A., et al., Characterizing advanced Parkinson's disease: OBSERVE-PD observational study results of 2615 patients. *BMC Neurol*, 2019. 19(1): p. 50.

<sup>4</sup> Rosebraugh, M., et al., Foslevodopa/foscarbidopa: A new subcutaneous treatment for Parkinson's disease. *Ann Neurol*, 2021. 90(1): p. 52-61.

<sup>5</sup> Müller, T., Pharmacokinetics and pharmacodynamics of levodopa/carbidopa cotherapies for Parkinson's disease. *Expert Opin Drug Metab Toxicol*, 2020. 16(5): p. 403-414.

- 4.4 Levodopa can be metabolised to dopamine peripherally. As dopamine cannot cross the blood brain barrier, this would result in a decreased efficacy of the drug. To address this, FosLD is combined with FosCD. FosCD, when converted into carbidopa (CD), acts to inhibit levodopa metabolism until levodopa crosses the blood brain barrier.
- 4.5 In most patients with PD, motor fluctuations and dyskinesia can be adequately managed through an oral LD based therapy. For patients whose symptoms are not adequately controlled with oral medication, device aided therapy (DAT) is an option. In Australia there are currently 3 DATs available: LCIG and continuous subcutaneous infusion of apomorphine available via the PBS, and deep brain stimulation available via the MBS. LCIG is currently the only dopaminergic based DAT for advanced PD.
- 4.6 The submission's clinical management algorithm positioned FosLD/FosCD as an alternative to LCIG, as a DAT that can be used in patients whose PD symptoms are not adequately controlled with oral LD. The proposed algorithm is consistent with the current restriction for LCIG.

For more detail on PBAC's view, see section 7 PBAC outcome.

## **5 Comparator**

- 5.1 The submission nominated LCIG as the comparator. LCIG is a DAT that allows for continuous administration of levodopa/carbidopa (LD/CD). The initiation of LCIG requires surgery to place a gastrojejunostomy tube (j-tube) through which the intestinal gel is delivered. The pharmacologically active components of LCIG, levodopa/carbidopa, are the same two compounds found in the oral LD/CD used to treat PD.
- 5.2 The main argument provided in support of this nomination was that LCIG is the only levodopa/carbidopa DAT listed on the PBS for patients with advanced PD who have severe motor fluctuations not adequately controlled by oral therapy.
- 5.3 The ESC considered the nominated comparator was appropriate, although it has relatively poor uptake. The submission stated that there is a modest use due to capacity constraints within the health care system to initiate LCIG in hospital-based movement disorder clinics, as well as patient and carer lack of acceptance of, or a contraindication with, surgery.
- 5.4 The evaluation noted oral LD/CD may represent a potential comparator as patients may remain on oral LD/CD even when their motor fluctuations are not adequately controlled. The ESC indicated that even though patients might remain on oral agents, those agents are usually markedly reduced or ceased.

For more detail on PBAC's view, see section 7 PBAC outcome.

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The Sponsor requested a hearing for this item. The clinician discussed the current treatment options for patients no longer achieving adequate disease control on oral therapies, including LCIG and apomorphine subcutaneous infusion. The clinician stated LCIG is an invasive therapy and is logistically challenging to live with, whilst apomorphine has prohibitive side effects for many patients and 24-hour treatment is often not possible. The clinician stated that FosLD/FosCD was important in the armamentarium of DATs and described it as an important new and minimally invasive treatment option that can provide better accessibility and access to patients. The clinician stated it can be delivered in the outpatient setting, offering the opportunity for regional and rural patients who would otherwise not be able to access current options without travelling to hospital clinics in major centres to receive continuous levodopa. The clinician emphasised however, that there are a range of considerations for individual patients that would determine the most appropriate setting for commencement of FosCD/FosLD.
- 6.2 The clinician also stated the limitations of using LCIG and apomorphine have resulted in relatively low uptake, but FosLD/FosCD is more easily deliverable, able to be used 24 hours a day and does not require life-changing surgery to commence treatment, and therefore would be considered as a treatment option in double or even triple the number of patients currently being considered for or taking up LCIG or apomorphine.

### ***Consumer comments***

- 6.3 The PBAC noted and welcomed the input from health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from the health care professional described FosLD/FosCD as being safe and relatively easy to administer and given that current treatment options are difficult to use and not accessible in the outpatient setting, the listing will be a 'game changer' for (in particular) patients in rural and remote locations where gaining access to specialist centres is difficult. The PBAC also noted the input from the consumer organisation 'The Hospital Research Foundation Group (HRFG)' that discussed unique issues with the gastrostomy required for LCIG administration in the hot and humid Australian climate and described FosLD/FosCD as a less invasive treatment option that does not require invasive surgery to commence treatment.

### ***Clinical trials***

- 6.4 The submission was based on an anchored indirect comparison (Bucher approach) of FosLD/FosCD and LCIG using 2 randomised controlled trials with oral LD/CD as the common reference arm.
- M15-736: A phase III, double-blind, double-dummy, active-controlled, multi-centre study comparing FosLD/FosCD with oral LD/CD in patients with advanced

Parkinson’s disease that was not adequately controlled by oral therapy (n = 141). This was presented as the key trial providing efficacy data for FosLD/FosCD.

- Olanow 2014: A phase III, double-blind, double-dummy, active control, multi-centre study comparing LCIG with oral LD/CD in patients with advanced Parkinson’s disease that was not adequately controlled by oral therapy (n = 71). This trial has not previously been seen by the PBAC. LCIG was recommended by the PBAC at the November 2010 PBAC meeting, based on two randomised trials comparing LCIG with oral PD medications, non-randomised LCIG studies, and trials comparing deep brain stimulation (DBS) with standard of care (Levodopa with Carbidopa monohydrate, intestinal gel, Public Summary Document (PSD), March 2009 PBAC meeting).

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
<b>FosLD/FosCD trial</b>		
M15-736 NCT04380142	<p><b>Main study report:</b> A randomised, double-blind, double-dummy, active-controlled study comparing the efficacy, safety, and tolerability of ABBV-951 to oral carbidopa/levodopa in advanced Parkinson’s Disease [M15-736]</p> <p><b>Trial registry:</b> NCT04380142, Study Comparing Continuous Subcutaneous Infusion Of ABBV-951 With Oral Carbidopa/Levodopa Tablets For Treatment Of Motor Fluctuations In Adult Participants With Advanced Parkinson's Disease</p> <p><b>Main publication:</b> Soileau MJ, Aldred J, Budur K, Fisseha N, Fung VS, Jeong A, Kimber TE, Klos K, Litvan I, O'Neill D, Robieson WZ, Spindler MA, Standaert DG, Talapala S, Vaou EO, Zheng H, Facheris MF, Hauser RA. Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial</p>	<p>29 January 2022</p> <p>Clinicaltrials.gov, last update 18 November 2022</p> <p>Lancet Neurol. 2022 Dec;21(12):1099-1109</p>
<b>LCIG trial</b>		
Olanow 2014 NCT00357994 NCT00660387	<p><b>Main study report:</b> A Randomized, Double-Blind, Double-Dummy, Efficacy, Safety, and Tolerability Study of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects Receiving Optimized Treatments with Parkinson Medicinal Products Who Continue to Experience Persistent Motor Fluctuations</p> <p><b>Trial registry:</b> NCT00660387, Study of Efficacy, Safety and Tolerability of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects NCT00357994, Study of Efficacy, Safety and Tolerability of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects</p> <p><b>Main publication:</b> C Olanow, K Kieburtz, P Odin, et. al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study.</p>	<p>31 October 2012</p> <p>Clinicaltrials.gov, last updated 16 January 2015</p> <p>Lancet Neurol. 2014 Feb;13(2):141-9</p>

Source: Table 2-4, p50 of the submission.

6.6 The key features of the randomised trials included in the indirect comparison are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>FosLD/FosCD vs oral LD/CD</b>						
Study M15-736	141	R, DB, DD, AC, MC 12 weeks	Low	Patients with aPD that is not adequately controlled by oral medication	'On-time' 'Off-time' MDS-UPDRS part II PDQ-39 Safety	N/A
<b>LCIG vs oral LD/CD</b>						
Olanow 2014	71	R, DB, DD, AC, MC 12 weeks	Low	Patients with aPD that is not adequately controlled by oral medication	'On-time' 'Off-time' UPDRS part II PDQ-39 Safety	N/A

Source: Table 2-5, p57 of the submission.

