

An addendum from the November 2024 PBAC meeting has been included at the end of this document.

7.03 LEVODOPA WITH CARBIDOPA AND ENTACAPONE, Intestinal gel containing levodopa 20 mg with carbidopa monohydrate 5 mg and with entacapone 20 mg per mL, 47 mL, Lecigon[®], STADA PHARMACEUTICALS AUSTRALIA PTY LIMITED

1 Purpose

- 1.1 The early re-entry resubmission requested Section 100 (Highly Specialised Drugs (HSD) Program) Public and Private Hospital Authority Required and General Schedule Authority Required (STREAMLINED) listings for levodopa with entacapone and carbidopa intestinal gel (LECIG) for the treatment of advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment.
- 1.2 As an early re-entry resubmission, neither the economic analysis nor the financial estimates analysis have been independently evaluated.
- 1.3 The resubmission was based on the PBAC decision to not recommend LECIG for this indication at its March 2024 meeting. Table 1 outlines the issues raised by the PBAC in March 2024 and how these issues were addressed in the resubmission.

Table 1 Summary of key matters to be addressed

Matter of concern	Response	Addressed?
Submission of a sufficiently conservative equi-effective dosing approach to offset the uncertainties in the clinical evidence presented to support clinical claims. A conservative approach could acknowledge that 2 cartridges of LECIG contain 1880 mg levodopa whereas 1 cassette of LCIG contains 2000 mg levodopa, and that addition of entacapone has only a moderate impact on the PK of levodopa, so equi-effective dosing should be much closer to 2 LECIG cartridges : 1 LCIG cassette.	The resubmission proposed an equi-effective dose of 1.31 LECIG cartridge to 1.15 LCIG cassette.	Unclear. While an alternative equi-effective dose was proposed it is unclear if it is sufficiently conservative.
Recalculation of the financial implications using the revised LECIG price.	The financial implications were updated using the revised LECIG price proposed in the resubmission.	Y
Proposal of a risk-sharing arrangement that sufficiently mitigates financial risk to the PBS of any utilisation of LECIG cartridges beyond that estimated in the re-submission base-case.	The resubmission proposes that LECIG be included in the same risk-sharing arrangement as LCIG.	Y

Source: compiled from the March 2024 levodopa with carbidopa and entacapone PSD and the July 2024 early re-entry resubmission.

2 Background

2.1 LECIG was TGA registered on 29 August 2023 for the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.

2.2 The PICO from the previous submission is presented below.

Table 2: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised oral alternative pharmacological treatment
Intervention	Levodopa, entacapone and carbidopa monohydrate intestinal gel (LECIG)
Comparator	Levodopa, carbidopa monohydrate intestinal gel (LCIG)
Outcomes	Efficacy outcomes including Off-Time hours, activities of daily living, Parkinson's disease sleep Scale, Quality of life (Parkinson's Disease Questionnaire) and adverse events
Clinical claim	In adults with advanced Parkinson's Disease and severe motor fluctuations despite optimised oral alternative pharmacological treatment, LECIG is non-inferior in terms of efficacy and non-inferior in term of safety when compared to LCIG.

Source: Table 1, levodopa with carbidopa and entacapone March 2024 PSD.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The resubmission did not present a PBS restriction. The amended March 2024 submission restrictions are provided below. The pre-PBAC response confirmed that the sponsor accepted the restrictions listed below.

Section 100 (Highly Specialised Drugs Program) listing for a maximum quantity of 28 units

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LEVODOPA + CARBIDOPA + ENTACAPONE						
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW (HSD Public) NEW (HSD Private)	Published price Private: \$ Public: \$	4	28	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

Variant of Restriction Summary ToC: Authority Required: Streamlined

	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Advanced
	Condition: Parkinson Disease
	Indication: Advanced Parkinson disease
	Clinical criteria:

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	Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.
	AND
	Clinical criteria:
	The treatment must be commenced in a hospital-based movement disorder clinic.
	Administrative advice: Patient should have adequate cognitive function to manage administration with a portable continuous infusion pump.

Section 100 (Highly Specialised Drugs Program) listing for a maximum quantity of 56 units

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands/ manufacturer
LEVODOPA + CARBIDOPA + ENTACAPONE						
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW (HSD Public) NEW (HSD Private)	Published price Private: \$ Public: \$	8	56	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

Variant of Restriction Summary 10395/10353 / ToC: 10375/10363: Authority Required: Streamlined

	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Advanced
	Condition: Parkinson Disease
	Indication: Advanced Parkinson disease
	Clinical criteria:
	Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.
	AND
	Clinical criteria:
	The treatment must be commenced in a hospital-based movement disorder clinic.
	AND
	Clinical criteria:
	Patient must require continuous administration of levodopa without an overnight break; or
	Patient must require a total daily dose of more than 940 mg of levodopa.
	Administrative advice: Patient should have adequate cognitive function to manage administration with a portable continuous infusion pump.

General Schedule listing for a maximum quantity of 28 units

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LEVODOPA + CARBIDOPA + ENTACAPONE						
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW MP NP	Published price \$	4	28	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

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Variant of Restriction Summary 10091 / ToC: 10197: Authority Required: Streamlined	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioner
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: 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.
	Severity: Advanced
	Condition: Parkinson Disease
	Indication: Advanced Parkinson disease
	Treatment Phase: Maintenance therapy
	Clinical criteria:
	Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.
	AND
	Clinical criteria:
	Patient must have been commenced on treatment in a hospital-based movement disorder clinic.
	Administrative advice: Patient should have adequate cognitive function to manage administration with a portable continuous infusion pump.

