

## 5.13 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<sup>®</sup>, STADA PHARMACEUTICALS AUSTRALIA PTY LIMITED

### 1 Purpose of submission

- 1.1 This Category 2 submission requested Section 100 (Highly Specialised Drugs (HSD) Program) Public and Private Hospital Authority Required and General Schedule Authority Required (STREAMLINED) listings for levodopa/entacapone/carbidopa intestinal gel (LECIG) for the treatment of advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment.
- 1.2 Listing was requested based on a cost-minimisation approach of LECIG 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	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 1.1, p12 of the submission.

### 2 Background

#### **Registration status**

- 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. The TGA Delegate's Overview and the TGA Approval letter were provided in the submission. The TGA Advisory Committee on Medicines (ACM) December 2022 Minutes and associated documents related to the ACM process were provided with the Pre-Sub-Committee Response (PSCR).
- 2.2 In the Delegate's Overview, the TGA Delegate considered that there was evidence to suggest that LECIG may benefit patients with advanced Parkinson's disease. It was considered that the continuous enteral administration may provide a steady level of

levodopa and that the mode of administration will aid to minimise the motor complications that are observed with high systemic levels of levodopa. However, the TGA Delegate also considered that the quality of evidence from Study LSM-003 and the other data presented to the TGA were not sufficient to suggest that, if approved, patients treated with LECIG would experience those benefits. The data provided to the TGA were not considered as supportive of the proposed indication for LECIG (TGA Delegate’s Overview), despite the subsequent market authorization.

2.3 In the Delegate’s Overview, the TGA Delegate’s concerns were:

- Inadequate evidence to support efficacy and safety of LECIG for the proposed indication.
- The PK parameters of LECIG were only assessed in patients on a stable dose of LCIG and not in patients having severe motor fluctuations despite optimised oral alternative pharmacological treatment (proposed indication).
- The proposed dose and administration of LECIG was not well characterised.
- Comparative systemic exposure after enteral and oral administration of entacapone is unknown.
- Stability of LECIG during the proposed 24-hour use was uncertain.

2.4 Some concerns detailed in the TGA Delegate’s overview are consistent with the issues that have also been identified by the evaluation with the PBAC submission. The TGA approval indicates that the concerns were sufficiently addressed between the writing of the TGA Delegate’s Overview and approval. The ESC noted this is consistent with ACM Minutes showing ACM concluded that the product had an overall positive benefit-risk balance in the proposed indication.

2.5 LECIG has also gained approval in several European countries including Switzerland, Germany, and the United Kingdom.

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

### 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

#### 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	№.of Rpts	Available brands
LEVODOPA + CARBIDOPA + ENTACAPONE						
<i>levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges</i>	<i>NEW (HSD Public) NEW (HSD Private)</i>	Published price Private: \$5,816.37 Public: \$5,768.00	4	28	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

Public Summary Document - March 2024 PBAC Meeting

<b>Variant of Restriction Summary 10138/10161 / ToC: 10138/10161: Authority Required: Streamlined</b>	
<b>Concept ID</b>	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Severity:</b> Advanced
	<b>Condition:</b> Advanced Parkinson Disease
	<b>Indication:</b> Advanced Parkinson disease
	<b>Treatment Phase:</b> Initial and Continuing Maintenance therapy
	<b>Clinical criteria:</b>
	Patient must have severe disabling motor fluctuations not adequately controlled by <i>at least one of (i)</i> oral therapy, or <i>(ii)</i> gel formulation containing levodopa
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be commenced in a hospital-based movement disorder clinic.
	<b>AND</b>
	<b>Treatment Clinical criteria:</b>
	<i>Patients must have adequate cognitive function to manage administration with a portable continuous infusion pump.</i>

**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: \$11,584.37 Public: \$11,536.00	8	56	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