Abbreviations: AC = active controlled; aPD = advanced Parkinson's disease; DB = double blind; DD = double dummy; FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel; LD/CD = levodopa/carbidopa; MC = multi-centre; MDS = Movement Disorder Society; N/A = not applicable; PDQ = Parkinson's disease questionnaire; R = randomised; UPDRS = Unified Parkinson's disease rating scale.

'On-time' = reduction in Parkinson's disease symptoms following levodopa dose.

'Off-time' = time with Parkinsonian features before the onset of benefit from the subsequent levodopa dose.

Note: UPDRS part II and MDS-UPDRS part II are identical.

6.7 The ESC noted the trials have small numbers and short duration (12 weeks). The ESC also noted there was a shorter mean time since diagnosis in Study M15-736 for FosLD/FosCD of 8.58 years compared to the mean time since diagnosis in Olanow 2014 of 10.09 years.

6.8 The PBAC noted that a high number of patients discontinued Study M15-736, with 35% of patients discontinuing FosLD/FosCD (26/74) and 7% of patients discontinuing oral LD/CD (5/67). In comparison, the PBAC noted that in Olanow 2014, 5% of patients discontinued LCIG (2/37) and 9% of patients discontinued oral LD/CD (3/34).

### **Comparative effectiveness**

6.9 The results of the primary efficacy measures for M15-736 are presented in Table 4.

**Table 4: Key efficacy endpoints in M15-736**

FosLD/FosCD (N=74)			Oral LD/CD (N=67)			LS Mean difference (SE)	P value
Mean baseline (SD)	Mean change (SD)	LS mean change (SE)	Mean baseline (SD)	Mean change (SD)	LS mean change (SE)	-	-
<b>Hours of average daily normalised 'On-time' without troublesome dyskinesia</b>						1.75 (0.65)	<b>0.0083</b>
9.20 (2.42)	3.36 (3.62)	2.72 (0.52)	9.49 (2.62)	0.85 (3.46)	0.97 (0.50)		
<b>Hours of average daily normalised 'Off-time'</b>						-1.79 (0.63)	<b>0.0054</b>
6.34 (2.27)	-3.41 (3.76)	-2.75 (0.50)	5.91 (1.88)	-0.93 (3.31)	-0.96 (0.49)		
<b>MDS-UPDRS Part II score</b>						-1.58 (1.05)	0.1318
15.31 (6.93)	-3.76 (6.98)	-2.65 (0.82)	13.27 (6.37)	-0.48 (4.91)	-1.06 (0.79)		
<b>PDQ-39 score</b>						-4.10 (2.04)	<b>0.0470</b>
29.31 (15.84)	-5.66 (13.71)	-6.38 (1.83)	26.52 (13.89)	-0.57 (8.79)	-2.28 (1.75)		

Source: Table 2-17, p79 and Table 2-18, p80 of the submission.

Abbreviations: FosLD/FosCD = Foslevodopa/foscarbidopa; LD/CD = levodopa/carbidopa; LS = least squares; MDS = Movement Disorder Society; PDQ = Parkinson's disease questionnaire; SD = standard deviation; SE = standard error; UPDRS = unified Parkinson's disease rating scale.

Bold = statistically significant.

The MDS-UPDRS part II score ranges from 0 – 52 with higher scores indicating more severe impairment.

The PDQ-39 score ranges from 0 – 100 with higher scores associated with more severe disease symptoms.

6.10 The submission proposed minimal clinically important differences (MCIDs) for 'Off-time', MDS-UPDRS, and PDQ-39. These are summarised in Table 5.

**Table 5: Details of minimal clinically important differences (MCID) proposed in the submission**

Outcome	Proposed MCID (change from baseline)	Source in submission
'Off-time' per day	-1.3 hours MCID was calculated as the mean change in patients who received active treatment and rated themselves "a little better" on patient global impression of improvement	Hauser et al (2014). Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis 2014; doi: 10.1155/2014/467131
UPDRS Part II and MDS-UPDRS Part II	-2.3 MCID was calculated as the mean change in patients who received active treatment and rated themselves "a little better" on patient global impression of improvement	Hauser et al (2014) as above
PDQ-39	-4.72 The study utilised both anchor-based and distribution-based techniques to calculate the MCID for PDQ-39	Horvath et al (2017). Changes in quality of life in Parkinson's disease: How large must they be to be relevant? Neuroepidemiology 2017; 48 (1-2): 1-8

Source: Tables 2-14 to 2-16, pp74-75 of the submission

Abbreviations: MCID = minimally clinically important difference; MDS = Movement Disorder Society; PDQ = Parkinson's disease questionnaire; UPDRS = Unified Parkinson's disease rating scale.

Note: UPDRS part II and MDS-UPDRS part II are identical.

6.11 In the M15-736 trial comparing FosLD/FosCD to oral LD/CD, the FosLD/FosCD arm had statistically significant improvements in 'On-time' without troublesome dyskinesia, 'Off-time', and the PDQ-38 quality of life score.

6.12 The observed improvement in average daily 'Off-time' of -2.75 hours in the FosLD/FosCD arm was greater than the nominated MCID of -1.3 hours, as well as being statistically significant, when compared to oral LD/CD. Average daily 'On-time' did not have a nominated MCID.

- 6.13 The improvement in MDS-UPDRS part II of -2.65 for FosLD/FosCD was greater than the nominated MCID of -2.3 change from baseline. However, when compared to oral LD/CD the change was not statistically significant.
- 6.14 The submission noted that participants in the FosLD/FosCD treatment group had a 6.38-point reduction (least square mean change), indicating a clinically meaningful improvement in PDQ-39 (MCID -4.72). This compares to a 2.28-point reduction for patients in the oral LD/CD arm at week 12. The least squares mean difference between the two arms at 12 weeks was -4.10, which did not meet the MCID threshold of -4.72.
- 6.15 As the trial was only 12 weeks long, it was not possible to assess the long-term efficacy of FosLD/FosCD.
- 6.16 The results of the indirect comparison of FosLD/FosCD with LCIG in terms of the key efficacy measures are presented in Table 6.

**Table 6: Indirect treatment comparison of effectiveness of FosLD/FosCD versus levodopa/carbidopa intestinal gel**

M15-736			Olanow 2014			Indirect estimates <sup>a</sup> (95% CI), p-value
FosLD/FosCD (N=74)	Oral LD/CD (N=67)	Difference	LCIG (N=37)	Oral LD/CD (N=34)	Difference	
<b>Hours of average daily normalised 'On-time' without troublesome dyskinesia, LS mean change from baseline (SE)</b>						
2.72 (0.52)	0.97 (0.50)	1.75 (0.65)	4.11 (0.75)	2.24 (0.76)	1.86 (0.65)	-0.11 (-1.93, 1.71), p=0.906
<b>Hours of average daily normalised 'Off-time', LS mean change from baseline (SE)</b>						
-2.75 (0.50)	-0.96 (0.49)	-1.79 (0.63)	-4.04 (0.65)	-2.14 (0.66)	-1.91 (0.57)	0.12 (-1.56, 1.80) p=0.889
<b>UPDRS/MDS-UPDRS Part II score, LS mean change from baseline (SE)</b>						
-2.65 (0.82)	-1.06 (0.79)	-1.58 (1.05)	-1.8 (1.3)	1.3 (1.3)	-3.0 (1.1)	1.42 (-1.63, 4.47), p=0.361
<b>PDQ-39 score, LS mean change from baseline (SE)</b>						
-6.38 (1.83)	-2.28 (1.75)	-4.10 (2.04)	-10.9 (3.3)	-3.9 (3.2)	-7.0 (2.8)	2.90 (-3.98, 9.78), p=0.409

Source: Table 2-22, p88 of the submission.

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; LD/CD = levodopa/carbidopa; LS = least squares; MDS = movement disorder society; PDQ = Parkinson's disease questionnaire; SE = standard error; UPDRS = unified Parkinson's disease rating scale.

Note: UPDRS part II and MDS-UPDRS part II are identical.

The UPDRS/MDS-UPDRS part II score ranges from 0 – 52 with higher scores indicating more severe impairment.

The PDQ-39 score ranges from 0 – 100 with higher scores associated with more severe disease symptoms.

<sup>a</sup> Calculated using the Bucher single pairwise method.

MCIDs proposed in the submission: Off time of -1.3 hours change from baseline, MDS-UPDRS -2.3 change from baseline, PDQ-39 -4.72 change from baseline.

There was no pre-specified MCID for 'On-time' without troublesome dyskinesia.