General Schedule listing for a maximum quantity of 56 units

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No.of Rpts	Available brands
LEVODOPA + CARBIDOPA + ENTACAPONE						
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW	Published price \$■■■	8	56	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

Variant of Restriction Summary 10374 / ToC: 10386: Authority Required: Streamlined	
Concept ID (for internal Dept. use)	Category / Program: General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioner
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: 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.
	Severity: Advanced
	Condition: Parkinson Disease
	Indication: Advanced Parkinson disease
	Treatment Phase: Maintenance therapy
	Clinical criteria:
	Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.

	AND
	Clinical criteria:
	Patient must have been commenced on treatment in a hospital-based movement disorder clinic
	AND
	Clinical criteria:
	Patient must require continuous administration of levodopa without an overnight break; or
	Patient must require a total daily dose of more than 940 mg of levodopa
	Administrative advice: Patient should have adequate cognitive function to manage administration with a portable continuous infusion pump.

- 3.2 The resubmission requested an ex-manufacturer price for LECIG (\$████) that is █████% lower than the approved ex-manufacturer price (AEMP) for Levodopa, carbidopa monohydrate intestinal gel (LCIG) (\$1,442.00). The resubmission stated that LECIG price is based on the equi-effective dose of LECIG and LCIG and that the price reduction aimed to make LECIG cost neutral to the PBS. The resubmission also acknowledged that, as LCIG has a Special Pricing Arrangement (SPA), the AEMP of LECIG based on effective prices will be lower.
- 3.3 The listing provided for either 4 or 8 packs of 7 cartridges, allowing for 1 or 2 vials per day respectively over 28 days. With 5 repeats this would permit 6 months of therapy. This is in line with the LCIG PBS listing.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from individuals (2) via the Consumer Comments facility on the PBS website. The PBAC noted that, consistent with the Consumer input for the March 2024 submission, the input focused on a treatment other than LECIG, but was useful in emphasising the impact of advanced Parkinson’s Disease on people with the condition. In addition, the July 2024 input discussed the benefits of dose administration across an extended period over oral therapy where regular dosing is required.

Clinical evidence

- 4.3 No new clinical evidence was presented in the resubmission.
- 4.4 The March 2024 submission was based on one head-to-head study comparing LECIG to LCIG (n=11), the LSM-003 study. Additionally, an unanchored, unadjusted indirect comparison was carried out between the single arm ELEGANCE, GLORIA, and DUOGLOBE studies (paragraph 6.3, levodopa with carbidopa and entacapone Public Summary Document [PSD], March 2024 PBAC Meeting).

- 4.5 In March 2024, the PBAC noted that while the clinical claim was that LECIG was non-inferior in terms of both efficacy and safety compared to LCIG, Study LSM-003's primary outcome was a pharmacokinetic measure of systemic exposure to levodopa ($AUC_{0-14\text{ hr}}$), with the Treatment Response Scale outcome considered an exploratory outcome. At that time, the PBAC agreed with the evaluation that Study LSM-003 was not appropriately designed to rule out differences in clinical effectiveness outcomes such as the Treatment Response Scale across arms. In March 2024, the PBAC also noted that the trial was open label, meaning bias in assessment of clinical effectiveness outcomes could not be minimised to the extent likely with a blinded trial design. The PBAC did note the view put forward in the submission that pharmacodynamic effects of LECIG closely follow plasma levodopa levels. At that time, the PBAC was unconvinced that this was the optimal approach for any study pivotal to the demonstration of the clinical claims made in the submission, because LECIG is not a generic version of LCIG (e.g. includes an additional active ingredient, entacapone, a COMT inhibitor), but did accept that pharmacokinetic outcomes from Study LSM-003 helped inform the clinical claim of non-inferior effectiveness (paragraph 7.5, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).
- 4.6 In March 2024, the PBAC noted the submission's presentation of additional LECIG data from the single-arm study ELEGANCE, and single-arm trials of LCIG (DUOGLOBE, GLORIA), however considered that these studies were also relatively uninformative for the purpose of decision-making. Because of the studies' single-arm designs, comparisons between LECIG and LCIG were unanchored, as well as being unadjusted despite likely differences across the trial populations (paragraph 7.6, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).
- 4.7 The PBAC noted that in Study LSM-003 patients received LECIG morning doses corresponding to 80% (n = 5) or 90% (n = 6) of their individual morning dose of LCIG, 80% of the LCIG maintenance dose, and 80% of extra doses (Senek 2017).

Clinical claim

- 4.8 In March 2024, the PBAC considered the clinical evidence that was presented in the submission (to support the clinical claim of non-inferior effectiveness of LECIG relative to LCIG) to have significant limitations, but on balance agreed with ESC and concluded that the clinical claim was likely reasonable (paragraph 7.7, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting). In March 2024 the PBAC also considered that the claim of non-inferior comparative safety was likely reasonable (paragraph 7.8, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting). The PBAC reaffirmed its March 2024 advice regarding the claim of non-inferior comparative effectiveness and safety.

Economic analysis

4.9 In March 2024, the PBAC noted the cost-minimisation approach (CMA) proposed by the submission was based on steady state dose-adjusted plasma levodopa concentrations observed in the LSM-003 study and assumed one cartridge of LECIG per day was equivalent to one cassette of LCIG per day (i.e. 1:1). At that time, the PBAC agreed with the ESC that the submission’s proposed equi-effective dose of 1:1 was not reasonable, and underestimated use of LECIG cartridges relative to LCIG cassettes. In March 2024, the PBAC noted the impact of the different equi-effective doses (Table 3) on the CMA in the sensitivity analyses presented. The PBAC noted the Pre-Sub-Committee Response (PSCR) argument for using the ELEGANCE trial to inform dose comparison with LCIG, given its larger sample size than Study LSM-003. In March 2024, the PBAC did not accept the equi-effective dosing put forward in the PSCR and agreed with the ESC that this approach may still be an underestimate. At that time, the PBAC considered that, in the context of a claim of non-inferiority supported by clinical evidence with significant limitations, a more conservative approach to calculation of the equi-effective dose was required. However, the PBAC found the submission’s initial equi-effective dose suggestion to lack face validity, and found no reliable basis to arrive at a more accurate view of the equi-effective dose (paragraph 7.9, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).