<b>Variant of Restriction Summary 10395/10353 / ToC: 10375/10363: Authority Required: Streamlined</b>	
<b>Concept ID</b>	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Severity:</b> Advanced
	<b>Condition:</b> Advanced Parkinson Disease
	<b>Indication:</b> Advanced Parkinson disease
	<b>Treatment Phase:</b> Initial and Continuing Maintenance therapy
	<b>Clinical criteria:</b>
	Patient must have severe disabling motor fluctuations not adequately controlled by <i>at least one of (i)</i> oral therapy, or <i>(ii)</i> gel formulation containing levodopa
	<b>AND</b>
	<b>Clinical criteria:</b>

Public Summary Document - March 2024 PBAC Meeting

	The treatment must be commenced in a hospital-based movement disorder clinic
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Treatment Clinical criteria:</b>
	Patients must 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 \$5,903.09	4	28	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd

**Variant of Restriction Summary 10091 / ToC: 10197: Authority Required: Streamlined**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioner
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Administrative Advice:</b> <b>Shared Care Model:</b> 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.
	<b>Severity:</b> Advanced
	<b>Condition:</b> Advanced Parkinson Disease
	<b>Indication:</b> Advanced Parkinson disease
	<b>Treatment Phase:</b> Continuing Maintenance therapy
	<b>Clinical criteria:</b>
	Patient must have severe disabling motor fluctuations not adequately controlled by <i>at least one of (i) oral therapy, or (ii) gel formulation containing levodopa</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must <del>be</del> have been commenced on treatment in a hospital-based movement disorder clinic
	<b>AND</b>
	<b>Treatment Clinical criteria:</b>
	Patients must 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						

Public Summary Document - March 2024 PBAC Meeting

levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL intestinal gel, 7 x 47 mL cartridges	NEW	Published price \$11,698.13	8	56	5	Lecigon / STADA Pharmaceuticals Australia Pty Ltd
<b>Variant of Restriction Summary 10374 / ToC: 10386: Authority Required: Streamlined</b>						
<b>Concept ID</b>	<b>Category / Program:</b> General Schedule (Code GE)					
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioner					
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]					
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
	<b>Administrative Advice:</b> <b>Shared Care Model:</b> 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.					
	<b>Severity:</b> Advanced					
	<b>Condition:</b> Advanced Parkinson Disease					
	<b>Indication:</b> Advanced Parkinson disease					
	<b>Treatment Phase:</b> Continuing Maintenance therapy					
	<b>Clinical criteria:</b>					
	Patient must have severe disabling motor fluctuations not adequately controlled either by (i) oral therapy, or (ii) gel formulation containing levodopa					
	AND					
	<b>Clinical criteria:</b>					
	Patient must have been commenced on treatment in a hospital-based movement disorder clinic					
	AND					
	<b>Clinical criteria:</b>					
	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					
	AND					
	<b>Treatment Clinical criteria:</b>					
	Patients must have adequate cognitive function to manage administration with a portable continuous infusion pump.					

- 3.2 The submission requested the same public approved ex-manufacturer price (AEMP) as LCIG (\$1,442) and acknowledged that, as LCIG has a Special Pricing Arrangement (SPA), the AEMP of LECIG based on effective prices will be lower. The requested listing provides 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.
- 3.3 To be eligible for the packs of 8 (56-unit listing) patients must require continuous administration of levodopa without an overnight break OR they must require a total daily dose of more than 940 mg of levodopa (each LECIG cartridge contains 940 mg of levodopa). This is consistent with the PBS listing for LCIG which requests that, to be eligible for the packs of 8, patients must require continuous administration of levodopa without an overnight break OR patients need to require a total daily dose of more than 2000 mg of levodopa (each LCIG cassette contains 2000 mg of levodopa).

- 3.4 The requested listing does not fully align with the key trial. In LSM-003, patients must have already been on LCIG and been stable for at least 30 days prior to inclusion in the trial. In contrast, the proposed listing would allow patients who are on oral therapy (with motor fluctuations that are not adequately controlled) to initiate LECIG. The PSCR stated the proposed indication is intended to include patients with advanced disease switching directly from oral combination treatments as well as those who have already received another type of invasive treatment such as LCIG or subcutaneous apomorphine and argued that this was consistent with the final TGA indication. The ESC considered it would be appropriate to amend the clinical criterion 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’.