- 6.17 Overall, the evaluation noted the indirect comparisons were based on small patient numbers and considered them to be unreliable, as reflected by the wide confidence intervals. For all outcomes, there was no statistically significant difference between FosLD/FosCD and LCIG. The point estimates of the differences in change from baseline generally favoured LCIG, although the lower and upper limits met the MCIDs proposed in the submission. There was no MCID nominated in the submission for 'On-time' without troublesome dyskinesia. Additionally, the differences in outcome rates between the common comparator arms indicates the existence of transitivity issues between the two trials.
- 6.18 The mean time since diagnosis in M15-736 was 8.58 years compared to 10.09 years in Olanow 2014. Subgroup analysis of Study M15-736 indicated that there may be a significant treatment effect variation in terms of the difference in mean change from

baseline in 'Off-time' by time since diagnosis (Difference between oral LD/CD and FosLD/FosCD (< 10 years: -1.84; ≥ 10 years: -0.70; p-value= 0.039). However, subgroup analysis by duration of disease was not reported in Olanow 2014 and thus the impact of this variable on the indirect estimate of treatment effect is unknown.

### Comparative harms

6.19 A summary of key adverse events in trial M15-736 and Olanow 2014 is presented in Table 7.

**Table 7: Summary of key adverse events in the trials**

Events, n (%)	M15-736		Olanow 2014	
	FosLD/FosCD	Oral LD/CD	LCIG	Oral LD/CD
n	74	67	37	34
Any TEAE	63 (85.1)	42 (62.7)	35 (94.6)	34 (100)
Serious TEAE	6 (8.1)	4 (6.0)	5 (13.5)	7 (20.6)
AE Leading to death	0	1 (1.5)	0	0
AE leading to discontinuation	16 (21.6)	1 (1.5)	1 (2.7)	2 (5.9)
Drug-related TEAE	52 (70.3)	15 (22.4)	NR	NR
Device-related TEAE	46 (62.2)	8 (11.9)	34 (91.9)	29 (85.3)
Surgery-related TEAE	0	0	2 (5.4)	3 (8.8)
<b>TEAE of special interest</b>				
Hallucinations	11 (14.9)	2 (3.0)	1 (2.7)	1 (2.9)
Falls and associated injuries	6 (8.1)	25 (37.3)	4 (10.8)	4 (11.8)
Infusion site infection	21 (28.4)	2 (3.0)	4 (10.8)	8 (23.5)
Infusion site reaction	46 (62.2)	5 (7.5)	30 (81.1)	23 (67.6)
Polyneuropathy	0	1 (1.5)	1 (2.7)	3 (8.8)
Weight loss	1 (1.4)	17 (25.4)	0	2 (5.9)

Source: Table 2-21, p86 of the submission.

Abbreviations: AE = adverse event; FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel; LD/CD = levodopa/carbidopa; n = number of patients; TEAE = treatment emergent adverse events

6.20 Data pertaining to i) falls and associated injuries could not be verified from the M15-736 clinical study report, and ii) hallucinations could not be verified from the Olanow 2014 publication.

6.21 In M15-736 the FosLD/FosCD arm had higher treatment emergent adverse events (TEAEs) than oral LD/CD overall (85.1% vs 62.7%). There was a high rate of adverse events (AEs) leading to discontinuation (FosLD/FosCD = 21.6% vs oral LD/CD = 1.5%). The submission stated that most of the AEs leading to discontinuation in the FosLD/FosCD arm were due to infusion site adverse events (14.9%) or difficulty with the drug delivery system (6.8%). The rate of AEs leading to discontinuation in Olanow 2014 did not differ greatly across the two arms (LCIG = 2.7% vs. oral LD/CD = 5.9%).

6.22 The submission did not explain why the proportions of patients with device related TEAEs (FosLD/FosCD = 62.6% vs oral LD/CD = 11.9%) and infusion site reactions (FosLD/FosCD = 62.6% vs oral LD/CD = 7.5%) were higher in the FosLD/FosCD arm compared to the oral LD/CD arm despite both arms using the continuous subcutaneous infusion device.

- 6.23 Hallucinations were higher in the FosLD/FosCD arm compared to the oral LD/CD (14.9% vs 3.0%) arm but falls and associated injuries were lower (FosLD/FosCD = 8.1% vs oral LD/CD = 37.3%). The latter may have been due to changes in dyskinesia.
- 6.24 In Olanow 2014 the two arms were more even in terms of the AE rates, with the exception of infusion site infection (LCIG = 10.8% vs oral LD/CD = 23.5%) and infusion site reactions (LCIG = 81.1% vs 67.6%).
- 6.25 The high rate of discontinuation for FosLD/FosCD resulted in a mean duration of treatment of 62.4 days compared to 81.5 days for oral LD/CD in M15-736 and compared to 82.3 days for LCIG and 78.7 days for oral LD/CD in Olanow 2014. The applicability of the observed mean treatment duration of FosLD/FosCD to clinical practice remains unknown.
- 6.26 Additionally, as the trial was only 12 weeks long, there was inadequate follow-up to capture long-term safety associated with the continuous use of FosLD/FosCD. This is important as patients are likely to be on FosLD/FosCD for extended periods of time.
- 6.27 The submission provided additional safety data from M15-741 (an open-label, single arm, 52-week study of FosLD/FosCD) and its extension study (M15-737). It was reported that, with a median treatment exposure of 24 weeks, 92.4% of patients experienced an AE and 24.7% of patients experienced a serious adverse event. It is important to note that as M15-741 and M15-737 were open-label, single arm studies, they do not provide any comparative evidence against oral LD/CD or LCIG. Furthermore, the median duration of treatment with LCIG has been found to be 7.8 years<sup>6</sup> and several studies have reported safety and efficacy data out to 5 years<sup>7</sup>. As such, the safety data for FosLD/FosCD from M15-741/M15-737 may not reflect the long-term safety of FosLD/FosCD. It is important to note the absence of this evidence especially given the differences in administration and mean total daily dose in FosLD/FosCD compared to other dopaminergic treatments.
- 6.28 As FosLD/FosCD is a 24-hour infusion, the evaluation stated that it would be expected that there would be a higher rate of infusion site reactions.
- 6.29 The pump used to deliver FosLD/FosCD allows for patients to administer an extra dose (up to one per hour) if enabled by their health care provider. The pump also allows for patients to administer a loading dose if the infusion has been interrupted for longer than 3 hours. The M15-736 clinical study report indicates that these functions of the pump were not available. As such, the mean total daily dose as reported in M15-736 may not reflect the mean total daily dose in clinical practice where patients or health care providers may use these pump functions; and this was not accounted for in the

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<sup>6</sup> Moes, H.R., et al., Predictors of time to discontinuation of levodopa-carbidopa intestinal gel infusion: A retrospective cohort study. *J Parkinsons Dis*, 2020. 10(3): p. 935-944.

<sup>7</sup> Antonini, A., et al., The long-term impact of levodopa/carbidopa intestinal gel on 'Off-time in patients with advanced Parkinson's disease: A systematic review. *Adv Ther*, 2021. 38(6): p. 2854-2890.

determination of the equi-effective doses in the economic analysis. The trial may have underestimated the occurrence of AEs in clinical practice.

6.30 The results of the indirect comparison for TEAEs are shown in Table 8.

**Table 8: Indirect treatment comparison of safety results, FosLD/FosCD versus LCIG**

FosLD/FosCD versus LCIG	Indirect OR (95% CI) <sup>a</sup>	Indirect RR (95% CI) <sup>a</sup>	Indirect RD (%) (95% CI) <sup>a</sup>
TEAE	16.57 (0.69, 397.24)	<b>1.43 (1.14, 1.80)</b>	<b>27.9 (11.2, 44.5)</b>
SAE	2.31 (0.38, 14.17)	2.07 (0.41, 10.35)	9.2 (-10.2, 28.6)
Hallucination	6.19 (0.25, 153.21)	5.42 (0.24, 120.63)	12.12 (0.21, 24.03)
Falls and associated injuries	0.16 (0.03, 0.95)	0.24 (0.05, 1.11)	-28.25 (-48.00, -8.50)

Source: Table 2-23, p88 of the submission.

Abbreviations: CI = confidence interval; FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel; OR = odds ratio; RD = risk difference; RR = risk ratio; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Bold = statistically significant.

<sup>a</sup> Calculated using the Bucher single pairwise method.