Table 3 Summary of the equi-effective doses presented

	LECIG dose per day	LCIG dose per day	Source	Comment
Resubmission base case	1.31 cartridges	1.15 cassette	ELEGANCE, GLORIA and Phase III Program.	The LECIG dosing data reflects the average number of cartridges per day at 12 months of treatment.
March 2024 Submission's base case	1.00 cartridge	1.00 cassette	Mean levodopa dose per day from the LSM-003, ELEGANCE, GLORIA, DUOGLOBE studies.	The mean dose does not accurately account for all patients requiring at least one cartridge of LECIG and a proportion requiring a partial second cartridge per day. ^a
March 2024 Evaluation's sensitivity analysis	1.13 cartridges	1.00 cassette	Assuming 50% of patients used one LECIG cartridge (in line with the median levodopa dose in LSM-003) and 50% had the maximum dose reported in LSM-003.	This appropriately represented the proportion of patients using only one cartridge. However, for patients who require more, this might slightly overestimate the amount of levodopa used in the second cartridge and, thus, overestimate the number of LECIG cartridges required per day.
March 2024 Evaluation's sensitivity analysis	1.07 cartridges	1.00 cassette	Assuming normal distribution of levodopa dosing, based on the mean, SD and maximum dose reported in the LSM-003 study.	The normal distribution likely underestimated the levodopa dosing for patients receiving LECIG in the LSM-003 study and, thus, underestimated the number of LECIG cartridges required per day.
March 2024 Evaluation's sensitivity analysis	1.24 cartridges	1.15 cassette ^b	ELEGANCE, GLORIA and Phase III Program.	The LECIG dosing data reflects Day 1 of treatment and levodopa doses are expected to increase once reaching steady state. The March 2024 pre-PBAC response (p2) clarified that the value of 1.24 cartridges per day for LECIG includes patients on infusion times of >18 hrs over the day.
Approach referenced in March 2024 submission	1.50 cartridges	1.00 cassette	Submission's analysis of patients using more than 1 cartridge of LECIG per day	May overestimate LECIG dosing if applied to all patients.

Source: Table 3.1 of the resubmission, Table 10, levodopa with carbidopa and entacapone PSD, March 2024 PBAC meeting.

LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel

Blue shading indicates data previously seen by the PBAC.

^a As LECIG cartridges have a shelf-life of 24 hours once opened, the second LECIG cartridge opened later that day can be used for the next day.

^b Partial LCIG cartridges are the result of weighting the proportion of patients who require one and two cassettes a day of LCIG (not partial cartridges being consumed per day).

4.10 The resubmission proposed the following equi-effective dosing:

- 1.31 cartridge of LECIG (each cartridge contains 47 mL with a total of 940 mg of levodopa)
- 1.15 cassette of LCIG (each cassette contains 100 mL with a total of 2,000 mg of levodopa).

For LECIG this was based on updated dosing data from the ELEGANCE study which reports an average of 1.31 cartridges per day of LECIG at 12 months of treatment (mean observed at baseline [1.22] plus change from baseline at visit 3 [0.09], Table 4). The resubmission stated it was unlikely that patients would need to increase levodopa dose after 12 months of treatment. A source for the updated dosing data from the ELEGANCE study was not provided. The pre-PBAC response provided an interim analysis of the updated dosing data from the ELEGANCE study. The pre-PBAC response argued that the equi-effective dosing from the ELEGANCE interim analysis were supported by other published data and clinical protocols that reported a smaller maintenance dose requirement for LECIG compared to LCIG. For LCIG, the resubmission suggested the use of 1.15 cassettes per day based on the weighted mean number of LCIG cassettes used per day from the GLORIA and Phase III Program. As per Table 3, the March 2024 evaluation had included LCIG dosing of 1.15 cassettes in a sensitivity analysis. Data on the PBS mean and median quantities dispensed per day for LCIG item codes¹ were calculated by the DUSC Secretariat. This was done using a lookback period to the first listing date (May 2011) to identify the first ever initiation for each patient. First initiations after 1 January 2019 were retained (n=491 patients). The total time of supply in days for each patient was calculated as the time between the first date of initiation and the date of the last supply of LCIG. The total PBS quantity supplied over the total time of supply was derived and the average quantity per day was calculated as the total PBS quantity divided by the total time of supply. The mean and median average daily LCIG quantities were 1.6 cassettes and 1.2 cassettes respectively. The mean daily LCIG quantity from the PBS data (1.6 cassettes) is higher than that proposed in the resubmission from trial data (1.15 cassettes). The characteristics of patients included in the PBS data are unknown. It is possible that in clinical practice some patients need higher doses of LCIG than a trial setting (hence the higher mean than median reported) and likely that the same would apply to LECIG.

Table 4 Average daily number of cartridges from ELEGANCE study

Statistic	N	Mean	SD	LCLM	UCLM	p-value
Observed at baseline	163	1.22	0.31	1.17	1.27	-
Change from baseline at visit 2 (3-6-months)	150	0.03	0.24	-0.01	0.07	0.1286
Change from baseline at visit 3 (6-12-months)	72	0.09	0.28	0.02	0.16	0.0084

Source: Table 3.3, the resubmission.

Abbreviations: N: number of patients, SD: standard deviation, LCLM: lower confidence interval, UCLM: upper confidence interval.