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

## 4 Population and disease

- 4.1 Parkinson’s disease is a neurodegenerative disorder that affects movement 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 Parkinson’s disease<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 the disease 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>.
- 4.3 The proposed intervention is levodopa/entacapone/carbidopa intestinal gel (LECIG). The initiation of LECIG requires surgery to place a gastrojejunostomy tube (j-tube) through which the intestinal gel is delivered. Once delivered through the j-tube, and absorbed, levodopa can cross the blood-brain barrier. In the brain, levodopa is converted to the active neurotransmitter, dopamine. This acts to increase the concentration of dopamine in the brain and allows it 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>4</sup>.
- 4.4 Levodopa can be metabolised to dopamine peripherally. As dopamine cannot cross the blood-brain barrier, this results in a decreased efficacy of the drug. To address this,

---

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

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

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

<sup>4</sup> Müller, T. (2020). Pharmacokinetics and pharmacodynamics of levodopa/carbidopa cotherapies for Parkinson’s disease. *Expert Opin Drug Metab Toxicol*, 2020. 16(5): p. 403-414.

levodopa is combined with carbidopa and entacapone which both act to inhibit levodopa metabolism until levodopa crosses the blood-brain barrier.

- 4.5 In most patients with early and mid-stage Parkinson's Disease, motor fluctuations and dyskinesia can be adequately managed through an oral levodopa (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. The intestinal gel, LCIG, and the continuous subcutaneous infusion of apomorphine are both subsidised via the PBS, and deep brain stimulation is subsidised via the MBS. LCIG is currently the only levodopa-based DAT for advanced Parkinson's Disease. The pump required for LECIG is smaller and lighter than the pump required for LCIG. A small study found that patients who switch directly from LCIG to LECIG had favourable views on the pumps smaller size, user-friendliness, and the ease of changing the cassette<sup>5</sup>.
- 4.6 The submission's clinical management algorithm positioned LECIG as an alternative to LCIG, as a DAT that can be used in patients whose Parkinson's disease symptoms are not adequately controlled with oral LD. The proposed algorithm is consistent with the current restriction for LCIG. However, it should be noted that the use of DATs in practice can be complicated, and their use is based on patient preference and/or if there are contraindications based on factors such as age, cognitive impairment, or being unable to have a J-tube placed. Additionally, the invasiveness of the different therapies can influence the selection of the DATs<sup>6</sup>.

*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). Like LECIG, the initiation of LCIG requires surgery to place a 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 Parkinson's disease.
- 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 Parkinson's disease who have severe motor fluctuations not adequately controlled by oral therapy.

---

<sup>5</sup> Öthman M, Widman E, Nygren I, Nyholm D. (2021). Initial Experience of the Levodopa-Entacapone-Carbidopa Intestinal Gel in Clinical Practice. *J Pers Med.* 2021 Mar 31;11(4)

<sup>6</sup> Timpka J, Nitu B, Datieva V, Odin P, Antonini A. (2017). Device-Aided Treatment Strategies in Advanced Parkinson's Disease. *Int Rev Neurobiol.* 2017;132:453-74