6.31 The indirect comparisons were based on small patient numbers as reflected by the wide confidence intervals and were not reliable. The results indicated that TEAEs were statistically significantly worse with FosLD/FosCD than with LCIG. However, the indirect estimates are difficult to interpret as the estimates include any AE regardless of severity. Serious adverse events (SAEs), hallucinations, and falls did not show any statistically significant difference (probably due to small numbers), although the absolute differences were large. Confounding the results is the difference in mean treatment duration between the indirectly compared FosLD/FosCD and LCIG trial arms, with FosLD/FosCD having a shorter treatment exposure. Additionally, the differences in AE rates between the common comparator arms indicates the existence of transitivity issues between the two trials.

### **Benefits/harms**

6.32 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

### **Clinical claim**

6.33 The submission described FosLD/FosCD as non-inferior in terms of effectiveness compared to LCIG. During the evaluation the indirect comparisons were considered not reliable given they were based on small patient numbers as reflected by the wide confidence intervals of the indirect estimates of treatment effect. The lack of precision with the results makes the indirect results difficult to interpret. The ESC considered the claim of non-inferior effectiveness compared to LCIG to be reasonable.

6.34 The submission described FosLD/FosCD as non-inferior in terms of safety compared to LCIG. For similar reasons, the indirect comparisons of safety lacked precision. In addition, AEs for the common reference arm (oral LD/CD) varied between the studies. The mean time since diagnosis was also shorter (8.58 years) in Study M15-736 compared to that in Olanow 2014 (10.09 years). This reflects heterogeneity between

the study populations that are being indirectly compared making the interpretation of comparative safety also difficult. During the evaluation the claim of non-inferior safety was considered not well established as the indirect comparison of safety of FosLD/FosCD vs LCIG resulted in a RR of 1.43 (1.14, 1.80; 95% CI) for TEAEs. The ESC considered the claim of non-inferior safety to be poorly supported noting the high rates of discontinuation of FosLD/FosCD in Studies M15-736 and M15-741 and the higher overall frequencies of some specific treatment-related AEs for FosLD/FosCD compared to LCIG. The Pre-PBAC Response argued it was biologically plausible to expect comparable safety between FosLD/FosCD and LCIG, and the available pharmacokinetic data further supported this conclusion.

- 6.35 The PBAC considered that the claim of non-inferior comparative effectiveness to LCIG may be supported, but that additional detail and analyses to further support this claim were required (discussed further in paragraph 7.9).
- 6.36 The PBAC considered that the claim of non-inferior comparative safety to LCIG appeared to be poorly supported.

**Economic analysis**

- 6.37 The submission presented a CMA, which compared FosLD/FosCD, administered as a 24-hour continuous subcutaneous infusion, with LCIG, administered as a 16-hour daytime continuous infusion through a PEG-J tube.
- 6.38 The ESC noted that given the estimated high cost associated with the listing of FosLD/FosCD due to a substantially expanded market versus that for LCIG (\$60 million to < \$70 million over the first 6 years, see paragraph 6.55 for detail) a cost-effectiveness analysis may have been appropriate. The ESC also noted a CMA may not be appropriate if the claim of non-inferior safety is not supported, especially as the CMA has not accounted for the high rate of discontinuations with FosLD/FosCD.
- 6.39 The key assumptions and components of the CMA presented in the submission are summarised in Table 9.

**Table 9: Key components and assumptions of the cost-minimisation approach**

Component	Claim or assumption
Treatments	FosLD/FosCD vs. LCIG
Therapeutic claim: effectiveness	Based on evidence presented in Section 2 of the submission, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented in Section 2 of the submission, safety is assumed to be non-inferior
Evidence base	Indirect comparison of FosLD/FosCD (study M15-736) and LCIG (Olanow 2014)
Equi-effective doses	1.32 vials of FosLD/FosCD per day = 1.10 cassettes of LCIG per day
Direct medicine costs	Costs per patient per course of acute therapy, 1.32 vials of FosLD/FosCD compared to 1.1 cassettes of LCIG.
Other costs or cost offsets	Initiation costs of \$110.76 for FosLD/FosCD and \$14,384.59 for LCIG, respectively. No difference in monitoring and safety costs was assumed. The Sponsor stated that they will provide pumps and ancillaries free of charge to all patients on FosLD/FosCD and make back-up pumps available in case of malfunction.

Source: Table 3-1, p98 of the submission.

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel

- 6.40 The submission used an incorrect effective price for LCIG in its CMA (\$ [REDACTED]) and this was corrected in the PSCR ) to \$ [REDACTED] per pack. The PSCR updated the costs for the AR-DRG codes used for LCIG initiation (G05A and G05B for surgical insertion of the PEG-J tube) with the weighted cost being \$14,385, a decrease from the \$16,123 applied in the submission. For the initiation cost for FosLD/FosCD the submission utilised an older fee for MBS item 105 (\$45.40 instead of \$46.15) and with the updated MBS fee, the initiation cost increased to \$110.76 from \$108.96. These values have been updated in the CMA, see Table 10.
- 6.41 The ESC considered that the initiation cost for FosLD/FosCD (\$110.76), based on an MBS item for physician consults, was low and likely to be an underestimate as the training of patients and carers to use the pump and undertake the infusions is resource intensive and the clinicians will need the support of a multidisciplinary team. The Pre-PBAC Response argued the initiation costs were derived from the pivotal trial and it was expected that with appropriate training and continued use, the majority of patients would achieve dose optimisation in one visit and therefore the proposed FosLD/FosCD costs were reasonable.
- 6.42 The submission, based on the average number of vials/cassettes utilised by patients per day in the M15-736 and the Olanow 2014 studies, established the equi-effective doses as 1.32 vials of FosLD/FosCD per day and 1.10 cassettes of LCIG per day. If FosLD/FosCD is accepted as non-inferior in terms of effectiveness compared with LCIG, during the evaluation it was considered the equi-effective doses proposed in the submission appear reasonable.
- 6.43 The derivation of the costs for surgical insertion of the PEG-J tubes utilising the AR-DRG codes G05A (Minor small and large bowel interventions, major complexity) and G05B (Minor small and large bowel interventions, minor complexity) as in the submission's CMA were not adequately justified and may be substantially overestimated. The PSCR stated AR-DRG codes G05A and G05B are considered the most applicable codes for the insertion of the PEG-J tube. The initiation cost of LCIG was a key driver of the AEMP per pack of FosLD/FosCD. For reference, the MBS item 30481 relating to the initial procedure for percutaneous gastrostomy has a fee of \$377.40. The procedure would require going under general anaesthesia (MBS item 20745, \$146.65). Thus, utilising the MBS fees for items 30481 and 20745, the total costs for PEG-J insertion and anaesthesia would be less than \$1,000 per patient. However, these estimations do not include inpatient stay costs for dose titration. The PSCR considered application of MBS costs to be incorrect as they only account for the professional services components of the procedure and not the entire cost of the hospital stay. The PSCR further stated that the average hospital stay was 5.5 days, which was consistent with the average length of stay weighted across the G05A (3.7 days) and G05B (9.8 days) AR-DRGs (4.9 days). The ESC noted the initiation cost of LCIG was a key driver of the AEMP per pack of FosLD/FosCD.

- 6.44 The CMA utilised a treatment duration of 2 years. Treatment duration was identified as an uncertainty during the evaluation as patients may be on treatment for up to 10 years. The PSCR asserted that a 10-year treatment duration was not appropriate given that average LCIG treatment persistence was 49.6 months (4.13 years) based on 10% PBS utilisation data, and patients are on average over 65 years of age and physically frail. Sensitivity analyses for treatment durations of 4.13 years, 5 years, 7 years, and 10 years are included in Table 11. The AEMP per pack for FosLD/FosCD reduces with application of a longer treatment duration as the high initiation costs assumed by the submission for LCIG are diluted when longer periods are used. The ESC considered that an appropriate time horizon for the analysis would be 5 years.
- 6.45 The results of the CMA are presented in Table 10. The results of the sensitivity analyses are presented in Table 11.

**Table 10: Results of the cost-minimisation approach (evaluation-corrected base case)**

Component	FosLD/FosCD	LCIG
Cost per pack (7 units)*	\$	\$
Units per day	1.32	1.10
Cost per unit	\$	\$
Initiation costs	\$110.76	\$14,384.59
<b>Total treatment cost per 24 months (730.5 days)</b>	\$	\$
Difference	<b>\$0.00</b>	

\*Source: Table 3, p5 of the PSCR.