- 4.11 As per the March 2024 submission, no additional costs or cost offsets were included in the CMA.
- 4.12 The resubmission requested an ex-manufacturer price for LECIG of \$█, stating that it was based on the equi-effective dose of LECIG and LCIG. The ex-manufacturer price calculated by the resubmission was based on the average dispensed price. The

¹ Item codes: 08970D, 09743T, 09744W, 11910W, 11913B, 11919H.

resubmission calculated this by applying two weights to the dispensed price for maximum quantity (DPMQ) price per cassette: proportion of PBS items with a maximum quantity of 4 (24.1%) and 8 packs (75.9%); and the proportion of each program code for each maximum quantity (4 and 8 packs). Using the published AEMP of LCIG an ex-manufacturer price for LECIG of \$1,442 was calculated using LECIG:LCIG equi-effective doses of 1.31:1.15 (Table 5).

Table 5 Results of the cost-minimisation approach based on the published AEMP of LCIG

Component	LECIG	LCIG
Proposed AEMP/AEMP per pack	\$1,442	\$1,442
Cartridges/cassettes per pack	7	7
Cost per cartridge/cassette	\$206	\$206
Cartridge/cassette used per day	1.31	1.15
Cost per day	\$206	\$206
Difference in cost per day	\$0	

Source: Constructed during the preparation of the Submission Overview.

AEMP = approved ex-manufacturer price; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel.

4.13 In March 2024, the PBAC suggested that a conservative approach could acknowledge that 2 cartridges of LECIG contain 1880 mg levodopa whereas 1 cassette of LCIG contains 2000 mg levodopa, and that addition of entacapone has only a moderate impact on the PK of levodopa, so equi-effective dosing should be much closer to 2 LECIG cartridges: 1 LCIG cassette (paragraph 7.12, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting). The resubmission acknowledged the conservative approach suggested by the PBAC. However, the resubmission also acknowledged that a dosing approach close to 2 LECIG cartridges: 1 LCIG cassette would result in an assumption of 6% reduction of levodopa with LECIG compared to LCIG (from 2,000 mg to 1,880 mg) whereas the LSM-003 study has shown a reduction of 23% (mean levodopa dose per day: LECIG = 875 mg, LCIG = 1,142 mg). An equi-effective dose of 1.31 cartridges of LECIG:1.15 cassettes of LCIG is equivalent to 1.14 cartridges of LECIG:1 cassette of LCIG which is equivalent to a 46% reduction in the levodopa dose and is very different to an equi-effective dose of 2 cartridges of LECIG:1 cassette of LCIG. The impact of use of the published price of LCIG and an equi-effective dose of 2 cartridges of LECIG:1 cassette of LCIG are reported in the sensitivity analysis in Table 6.

Table 6 Sensitivity analysis based on the published AEMP of LCIG

Component	LECIG	LCIG
Proposed AEMP/AEMP per pack	\$1,442	\$1,442
Cartridges/cassettes per pack	7	7
Cost per cartridge/cassette	\$206	\$206
Cartridge/cassette used per day	2	1
Cost per day	\$412	\$206
Difference in cost per day	\$206	

Source: Constructed during the preparation of the Submission Overview.

AEMP = approved ex-manufacturer price; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel.

Estimated PBS usage and financial implications

- 4.14 In March 2024, the PBAC did not accept the financial estimates presented as it did not accept the equi-effective dosing assumptions on which they were based. At that time, the PBAC considered that revised financial estimates based on a more conservative approach to calculation of the equi-effective dose were required (paragraph 7.10, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).
- 4.15 The resubmission presented revised financial estimates using the revised LECIG price of \$| and a substitution rate based on the proposed equi-effective doses of 1.31:1.15 for LECIG and LCIG respectively and reported a cost saving to the PBS/RPBS. The financial estimates reported in Table 7 were updated with an ex-manufacturer price for LECIG of \$| and have returned a net cost of \$0 to < \$10 million in Year 1 increasing to \$0 to < \$10 million in Year 6. The differences occur as the substitution rate means additional scripts for LECIG and hence additional mark-ups. When the CMA is based on DPMQ (as per the resubmission) the financial estimates are close to cost neutral. When the CMA is based on AEMP a net cost to the PBS/RPBS is reported.

Table 7 Estimated use and financial implications

	2024	2025	2026	2027	2028	2029
Projected number of advanced Parkinson’s disease intestinal gel market						
Maximum quantity of 4 (pk) LCIG scripts	- ¹	- ¹	- ⁶	- ⁶	- ⁶	- ⁶
Maximum quantity of 8 (pk) LCIG scripts	- ¹	- ¹	- ¹	- ¹	- ¹	- ¹
Market share of LECIG	%	%	%	%	%	%
Substitution rate (1.31/1.15)	1.1390	1.1390	1.1390	1.1390	1.1390	1.1390
Maximum quantity of 4 (pk) LECIG scripts	¹	¹	¹	¹	¹	¹
Maximum quantity of 8 (pk) LECIG scripts	¹	¹	¹	¹	¹	¹
Estimated financial implications of LECIG						
Maximum quantity of 4 (pk) LECIG scripts costs, less copayments	²	²	³	³	⁴	⁴
Maximum quantity of 8 (pk) LECIG scripts costs, less copayments	²	²	²	²	²	²
Maximum quantity of 4 (pk) LECIG scripts costs, less copayments – revised *	²	²	³	³	⁴	⁴
Maximum quantity of 8 (pk) LECIG scripts costs, less copayments – revised *	²	²	²	²	²	²
Estimated cost savings due to reduction in LCIG scripts						
Maximum quantity of 4 (pk) LCIG scripts cost savings, less copayments	⁵	⁵	⁵	⁵	⁵	⁵
Maximum quantity of 8 (pk) LCIG scripts cost savings, less copayments	⁵	⁵	⁵	⁵	⁵	⁵
Net financial implications to the RPBS/PBS						
Total	⁵	⁵	⁵	²	²	²
Total – revised *	²	²	²	²	²	²

Source: Constructed during the preparation of the submission overview, based on the “LECIGON_BIM Workbook_Early re-entry” excel workbook provided with the resubmission.

DPMQ = dispensed price for maximum quantity; HSD = highly specialised drugs; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel; PBS = Pharmaceutical Benefits Scheme; pk = packs; RPBS = Repatriation Pharmaceutical Benefits Scheme.