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel

**Table 11: Results of the sensitivity analyses (evaluation-corrected base case)**

	FosLD/FosCD	LCIG
<b>Base case</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>LCIG initiation costs: \$1,000</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>LCIG initiation costs: \$5,000</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>LCIG initiation costs: \$10,000</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>AR-DRG for LCIG initiation - minor complexity only, \$12,178 (base case: AR-DRG for major and minor complexity, \$14,385)</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>Treatment duration 4.13 years – PSCR stated average treatment duration for LCIG on PBS (base case: 2 years)</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>Treatment duration 5 years as recommended by ESC (base case: 2 years)</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>Treatment duration 10 years (base case: 2 years)</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$
<b>Treatment duration 4.13 years and AR-DRG minor complexity only (base case: 2 years; DRG major + minor)</b>		
Cost per unit	\$	\$
AEMP per pack	\$	\$

Source: conducted during the evaluation and during preparation of the ESC Advice

Abbreviations: AEMP = approved ex-manufacturer price; AR-DRG = Australian Refined Diagnosis Related Groups; DPMQ = dispensed price maximum quantity; FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel

<sup>a</sup> With NHCCD Round 24 costs.

6.46 The Pre-PBAC Response stated the Sponsor was amenable to accept a revised AEMP of \$|, based on the sensitivity scenario in Table 11 with a treatment duration of 4.13 years.

### **Drug cost/patient/year**

6.47 Using the proposed base case effective price (with corrections applied during the evaluation but not updated based on revised price in the sponsor’s Pre-PBAC Response), the drug cost/patient/year was estimated to be \$|for FosLD/FosCD (\$|\*365.25\*1.32) and \$|for LCIG (\$|\*365.25\*1.10).

**Table 12: Drug cost/patient/year (evaluation-corrected base case)**

	FosLD/FosCD			LCIG		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean number of vials	1.32 <sup>a</sup>	1.32	1.32	1.10 <sup>b</sup>	1.10	1.10
Mean duration	62.4 days <sup>c</sup>	730.5 days <sup>d</sup>	1,314.9 days <sup>e</sup>	82.3 days <sup>f</sup>	730.5 days <sup>g</sup>	1,607.1 days <sup>h</sup>
Cost/patient per 28-day cycle <sup>i</sup>	\$█	\$█	\$█	\$█	\$█	\$█
Cost/patient/course	\$█	\$█	\$█	\$█	\$█	\$█

Source: compiled during the evaluation.

<sup>a</sup> Based on the average number of vials utilised by patients per day from patient diaries enrolled in M15-736 as presented in Table 3-2, p100 of the submission.

<sup>b</sup> Based on the average number of cassettes utilised by patients from the Olanow 2014 study

<sup>c</sup> As presented in Table 2-10, p66 of the submission

<sup>d</sup> Based on a treatment duration of 2 years utilised in the CMA.

<sup>e</sup> Calculated by applying 65% treatment continuation in Year 1 and 89% for Years 2-6 (average treatment of 3.6 years per patient)

<sup>f</sup> As presented in Table 2-10, p66 of the submission

<sup>g</sup> Based on a treatment duration of 2 years utilised in the CMA.

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

<sup>i</sup> Based on a cost per unit of \$█ for FosLD/FosCD and \$█ for LCIG (as per Table 10).

Note: the grandfathered patients have not been included to estimate the mean duration of treatment applied in the financial estimations.

### Estimated PBS usage and financial implications

6.48 This submission was not considered by DUSC. The submission utilised a mixed epidemiological and market-share approach to estimate the extent of use of FosLD/FosCD and the financial impact of listing on the PBS. The key inputs for the financial analysis are summarised in Table 13.

**Table 13: Key inputs for financial estimates**

Data	Value	Source	Comment
<b>Eligible population</b>			
Prevalent aPD patients (patients taking ≥5 LD tablets per day)	Yr 1: 25,374 Yr 2: 26,666 Yr 3: 28,024 Yr 4: 29,451 Yr 5: 30,950 Yr 6: 32,526	10% PBS linkable data	This approach was reasonable, although the data used to estimate the prevalent aPD patients could not be verified.
Patients meeting the 5-2-1 criteria despite high dose oral Tx (20%) (i.e., taking ≥5 tablets of LD per day; having at least 2 hours of the day with “Off” symptoms and at least 1 hour of troublesome dyskinesia)	Yr 1: 5,075 Yr 2: 5,333 Yr 3: 5,605 Yr 4: 5,890 Yr 5: 6,190 Yr 6: 6,505	Aldred 2020 <sup>8</sup>	This was consistent with 20% of all patients in the study met all three of the 5-2-1 criteria and is consistent with the proposed restriction.
Patients eligible for treatment via LCIG or FosLD/FosCD (60%)	Yr 1: 3,045 Yr 2: 3,200 Yr 3: 3,363 Yr 4: 3,534 Yr 5: 3,714 Yr 6: 3,903	Weintraub 2018 <sup>9</sup>	The prevalence of cognitive impairment in PD patients ranges between 9% and 64%. <sup>10</sup> Thus, excluding 40% of patients for treatment with LCIG or FosLD/FosCD falls within a reasonable range but remains highly uncertain.

<sup>8</sup> Application of the ‘5-2-1’ screening criteria in advanced Parkinson’s disease: interim analysis of DUOGLOBE | Neurodegenerative Disease Management (futuremedicine.com)

<sup>9</sup> Initial cognitive changes in Parkinson’s disease - Weintraub - 2018 - Movement Disorders - Wiley Online Library

<sup>10</sup> Parkinson’s Disease–Mild Cognitive Impairment (PD-MCI): A Useful Summary of Update Knowledge - PMC (nih.gov)

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Data	Value	Source	Comment
Total patients initiating LCIG (█% of all eligible patients)	Yr 1: █ <sup>1</sup> Yr 2: █ <sup>1</sup> Yr 3: █ <sup>1</sup> Yr 4: █ <sup>1</sup> Yr 5: █ <sup>1</sup> Yr 6: █ <sup>1</sup>	Based on 'commercial insights' of the average LCIG initiation rate between 2018 and 2022.	This was generally comparable with the average growth rate of LCIG use between 2018 and 2022 based on the PBS utilisation data (around 4.75%).
Grandfathered patients	█ <sup>1</sup>	Based on █ <sup>1</sup> patients enrolled in the Patient Familiarisation Program and █ <sup>1</sup> patients from the long-term extension phase of the FosLD/FosCD trials.	
<b>Treatment utilisation</b>			
Uptake rate in the LCIG substitution group	Yr 1: 20% Yr 2: 40% Yr 3: 40% Yr 4: 45% Yr 5: 50% Yr 6: 50%	Assumption	Owing to FosLD/FosCD's more convenient mode of administration (subcutaneous infusion) compared with LCIG (surgical insertion), the uptake of FosLD/FosCD (50% in year 6) may be an underestimation. The ESC noted there may also be a small percentage of patients treated with LCIG who will switch to FosLD/FosCD. The Pre-PBAC Response stated that consultation with advisory boards stated that switching from LCIG was unlikely, however a small number of patients (<5%) may have PEG tube-associated infections that may warrant switching.
Uptake rate in the non-LCIG substitution group	Yr 1: 0.1% Yr 2: 0.5% Yr 3: 1.5% Yr 4: 3.5% Yr 5: 4.5% Yr 6: 5.0%	Assumption	These estimates were based on the sponsor's commercial insights and are highly uncertain. During the evaluation it was noted that if FosLD/FosCD is perceived to be less invasive, uptake in patients receiving oral therapies who were unwilling to receive LCIG may be substantially higher. The PBAC considered the uptake in this patient population to be uncertain, and AEs such as hallucinations may temper uptake.
<b>Treatment continuation</b>			
LCIG patients	85%	Derived from the M15-736 trial and Olanow 2014 study.	While the treatment continuation rates have been derived from the clinical trials for FosLD/FosCD and LCIG, treatment continuation was not an input in the CMA. Treatment continuation rates across all patients for all years were applied in a sensitivity analysis.
FosLD/FosCD patients	65% in year 1, 89% in years 2-6		
Grandfathered patients	65%		
Number treated	Yr 1: █ <sup>1</sup> Yr 2: █ <sup>1</sup> Yr 3: █ <sup>1</sup> Yr 4: █ <sup>1</sup> Yr 5: █ <sup>2</sup> Yr 6: █ <sup>2</sup>	Based on uptake rates of 20%-50% in the LCIG substitution group and uptake rates of 0.1% - 5.0% in the non-LCIG substitution group.	During the evaluation it was considered the uptake rates in both groups are likely to be an underestimation of the true uptake in practice. The PBAC considered uptake to be uncertain.