* Revised during the preparation of the submission overview based on an ex-manufacturer price for LECIG of \$⁵

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$0 to < \$10 million

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ net cost saving

⁶ 5,000 to < 10,000

4.16 As per the March 2024 submission, the resubmission expected that the listing of LECIG will have no cost implications to the MBS.

Financial Management – Risk Sharing Arrangements

4.17 The resubmission noted that LCIG is currently under a Risk Sharing Arrangement with annual financial caps. The resubmission anticipated that LECIG would be included in the same Risk Sharing Arrangement as LCIG with no increase in the financial caps required.

For more detail on PBAC’s view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the S100 HSD and general schedule listing of levodopa with entacapone and carbidopa intestinal gel (LECIG) for the treatment of advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of LECIG would be acceptable if it were cost-minimised against levodopa, carbidopa monohydrate intestinal gel (LCIG), and if LECIG would be included in the same risk sharing arrangements as LCIG to contain risks associated with the potential use of higher doses of LECIG through the PBS versus trial data or in a broader population given the different device. The PBAC considered that, with the revised equi-effective dose recommended by the Committee (see paragraph 5.8), the resubmission had addressed the substantive outstanding issues identified at the March 2024 PBAC meeting.
- 5.2 With respect to the restriction, the PBAC recommended the PBS indication should be consistent with the LCIG PBS listing and state ‘Advanced Parkinson disease.’ In addition, the PBAC considered that it was appropriate for the clinical criteria to state ‘Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa’. Similar to LCIG PBS listings, the PBAC recommended listing LECIG with 2 different maximum quantities. For patients with daily dose lower or equal to 940 mg of levodopa, the LECIG listing with maximum quantity of 4 packs provides sufficient treatment for 28 days at the average daily dose. While the patients who require more than one cartridge per day (daily dose of levodopa higher than 940 mg), the LECIG listing with maximum quantity of 8 packs would be sufficient for 28 days. The PBAC also noted that one prescription and five repeats would provide for six months’ therapy for patients using average daily dose or higher dose of levodopa.
- 5.3 Consistent with the LCIG PBS listing, the PBAC noted that the initial therapy is intended to be commenced for patients by a hospital-based movement disorder clinic (S100 HSD listings) while maintenance therapy is intended for community dispensing (listings under the general schedule).
- 5.4 The PBAC recalled that in March 2024 the Committee had considered LCIG an appropriate comparator (paragraph 7.4, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).
- 5.5 The PBAC reaffirmed its March 2024 advice that the claim of non-inferior comparative effectiveness was subject to considerable uncertainty, given the nature of the clinical evidence presented in the submission but on balance was prepared to accept the clinical claim (paragraph 6.29, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).

- 5.6 The PBAC reaffirmed its March 2024 advice that the claim of non-inferior comparative safety was likely reasonable (paragraph 6.30, levodopa with carbidopa and entacapone PSD, March 2024 PBAC Meeting).
- 5.7 The PBAC noted the cost-minimisation approach (CMA) proposed by the resubmission assumed 1.31 cartridges of LECIG per day was equal to 1.15 cassettes of LCIG per day (i.e. 1.31:1.15) (see paragraph 4.10). The PBAC noted that for LECIG this was based on updated dosing data from the ELEGANCE study which reported an average of 1.31 cartridges per day of LECIG at 12 months of treatment. For LCIG the 1.15 cassettes per day was based on the weighted mean number of LCIG cassettes used from the GLORIA and Phase III Program. The PBAC noted an equi-effective dose of 1.31 cartridges of LECIG:1.15 cassettes of LCIG (equivalent to 1.14:1) is not substantively different to the March 2024 submission's proposed equi-effective dose of 1:1 which it had previously not accepted (see paragraph 4.9). The PBAC reaffirmed its March 2024 advice that, in the context of a claim of non-inferiority supported by clinical evidence with significant limitations, a conservative approach to the calculation of equi-effective dose was required (see paragraph 4.9). The PBAC did not consider the equi-effective dose proposed in the resubmission conservative.
- 5.8 The PBAC recalled that in March 2024 it had suggested that a conservative approach could acknowledge that 2 cartridges of LECIG contain 1880 mg levodopa whereas 1 cassette of LCIG contains 2000 mg levodopa, and that addition of entacapone has only a moderate impact on the PK of levodopa, so equi-effective dosing should be much closer to 2 LECIG cartridges : 1 LCIG cassette (see paragraph 4.13). The PBAC noted that Study LSM-003 was the only head-to-head study of LECIG to LCIG and also recalled that in March 2024 it helped inform the clinical claim of non-inferior effectiveness (see paragraph 4.5). The PBAC noted that in Study LSM-003 the LECIG dosing was administered at approximately 80% of the optimised LCIG dose (see paragraph 4.7). The PBAC considered it was sufficiently conservative to assume the levodopa dose as part of LECIG would be 80% of that as part of LCIG. As such, the PBAC considered the following equi-effective dosing appropriate for the CMA:
- 1.7 cartridges of LECIG (each cartridge contains 47 mL with a total of 940 mg of levodopa) per day
 - 1.0 cassette of LCIG (each cassette contains 100 mL with a total of 2,000 mg of levodopa) per day.
- 5.9 The PBAC considered the market share approached used to estimate the financial implications of listing LECIG appropriate with the exception of the substitution rate. The PBAC considered the substitution rate should be updated to reflect the equi-effective dosing it deemed appropriate (paragraph 5.8). In addition, the PBAC advised that the financial estimates should be amended to account for the outcomes of the CMA outlined in paragraph 5.8. The PBAC also requested that the Drug Utilisation Sub Committee undertake a utilisation analysis at an appropriate time period to review use of LECIG and LCIG.