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Data	Value	Source	Comment
Scripts dispensed	Yr 1: [redacted] <sup>2</sup> Yr 2: [redacted] <sup>2</sup> Yr 3: [redacted] <sup>2</sup> Yr 4: [redacted] <sup>2</sup> Yr 5: [redacted] <sup>3</sup> Yr 6: [redacted] <sup>3</sup>	Based on an average of 1.32 vials per patient per day and 13.04 scripts per patient per year.	
<b>Costs</b>			
Foslevodopa/Foscarbidopa			
56 vials, General Schedule	\$ [redacted]	Requested effective price	Derived using a cost-minimisation approach against LCIG. All prices have been updated based on updated AEMP for LCIG and initiation costs (see para 6.40 and 6.41), but not updated using the revised price proposed in the Pre-PBAC Response (see para 6.46).
56 vials, s100 Public	\$ [redacted]		
56 vials, s100 Private	\$ [redacted]		
28 vials, General Schedule	\$ [redacted]		
28 vials, s100 Public	\$ [redacted]		
28 vials, s100 Private	\$ [redacted]		
LCIG			
8970D	\$ [redacted]	Dispensed prices calculated based on sponsor's updated effective AEMP of \$ [redacted] per pack of 7 vials	The AEMP was updated from the \$ [redacted] used in the submission.
9743T	\$ [redacted]		
9744W	\$ [redacted]		
11919H	\$ [redacted]		
11913B	\$ [redacted]		
11910W	\$ [redacted]		
Patient co-payment	PBS: \$8.73 RPBS: \$4.00	PBS statistics for items: 11910W, 11913B, 11919H, 8970D, 9743T, 9744W in calendar year 2022.	
PBS/RPBS split	PBS: 97.17% RPBS: 2.83%	PBS statistics for items: 11910W, 11913B, 11919H, 8970D, 9743T, 9744W in calendar year 2022.	
MBS costs (applied to FosLD/FosCD patients)	\$46.15 per service	MBS item 105	The cost of 2.4 clinic visits was applied in the CMA for dose titration for patients initiating treatment with FosLD/FosCD.

Source: tabulated during evaluation from Tables 4-1, 4-2, 4-3 and 4-4 of the submission; updated AEMP for LCIG sourced from the PSCR. Abbreviations: aPD = advanced Parkinson's disease; FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel; LD = levodopa; MBS = Medicare Benefits Schedule; PBS = Pharmaceuticals Benefits Scheme; RPBS = Repatriation Pharmaceuticals Benefits Scheme; Tx = treatments

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 < 5,000

<sup>3</sup> 5,000 to < 10,000

6.49 The submission utilised an epidemiological approach to capture the number of Parkinson's disease patients receiving any form of pharmacological PD treatment in the 10% PBS linkable data. The average annual growth in patients receiving PD treatment was calculated to be 3.4%. The number of patients on levodopa-based treatment were then captured and estimated to grow at an average annual rate of 2.5%. From this data, the number of patients taking ≥ 5 oral levodopa tablets were captured and an average annual growth rate of 5% in advanced PD was calculated and used to forecast the prevalent advanced PD patients between 2024 and 2029. The

prevalent patients receiving any form of PD treatment and taking levodopa-based treatment were utilised to capture the number of patients who meet the advanced PD criteria, i.e., patients who take  $\geq 5$  oral levodopa tablets per day.

- 6.50 From the advanced PD patients pool, ██████% were assumed to initiate treatment with LCIG based on the sponsor's 'commercial insights', and thus, be eligible for treatment initiation with FosCD/FosLD. The initiation rate of █% applied in the submission was consistent with the growth rate estimated based on the Medicare PBS script statistics on LCIG between 2018 and 2022 (around 4.75%) and was reasonable. The Sponsor included a provision for < 500 grandfathered patients, < 500 from patients enrolled in a Patient Familiarisation Program and < 500 from the long-term extension phase of the FosLD/FosCD trials.
- 6.51 The submission applied uptake rates up to 50% to estimate the number of patients who would replace LCIG with FosLD/FosCD. Uptake rates of 20% in year 1 and 50% in year 6 were applied to estimate the total number of patients who would initiate treatment with FosLD/FosCD. From the patients who continued to receive treatment via oral levodopa, uptake rates of 0.1% in year 1 and 5% in year 6 were applied. Owing to FosLD/FosCD's more convenient mode of administration, during the evaluation it was considered the uptake rates utilised in the submission may not reflect the true extent of use of FosLD/FosCD in practice.
- 6.52 The ESC noted that the approach to the financial estimates appeared reasonable, although some inputs were highly uncertain or underestimates, e.g., the uptake rates, and the continuation rates.
- 6.53 The total number of scripts was calculated as 13.04 per patient per year for patients initiating treatment with FosLD/FosCD and 7.2 scripts per patient per year for patients initiating treatment with LCIG. The total number of patients and prescriptions are presented in Table 14.

**Table 14: Estimation of number of treated patients and prescriptions**

			Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Patients on PD treatment	3.4% growth rate	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
B	Patients on LD-based PD Tx	2.5% growth rate	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>
C	Patients on 5+ LD-based tablets	5% growth rate	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>5</sup>	█ <sup>5</sup>
D	Patients with severe disabling motor fluctuation	69% (C × 69%)	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
E	Patients remaining on orals	40% (D × 40%)	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
F	Eligible patients to commence LCIG or FosLD/FosCD	60% (D × 60%)	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
G	<b>Patients that initiate Tx with LCIG or FosLD/FosCD</b>	█ <sup>8</sup> % (F × █ <sup>8</sup> %)	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
<b>LCIG substitution group</b>								
H	Uptake rates		20%	40%	40%	45%	50%	50%
I	FosLD/FosCD initiation	G × H	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
J	FosLD/FosCD continuing <sup>a</sup>		-	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
K	LCIG initiation with FosLD/FosCD listing	G - I	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
L	LCIG continuing patients <sup>b</sup>		-	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
<b>Grandfathered patients</b>								
M	Grandfathered patients <sup>c</sup>		█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
<b>Non-LCIG substitution group (substitution from orals)</b>								
N	Eligible patients	F-I-J-K-L-M	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
O	Uptake rates		0.1%	0.5%	1.5%	3.5%	4.5%	5.0%
P	FosLD/FosCD initiation from oral LD	N × O	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
Q	FosLD/FosCD continuing <sup>d</sup>		-	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
<b>Total</b>								
R	Total patients	I+J+M+P+Q	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>7</sup>	█ <sup>7</sup>
S	<b>Total script numbers (13.04 scripts/patient/year)</b>	13.04 × R	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>6</sup>	█ <sup>6</sup>

Source: tabulated during evaluation from Tables 4-5 and 4-6 of the submission and from sheet "AbbVie BIM" of the "Attachment 8.1 UCM CMIN FosLDFosCD v LCIG\_final Feb 2022" workbook included in the submission.

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel; LD = levodopa; PD = Parkinson's disease; Tx = treatment.

<sup>a</sup> Assumed treatment continuation of 65% in year 1 patients; 89% in Years 2-6 patients.

<sup>b</sup> Assumed treatment continuation of 85% in patients in all years of treatment.

<sup>c</sup> Assumed treatment continuation of 65% in grandfathered patients in all years of treatment.

<sup>d</sup> Assumed treatment continuation of 65% in year 1 patients; 89% in Years 2-6 patients.

The redacted values correspond to the following ranges:

<sup>1</sup> 100,000 to < 200,000

<sup>2</sup> 70,000 to < 80,000

<sup>3</sup> 80,000 to < 90,000

<sup>4</sup> 20,000 to < 30,000

<sup>5</sup> 30,000 to < 40,000

<sup>6</sup> 5,000 to < 10,000

<sup>7</sup> 500 to < 5,000

<sup>8</sup> < 500

6.54 A summary of the net financial implications for the PBS/RPBS is provided in the Table 15. These estimates use the corrected effective price for LCIG and resultant corrected cost-minimised price for FosLD/FosCD, based on the evaluation-corrected base case price, however they have not been updated based on the revised price offered in the Sponsor’s Pre-PBAC Response (see paragraph 6.46).

**Table 15: Estimated use and financial implications (evaluation-requested base case)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated financial implications of FosLD/FosCD</b>						
Cost to PBS/RPBS less copayments	1	1	2	3	6	4
<b>Estimated financial implications for LCIG and oral LD</b>						
Cost to PBS/RPBS less copayments	5	5	5	5	5	5
<b>Net financial implications</b>						
Net cost to PBS/RPBS	1	1	1	2	2	3

Source: Amended during the preparation of the ESC Advice based on Table 4-9, p124 of the submission.

Abbreviations: FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel; LD = levodopa; PBS = Pharmaceuticals Benefits Scheme; RPBS = Repatriation Pharmaceuticals Benefits Scheme

The redacted values correspond to the following ranges:

- <sup>1</sup> \$0 to < \$10 million
- <sup>2</sup> \$10 million to < \$20 million
- <sup>3</sup> \$20 million to < \$30 million
- <sup>4</sup> \$40 million to < \$50 million
- <sup>5</sup> net cost saving
- <sup>6</sup> \$30 million to < \$40 million

6.55 The total cost to the PBS/RPBS of listing FosLD/FosCD was estimated to be \$40 million to < \$50 million in Year 6. The net cost to the PBS/RPBS, accounting for a reduction in the use of LCIG and oral LD was \$20 million to < \$30 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing, based on the effective price. During the evaluation it was considered that the financial estimates are likely an underestimation as higher uptake rates of FosLD/FosCD are expected due to its less invasive mode of administration than LCIG. Additionally, the financial estimations are based on varied treatment continuation rates across patients switching from the LCIG substitution group, non-LCIG substitution group and for the < 500 grandfathered patients. Revised estimates applying a treatment continuation of 90% and 100% across all patients are presented in Table 15.

6.56 Despite taking a cost-minimisation approach, the net cost to the PBS/RPBS is not neutral. A proportion of this increase in the net cost to the PBS/RPBS is a consequence of the higher yearly cost of FosLD/FosCD in the CMA due to the inclusion of substantial initiation costs associated with LCIG. While a higher cost for FosLD/FosCD may be reasonable, the magnitude of the increase in the cost to the PBS/RPBS is uncertain due to concerns with the initiation costs for LCIG and the duration of treatment in the CMA over which the initiation costs are dispersed. Further, a higher proportion of the net cost to the PBS/RPBS is attributed to the number of patients switching from oral LD/CD to FosLD/FosCD (oral LD is significantly cheaper and more oral LD/CD patients switch to FosLD/FosCD from Year 4 onwards when compared to those switching from LCIG). While the submission has accounted for the substitution of oral LD with

FosLD/FosCD in the financial estimations, the cost-effectiveness of FosLD/FosCD versus oral therapy has not been demonstrated in the submission. The Pre-PBAC Response argued the CMA approach was consistent with the clinic claims, and the cost to government is driven by the incremental uptake beyond expected replacement of LCIG alone, due hesitancy to take up LCIG and the minimally invasive manner of administration for FosLD/FosCD.

- 6.57 The financial estimations included cost savings as a consequence of a reduction in the costs for surgery required for treatment initiation with LCIG via PEG-J tubes. A small increase in costs to the MBS (\$18.96 per patient based on item 105, specialist attendance) has been applied to account for the professional attendances required to titrate the dose of FosLD/FosCD. The ESC noted this cost was not included in the CMA.
- 6.58 Sensitivity analyses considering the cost-minimised price of FosLD/FosCD, initiation costs as well as continuation rates are provided in Table 16.

**Table 16: Financial estimates – sensitivity analyses**

Analysis	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% change
<b>Base case</b>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	-
<b>Cost-minimised price for FosLD/FosCD (base case: \$█ per pack)</b>							
AR-DRG minor complexity: \$█	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	-4%
Treatment duration 4.13 years: \$█	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	-12%
Treatment duration 10 years: \$█	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	-18%
Treatment duration 4.13 years and AR-DRG minor: \$█	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	-13%
\$1,000 initiation cost for LCIG: \$█	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	-21%
\$5,000 initiation cost for LCIG: \$█	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	-15%
<b>Treatment continuation (base case: 85% for LCIG; 65% in Year 1 and 89% in Years 2 – 6 for FosLD/FosCD; 65% for grandfathered patients)</b>							
90% all patients	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>	+11%
100% all patients	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	+22%

Source: Excel workbook 'Attachment 8.1 UCM CMIN FosLDFosCD v LCIG\_final Feb 2022' provided with the submission.

Abbreviations: AR-DRG = Australian Refined Diagnosis Related Groups; FosLD/FosCD = foslevodopa/foscarbidopa; LCIG = levodopa carbidopa intestinal gel

<sup>a</sup> Updated to NHDC Round 24 costs.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

<sup>2</sup> \$10 million to < \$20 million

<sup>3</sup> \$20 million to < \$30 million

- 6.59 The sensitivity analyses demonstrated the financial estimates are sensitive to the cost-minimised price for FosLD/FosCD and the assumptions regarding treatment continuation. The PSCR stated applying a treatment persistence of 90-100% is unreasonable in clinical practice and rates should be based on clinical trial data (M15-

736: 65%; M15-741m sample 2: 89%<sup>11</sup>). It was further noted in the PSCR that while subcutaneous infusion of FosLD/FosCD offers a more convenient mode of administration compared to LCIG, the proper use of the delivery system remains complex, especially considering advanced PD is a movement disorder and treatment/assistance can be burdensome to carers/family. Thus, patients would not have a treatment continuation of 90% or above. The ESC noted the lower continuation rates for FosLD/FosCD, which would potentially lead to inferior efficacy, had not been accounted for in the CMA. The Pre-PBAC Response stated the requested adjustments to apply continuation rates comparable to LCIG were reasonable, however stated assumptions of switching from LCIG were not because of the low likelihood of this occurring in practice.

### Quality Use of Medicines

6.60 The Sponsor noted that listing of FosLD/FosCD would improve treatment accessibility with levodopa for advanced Parkinson’s disease patients. The Sponsor also stated that they will run a quality use of medicine specialist nursing support program for patients and clinicians initiating treatment with FosLD/FosCD.

### Financial Management – Risk Sharing Arrangements

6.61 The submission did not propose a Risk Sharing Arrangement (RSA). However, the Sponsor noted that if the Department deems a RSA to be necessary for FosLD/FosCD, the same rebate levels above the subsidisation cap that are in place for LCIG (a 10% rebate above the cap) could also apply to FosLD/FosCD. The evaluation stated that it could be appropriate for FosLD/FosCD to be included under the same RSA for LCIG given the uncertainty around the estimates of uptake rates utilised in the submission for patients switching from LCIG as well as oral levodopa for which the cost-effectiveness is unknown. The ESC agreed that a RSA could be considered given uncertainties around uptakes rates for switching from the gel.

6.62 For reference, the past 6 years of Commonwealth payments for LCIG are shown in Table 17 below.

Table 17: Commonwealth expenditure on LCIG, 2017 to 2023

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

Source: compiled during the evaluation.

For more detail on PBAC’s view, see section 7 PBAC outcome.

<sup>11</sup> The treatment duration was derived from clinical trial data provided by the applicant.

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of foslevodopa/foscarbidopa (FosLD/FosCD) for the treatment of advanced Parkinson's disease in patients with severe disabling motor fluctuations not adequately controlled by oral therapy. In not recommending the listing, the PBAC considered further data and analyses were required to address concerns regarding the impact of discontinuations in the pivotal FosLD/FosCD (M15-736) trial on both the estimated efficacy for FosLD/FosCD and the indirect comparison with levodopa/carbidopa intestinal gel (LCIG). The PBAC considered a number of inputs for the cost minimisation to be uncertain which likely resulted in the cost of FosLD/FosCD per patient being more than for LCIG, and noted the CMA did not include the costs associated with treating adverse events. The PBAC agreed with the submission that as a subcutaneous treatment option, the use of FosLD/FosCD in practice was likely to be greater than the current intestinal gel option and considered that a Risk Sharing Arrangement (RSA) would be appropriate for the listing. The PBAC considered the outstanding issues could be addressed in an early re-entry submission.
- 7.2 The key reason for not recommending FosLD/FosCD was the comparative clinical evidence.
- 7.3 The PBAC considered there was a clinical need for additional treatment modalities for patients experiencing severe motor symptoms from Parkinson's disease where oral therapies were no longer providing adequate control. The Committee considered that current treatment options had substantial limitations, as apomorphine subcutaneous infusion is associated with prohibitive side effects that precludes 24-hour administration for many patients and LCIG requires invasive surgery prior to commencing treatment. The Committee recognised that a subcutaneous pump modality like FosLD/FosCD provides a new and minimally invasive treatment option that can readily be used 24 hours a day and is deliverable in an outpatient setting (in some circumstances). The Committee recognised that this would provide benefits to regional and rural patients who otherwise may need to travel significant distances to access the current treatment options.
- 7.4 The PBAC noted the clinician input in the Sponsor hearing that many patients find LCIG to not be an acceptable treatment, that only a small number of patients were considered for this treatment option, that significantly more patients would likely consider, and be considered for, this less invasive treatment option, and that in some cases, administration could occur in an outpatient setting.
- 7.5 The Committee considered a listing in both the General Schedule and Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals) was reasonable, to allow for prescribing both in the community and from hospital-based specialists and movement disorder clinics. The PBAC considered that given the nature of FosLD/FosCD it was appropriate to allow for out of hospital initiation by a neurologist or physician with experience in the management of Parkinson's disease (or movement

disorders more broadly). For continuing therapy, the PBAC considered a General Schedule listing was appropriate.