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- 5.10 The PBAC noted that LCIG is currently under a Risk Sharing Arrangement with annual financial caps and recommended that LECIG be included in the same arrangement with no increase in the financial caps.
- 5.11 The PBAC recommended that LECIG should not be treated as interchangeable with any drugs.
- 5.12 The PBAC advised that LECIG is suitable for prescribing by nurse practitioners for maintenance therapy.
- 5.13 The PBAC recommended that the Early Supply Rule should not apply.
- 5.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because LECIG 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.
- 5.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands/ Manufacturer
LEVODOPA + CARBIDOPA + ENTACAPONE					
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW (HSD Public) NEW (HSD Private)	4	28	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd
Variant of Restriction Summary 10138/10161 / ToC: 10138/10161: Authority Required: Streamlined					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]				
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)				
	Administrative Advice: Special Pricing Arrangements apply.				
	Severity: Advanced				
	Condition: Parkinson Disease				
	Indication: Advanced Parkinson disease				
	Clinical criteria:				

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	Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.
	AND
	Clinical criteria:
	The treatment must be commenced in a hospital-based movement disorder clinic.
	Administrative advice: Patient 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/ manufacturer
LEVODOPA + CARBIDOPA + ENTACAPONE					
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW (HSD Public) NEW (HSD Private)	8	56	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd
Variant of Restriction Summary 10395/10353 / ToC: 10375/10363: Authority Required: Streamlined					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]				
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)				
	Administrative Advice: Special Pricing Arrangements apply.				
	Severity: Advanced				
	Condition: Parkinson Disease				
	Indication: Advanced Parkinson disease				
	Clinical criteria:				
	Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.				
	AND				
	Clinical criteria:				
	The treatment must be commenced in a hospital-based movement disorder clinic.				
	AND				
	Clinical criteria:				
	Patient must require continuous administration of levodopa without an overnight break; or				
	Patient must require a total daily dose of more than 940 mg of levodopa.				
	Administrative advice: Patient 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/ Manufacturer
LEVODOPA + CARBIDOPA + ENTACAPONE					
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW MP NP	4	28	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

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Variant of Restriction Summary 10091 / ToC: 10197: Authority Required: Streamlined	
Category / Program: GENERAL – General Schedule (Code GE)	
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioner	
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]	
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Severity: Advanced	
Condition: Parkinson Disease	
Indication: Advanced Parkinson disease	
Treatment Phase: Maintenance therapy	
Clinical criteria:	
Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.	
AND	
Clinical criteria:	
Patient must have been commenced on treatment in a hospital-based movement disorder clinic.	
Administrative advice: Patient 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/ Manufacturer
LEVODOPA + CARBIDOPA + ENTACAPONE					
levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW	8	56	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

Variant of Restriction Summary 10374 / ToC: 10386: Authority Required: Streamlined	
Category / Program: General Schedule (Code GE)	
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioner	
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]	
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Severity: Advanced	
Condition: Parkinson Disease	
Indication: Advanced Parkinson disease	
Treatment Phase: Maintenance therapy	
Clinical criteria:	
Patient must have severe disabling motor fluctuations not adequately controlled by at least one of: (i) oral therapy; (ii) intestinal gel formulation containing levodopa.	
AND	
Clinical criteria:	
Patient must have been commenced on treatment in a hospital-based movement disorder clinic	
AND	

	Clinical criteria:
	Patient must require continuous administration of levodopa without an overnight break; or
	Patient must require a total daily dose of more than 940 mg of levodopa
	Administrative advice: Patient should have adequate cognitive function to manage administration with a portable continuous infusion pump.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

7 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.

8 Sponsor's Comment

The sponsor had no comment.

Addendum to the July 2024 PBAC public summary document:

**3.01 LEVODOPA WITH CARBIDOPA AND ENTACAPONE,
Intestinal gel containing levodopa 20 mg with
carbidopa monohydrate 5 mg and with entacapone
20 mg per mL, 47 mL,
Lecigon[®],
STADA PHARMACEUTICALS AUSTRALIA PTY LIMITED**

9 Purpose

- 9.1 Levodopa with carbidopa and entacapone intestinal gel (LECIG cartridges) for the treatment of advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment was recommended at the July 2024 PBAC meeting.
- 9.2 Following the recommendation, the sponsor submitted a proposal for PBAC consideration on 25 September 2024. The proposal outlined an alternative to the equi-effective dosing recommended by the PBAC in July 2024 for LECIG cartridges and its comparator, levodopa with carbidopa intestinal gel (LCIG cassettes). The equi-effective doses proposed were used in a cost-minimisation approach (CMA) to determine a revised price offering for LECIG.

10 Background

Previous PBAC consideration

- 10.1 At the July 2024 PBAC meeting, the PBAC recommended the S100 HSD and general schedule listing of LECIG for the treatment of advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of LECIG would be acceptable if it were cost-minimised against LCIG, and if LECIG would be included in the same risk sharing arrangements as LCIG to contain risks associated with the potential use of higher doses of LECIG through the PBS versus trial data or in a broader population given the different device. The PBAC considered that, with the revised equi-effective dose recommended by the Committee, the resubmission had addressed the substantive outstanding issues identified at the March 2024 PBAC meeting (paragraph 5.1, levodopa with carbidopa and entacapone PBAC Public Summary Document [PSD], July 2024 PBAC Meeting). The revised equi-effective doses recommended by the Committee in July 2024 were:

- 1.7 cartridges of LECIG (each cartridge contains 47 mL with a total of 940 mg of levodopa) per day
- 1.0 cassette of LCIG (each cassette contains 100 mL with a total of 2,000 mg of levodopa) per day (paragraph 5.8, levodopa with carbidopa and entacapone PBAC PSD, July 2024 PBAC Meeting).

11 Consideration of the evidence

11.1 The sponsor proposal provided LECIG pharmacokinetic data, LCIG dosing data and LECIG dosing data to support an alternative equi-effective dose for LECIG:

- **Pharmacokinetic data:** The sponsor acknowledged that Study LCM-003 used mainly a 20% reduction of morning and maintenance infusion doses and but noted that this led to an accumulation in levodopa concentrations throughout the day (Senek, 2017), resulting in an increased risk of dyskinesia. The sponsor noted a pharmacokinetic modelling study by Senek et al (2020) based on plasma levodopa concentrations from the 11 patients in Study LCM-003 concluded a 35% reduction in the continuous maintenance dose results in similar drug exposure as LCIG. The Secretariat noted the TGA approved Product Information for LECIG states LECIG ‘contains entacapone, which enhances the effect of levodopa. It may therefore be necessary to reduce the total daily intake of LECIG by, on average, 20–35% compared to the patient’s previous dose of levodopa and carbidopa without catechol-O-methyl transferase (COMT) inhibitors.’
- **LCIG dosing data:**
 - A DUSC analysis (performed for the July 2024 LECIG PBAC consideration) reported that the mean dose of LCIG 1.6 cassettes with a median of 1.2 cassettes (paragraph 4.10, levodopa with carbidopa and entacapone PBAC PSD, July 2024 PBAC Meeting).
 - A 10% PBS sample data analysis presented to the PBAC in November 2019 reported an LCIG average daily dose of 1.7 cassettes.
- **LECIG dosing data:** Data from overseas market use indicates that LECIG patients on average purchase around 5.6 packs (≅39.2 cartridges) monthly (equivalent to 1.3 cartridges daily).

11.2 The sponsor argued that the potential for wastage should be considered in the derivation of equi-effective dosing. The Secretariat noted the TGA approved Product Information for LCIG states ‘The medicine cassettes are for single use only and should not be administered for longer than 16 hours even if some medicinal product remains.’ In contrast, the sponsor noted the LECIG TGA approved Product Information states ‘Once opened, a cartridge may be used into the next day, i.e. up to 24 hours

after it was first opened. The cartridge is removed from the pump after 24 hours of use or when used up, whichever occurs first.'

Economic analysis

11.3 The sponsor proposed the following approach to establish an equi-effective dose for LECIG:LCIG:

- 1.6 LCIG cassettes (3,200 mg levodopa) supplied per day (DUSC analysis)
- Assume 10% wastage = 2,880 mg (0.9 x 3,200) levodopa delivered to patient for LCIG
- Apply a 35% reduction in levodopa required for LECIG administration = 1,872 mg of levodopa for LECIG (2,880 x 0.65)
- Assume maximum potential for wastage for LECIG of 2 cartridges (i.e. 2 cartridges of 940 mg each = 1,880 mg)
- 1,872 mg levodopa for LECIG = 2,880 mg levodopa for LCIG which, taking into account wastage for LECIG, results in an equi-effective dose of 2 cartridges of LECIG = 1.6 cassettes for LCIG ($\cong 1:0.8$).

11.4 On the basis of the above, the sponsor proposed the following equi-effective dosing:

- 1.0 cartridge of LECIG (each cartridge contains 47 mL with a total of 940 mg of levodopa)
- 0.8 cassette of LCIG (each cassette contains 100 mL with a total of 2,000 mg of levodopa).

11.5 The PBAC noted the following approach assumed 10% wastage for LCIG, no wastage for LECIG and a 20% reduction levodopa required for LECIG administration:

- 1.6 LCIG cassettes (3,200 mg levodopa) supplied per day (DUSC analysis)
- Assume 10% wastage = 2,880 mg levodopa delivered to patient for LCIG
- Apply a 20% reduction in levodopa required for LECIG administration = 2,304 mg of levodopa for LECIG (2,880 x 0.8)
- 2,304 mg levodopa for LECIG = 2,880 mg levodopa for LCIG which results in an equi-effective dose of 2.45 cartridges of LECIG = 1.6 cassettes for LCIG ($\cong 1:0.65$).

11.6 The PBAC noted the approach outlined in paragraph 9.5 resulted in the following equi-effective dosing:

- 1.0 cartridge of LECIG (each cartridge contains 47 mL with a total of 940 mg of levodopa)
- 0.65 cassette of LCIG (each cassette contains 100 mL with a total of 2,000 mg of levodopa).

Table 8 Summary of the equi-effective doses presented

	LECIG dose per day	LCIG dose per day	LECIG:LCIG	Source	Comment
November 2024 PBAC advice	1.0 cartridges	0.65 cassette	1.0:0.65	See paragraph 11.5 for the approach taken.	The approach taken assumes a 20% reduction in levodopa required for LECIG and considers wastage for LCIG.
September 2024 sponsor proposal	1.0 cartridges	0.8 cassette	1.0 : 0.8	See paragraph 11.3 for the approach taken	The approach taken assumes a 35% reduction in levodopa required for LECIG and considers wastage for LCIG and LECIG.
July 2024 resubmission PBAC advice	1.7 cartridges	1.0 cassette	1 : 0.59	See paragraph 5.8 for the approach taken	PBAC recommended equi-effective dose from July 2024 consideration. The approach assumed a 20% reduction and does not consider wastage.
July 2024 Resubmission base case	1.31 cartridges	1.15 cassette	1 : 0.88	ELEGANCE, GLORIA and Phase III Program.	The LECIG dosing data reflects the average number of cartridges per day at 12 months of treatment.
March 2024 Submission's base case	1.00 cartridge	1.00 cassette	1 : 1	Mean levodopa dose per day from the LSM-003, ELEGANCE, GLORIA, DUOGLOBE studies.	The mean dose does not accurately account for all patients requiring at least one cartridge of LECIG and a proportion requiring a partial second cartridge per day. ^a

Source: Table 3, levodopa with carbidopa and entacapone PBAC PSD, July 2024 PBAC meeting, September 2024 sponsor proposal, updated during the preparation of the PBAC minutes

LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel

Blue shading indicates data previously seen by the PBAC.