- 7.6 The PBAC considered it was appropriate for the listing to include an administrative note requiring patients to have adequate cognitive function to be able to manage administration with a portable continuous infusion pump (paragraph 3.6), and that it was also appropriate for the restriction for the maximum quantity of 8 packs to include as clinical criteria that the “Patient must require continuous administration without an overnight break; OR Patient must require a total daily dose of more than 2400 mg of foslevodopa per day” (paragraph 3.3).
- 7.7 The PBAC considered there was a clinical place for FosLD/FosCD as an alternative to more invasive and/or less tolerable treatment options like apomorphine infusion and LCIG. The PBAC acknowledged the use of apomorphine and LCIG was limited for the reasons outlined in paragraph 7.3, and that given the relative simplicity of commencing and continuing FosLD/FosCD treatment, it was likely to be used in a larger population. The Committee considered LCIG to be an appropriate comparator given the extent of replacement of LCIG (in the first 6 years the majority of use of FosLD/FosCD is expected to replace LCIG, Table 14) and both treatments are used in the same patient population (patients with severe disabling motor fluctuations not adequately controlled by oral therapy).
- 7.8 The submission presented an anchored indirect comparison of FosLD/FosCD and LCIG using (i) M15-736: a randomised, double-blind, double-dummy study comparing FosLD/FosCD with oral LD/CD (n = 141) and (ii) Olanow 2014: a randomised, double-blind, double-dummy study comparing LCIG with oral LD/CD (n = 71). The PBAC noted the small sizes and short duration of the trials (12 weeks), as well as differences across the trials in inclusion criteria and patient characteristics (including duration of disease). The Committee also noted the high drop-out rates in M15-736 (paragraphs 6.8 and 6.21) and that missing data for patients who discontinued was assumed to be random in the primary analyses. A further concern in M15-736 was the apparent unblinding with more than 70%<sup>12</sup> of patients in each arm correctly guessing the treatment they were receiving despite the trial being double-dummy with all patients receiving both infusions and tablets (M15-736 Clinical Study Report Table 14.1\_15<sup>13</sup>). The PBAC noted the results for the common comparator (oral LD/CD) differed markedly across the trials for the key outcomes of ‘on-time’ and ‘off-time’ (Table 6) and that this may have been due to factors such as differences in the trial populations, improvements in standard care over time with M15-736 being conducted approximately 8 years later, or participant expectation and unblinding.
- 7.9 With regards to comparative effectiveness, the PBAC considered a claim of non-inferior comparative effectiveness was uncertain given the above, although may be supported. However, the Committee considered the impact of discontinuations in

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<sup>12</sup> The treatment duration was derived from clinical trial data provided by the applicant.

<sup>13</sup> The treatment duration was derived from clinical trial data provided by the applicant.

M15-736 on the both the estimated efficacy for FosLD/FosCD and the indirect comparison with LCIG required further exploration. As such, the PBAC 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, and sensitivity analyses that look at the impact of using alternative ways to handle the missing data.

- 7.10 The PBAC considered the claim of non-inferior comparative safety to be poorly supported and noted FosLD/FosCD was associated with more adverse events leading to discontinuation and reports of hallucination than LCIG. The PBAC also noted FosLD/FosCD was associated with higher rates of infusion site reactions and infections than oral LD/CD even though both treatment arms received infusions. The PBAC considered that the high rates of hallucinations observed with FosLD/FosCD (approximately 15%) may dissuade some patients from continuing therapy or lead to dose reductions in practice. The PBAC considered it would be appropriate to account for the costs of adverse events in the cost-minimisation approach (CMA).
- 7.11 Based on the CMA presented in the submission the PBAC considered the cost of FosLD/FosCD per patient was likely to be higher than the cost of LCIG. This was due to:
- The initiation cost for FosLD/FosCD being underestimated. The PBAC agreed with ESC that the training of patients and carers to use the pump and undertake the infusions will be resource intensive and the clinicians will need the support of a multidisciplinary team (paragraph 6.41). The PBAC further noted that not all patients would initiate FosLD/FosCD in the outpatient setting (paragraph 7.4);
  - The costs for the surgical insertion of the PEG-J tubes for LCIG being likely overestimated (paragraph 6.43);
  - The duration over which the CMA was conducted being too short. The PBAC noted the duration was increased from 2 years to 4.13 years in the Pre-PBAC Response on the basis that the average persistence with LCIG was stated to be 4.13 years (paragraph 6.44). The PBAC considered a time horizon of 4.13 years may be reasonable if there was more certainty that the surgical costs for LCIG were not overestimated;
  - It being unclear if additional doses for FosLD/FosCD were accounted for (paragraph 6.29); and
  - Not including costs associated with managing adverse events, and in particular the costs associated with treating the hallucination events with FosLD/FosCD.
- 7.12 The PBAC noted that despite taking a CMA the net cost to the PBS/RPBS was substantial (\$60 million to < \$70 million over 6 years), primarily due to uptake of FosLD/FosCD being greater than that for LCIG, and also due to the higher yearly cost of FosLD/FosCD associated with the inclusion of substantial initiation costs for LCIG in

the CMA. The PBAC agreed that the uptake of FosLD/FosCD was likely to be higher than for LCIG given reluctance by patients and clinicians to use LCIG in practice and the relative simplicity of use of FosLD/FosCD. However, the Committee considered that the extent of uptake of FosLD/FosCD in clinical practice was uncertain, and although the relative simplicity of FosLD/FosCD is likely to expand use, adverse events such as hallucinations may limit use in practice. Overall, the PBAC considered the uptake estimates in the submission to be plausible.

- 7.13 The PBAC noted the financial estimates presented in the submission assumed a different discontinuation rate for FosLD/FosCD (65% in year 1 followed by 89%) than for LCIG (85%), and during the evaluation sensitivity analyses were undertaken assuming treatment persistence of 90-100% for both treatments. The PBAC noted the comments in the PSCR that the persistence observed in the clinical trials was lower than 90% and that proper use of the FosLD/FosCD delivery system remains complex, especially considering advanced PD is a movement disorder and treatment/assistance can be burdensome to carers/family (paragraph 6.59), and considered treatment persistence in clinical practice would likely be lower than 90%. The PBAC considered, if possible, the persistence should be informed by that observed for LCIG on the PBS.
- 7.14 The PBAC considered given the uncertain use of FosLD/FosCD in practice and given 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 that the level of rebate would need to be higher than the % currently in place for LCIG.
- 7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for FosLD/FosCD using the early re-entry pathway. If the Sponsor accepts this pathway, provision of the following may address these outstanding issues without requiring further re-evaluation. The Committee considered an early re-entry submission should include:
- Additional data and analyses exploring the impact of drop-outs in Study M15-736 on the both the estimated efficacy for FosLD/FosCD and the indirect comparison with LCIG (paragraphs 7.8 and 7.9);
  - A revised CMA addressing the comments in paragraph 7.11;
  - Revised financial estimates incorporating the revised CMA price for FosLD/FosCD and potentially revised treatment persistence (paragraph 7.13); and
  - A RSA proposal (paragraph 7.14).

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the Sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.16 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **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**

AbbVie is disappointed that the PBAC did not recommend foslevodopa and foscarnidopa (Vyalev) given the high clinical need for an alternative treatment option in advanced Parkinson's disease. AbbVie acknowledges the option of early re-entry and will continue to work with the PBAC and the Department of Health and Aged Care to ensure funded availability as soon as possible.