11.7 The sponsor proposal requested a proposed published ex-manufacturer price for LECIG of \$|, stating that this was 9% lower than the price proposed in the July 2024 resubmission (\$|) (Table 5).

Table 9 Results of the cost-minimisation approach based on the published AEMP of LCIG using equi-effective dosing as per paragraph 9.4.

Component	LECIG	LCIG
Proposed AEMP/AEMP per pack	\$	\$
Cartridges/cassettes per pack	7	7
Cost per cartridge/cassette	\$	\$
Cartridge/cassette used per day	2	1.6
Cost per day	\$	\$
Difference in cost per day		\$0

Source: Table 1, September 2024 sponsor proposal.

AEMP = approved ex-manufacturer price; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel.

11.8 The PBAC noted the results of the cost-minimisation approach based on the published AEMP of LCIG using equi-effective dosing as per paragraph 11.6.

Table 10 Results of the cost-minimisation approach based on the published AEMP of LCIG using equi-effective dosing as per paragraph 9.6

Component	LECIG	LCIG
Proposed AEMP/AEMP per pack	\$	\$
Cartridges/cassettes per pack	7	7
Cost per cartridge/cassette	\$	\$
Cartridge/cassette used per day	2.45	1.6
Cost per day	\$	\$
Difference in cost per day		\$0

Source: Constructed during the preparation of the PBAC minutes

AEMP = approved ex-manufacturer price; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel.

For more detail on PBAC’s view, see section 12 PBAC outcome

12 PBAC Outcome

- 12.1 The PBAC provided further advice in regard to its July 2024 recommendation for the listing of levodopa with carbidopa and entacapone intestinal gel (LECIG cartridges) for the treatment of advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment. While the PBAC did not accept the alternative equi-effective dosing outlined in the sponsor proposal, it did accept revisions to the equi-effective dosing recommended by the Committee in July 2024. As such, the PBAC advised that the cost-effectiveness of LECIG would be acceptable if it were cost-minimised against levodopa, carbidopa monohydrate intestinal gel (LCIG) using the revised equi-effective doses recommended by the Committee (see paragraph 12.3). The PBAC reaffirmed its July 2024 advice that LECIG be included in the same risk sharing arrangements as LCIG to contain risks associated with the potential use of higher doses of LECIG through the PBS versus trial data or in a broader population given the different device.
- 12.2 The PBAC again reaffirmed its March 2024 advice that the claim of non-inferior comparative effectiveness was subject to considerable uncertainty, given the nature of the clinical evidence presented in the submission but on balance was prepared to accept the clinical claim (paragraph 6.2, levodopa with carbidopa and entacapone PBAC PSD, March 2024 PBAC Meeting). In addition, the PBAC again reaffirmed its March 2024 advice that the claim of non-inferior comparative safety was likely reasonable (paragraph 6.30, levodopa with carbidopa and entacapone PBAC PSD, March 2024 PBAC Meeting).
- 12.3 The PBAC noted the sponsor proposal outlining an alternative to the equi-effective dosing recommended by the PBAC in July 2024 for LECIG cartridges and LCIG cassettes. The PBAC noted the approach used to determine the alternative equi-effective doses proposed by the sponsor assumed a 35% reduction in levodopa required for LECIG administration and accounted for wastage of both LECIG and LCIG. The PBAC recalled its March 2024 advice that, in the context of a claim of non-inferiority supported by clinical evidence with significant limitations, a conservative approach to the calculation of equi-effective dose was required (see paragraph 4.9). The PBAC recalled

that in July 2024 it had noted that in Study LSM-003 the LECIG dosing was administered at approximately 80% of the optimised LCIG dose and had advised that it was sufficiently conservative to assume the levodopa dose as part of LECIG would be 80% of that as part of LCIG (see paragraph 5.8). This equates to a 20% reduction in levodopa required for LECIG administration. The PBAC noted the arguments proposed by the sponsor in support of the assumption of a 35% reduction in levodopa required for LECIG administration. However, the PBAC considered a 20% reduction remained appropriate as it addressed the Committees previous concerns regarding the need for a conservative approach to the calculation of equi-effective doses. The PBAC accepted the sponsors proposal to assume 10% wastage for LCIG and, noting the extended cartridge life for LECIG (see paragraph 11.2), considered that wastage considerations were not required for LECIG. As such, the PBAC considered the approach outlined in paragraph 11.5 was appropriate for determining equi-effective doses for LECIG cartridges and LCIG cassettes. The PBAC therefore considered the following revised equi-effective dosing appropriate for the CMA:

- 1.0 cartridge of LECIG (each cartridge contains 47 mL with a total of 940 mg of levodopa)
- 0.65 cassette of LCIG (each cassette contains 100 mL with a total of 2,000 mg of levodopa).

- 12.4 The PBAC re-iterated its previous consideration that the market share approached used to estimate the financial implications of listing LECIG was appropriate with the exception of the substitution rate. The PBAC considered the substitution rate should be updated to reflect the revised equi-effective dosing it deemed appropriate (paragraph 12.3). In addition, the PBAC advised that the financial estimates should be amended to account for the outcomes of the CMA outlined in paragraph 12.3. The PBAC re-iterated its previous consideration that the Drug Utilisation Sub Committee undertake a utilisation analysis at an appropriate time period to review use of LECIG and LCIG (see paragraph 5.9).
- 12.5 The PBAC re-iterated its previous consideration that LECIG be included in the same Risk Sharing Arrangement with LCIG with no increase in the financial caps (see paragraph 5.10).
- 12.6 The PBAC recalled that its July 2024 recommendation was on a cost-minimisation basis and maintained its July 2024 advice that, because LECIG 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.

Outcome:

Advice Provided

13 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.

14 Sponsor's Comment

The sponsor had no comment.