- 5.3 The ESC considered that the nominated comparator is appropriate as LCIG is currently used to treat the population targeted by the proposed restriction. However, it is unclear what proportion of the eligible population is currently treated with LCIG.
- 5.4 Apomorphine is a device assisted therapy used to treat advanced Parkinson's disease that does not respond to other therapies. The current proposed wording for the LECIG PBS listing does not place LECIG in a later line than apomorphine. As apomorphine is less invasive than LECIG and LCIG, it is expected that patients may prefer to use it in an earlier line than the other DATs. The selection of which DAT to use is complicated and dependent upon patient preference and clinician input.
- 5.5 There may be some use of concomitant LCIG intestinal gel and entacapone tablets. Based on Departmental analysis of PBS data, this is likely to occur in <5% of patients on LCIG intestinal gel, so it is reasonable not to consider this combination of therapies a relevant comparator.
- 5.6 Foslevodopa with foscarnidopa (solution for subcutaneous infusion) was submitted for consideration at the July 2023 PBAC meeting, for use in advanced Parkinson's disease. PBAC Outcomes for that meeting state that the "item is to be considered at a future PBAC meeting". No foslevodopa with foscarnidopa product was on the Australian Register of Therapeutic Goods at the time of PBAC consideration of LECIG.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from an individual (1), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The PBAC noted 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.

### ***Clinical studies***

- 6.3 The 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.
- 6.4 Details of the studies 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
LSM-003 NCT02448914	<p>Clinical Study Report: A Study to Compare Plasma Levels of Levodopa, Carbidopa and Entacapone After TRIGEL or Duodopa® Infusion in PD Patients</p> <p>Senek M, Nielsen EI, Nyholm D. Levodopa-entacapone-carbidopa intestinal gel in Parkinson's disease: A randomized crossover study.</p> <p>Senek M, Nyholm D, Nielsen EI. Population pharmacokinetics of levodopa gel infusion in Parkinson's disease: effects of entacapone infusion and genetic polymorphism.</p>	<p><a href="https://clinicaltrials.gov/show/NCT02448914">https://clinicaltrials.gov/show/NCT02448914</a></p> <p><i>Mov Disord</i> 2017; 32(2): 283-286</p> <p><i>Sci Rep</i> 2020; 10(1): 18057</p>
ELEGANCE* (NCT05043103)	<p>Long-Term Observational Study on Effectiveness and Safety of Lecigon® in Patients With Advanced Parkinson's Disease</p> <p>Chaudhuri K., Poewe W., Ebersbach G., Antonini A. ELEGANCE – Prospective study of levodopa–entacapone–carbidopa intestinal gel (LECIG) in advanced Parkinson's disease.</p> <p>Jost W., Dafsari H., Ebersbach G., Warnecke T. ELEGANCE – A prospective non-interventional study of the long-term effectiveness and safety of levodopa–entacapone–carbidopa intestinal gel (LECIG) in patients with advanced Parkinson's disease in routine care.</p>	<p><a href="https://clinicaltrials.gov/study/NCT05043103">https://clinicaltrials.gov/study/NCT05043103</a></p> <p><i>European Journal of Neurology</i> 2022; 29(439) Supplement 1.</p> <p><i>Clinical Neurophysiology</i> 2022; 137 (e61)</p>
DUOGLOBE	<p>Standaert DG, Aldred J, Anca-Herschkovitsch M, Bourgeois P, Cubo E, Davis TL, Iansek R, Kovács N, Pontieri FE, Siddiqui MS, Simu M, Bergmann L, Kukreja P, Robieson WZ, Chaudhuri KR. DUOGLOBE: One-Year Outcomes in a Real-World Study of Levodopa Carbidopa Intestinal Gel for Parkinson's Disease.</p>	<p><i>Mov Disord Clin Pract</i> 2021; 12;8(7):1061-1074.</p>
GLORIA	<p>Antonini A, Yegin A, Preda C, Bergmann L, Poewe W; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes.</p> <p>Antonini A, Poewe W, Chaudhuri KR, Jech R, Pickut B, Pirtošek Z, Szasz J, Valldeoriola F, Winkler C, Bergmann L, Yegin A, Onuk K, Barch D, Odin P; GLORIA study co-investigators. Levodopa-carbidopa intestinal gel in advanced Parkinson's: Final results of the GLORIA registry.</p>	<p><i>Parkinsonism Relat Disord</i> 2015; 21(3):231-5.</p> <p><i>Parkinsonism Relat Disord</i> 2017; 45:13-20.</p>

Source: Table 2.3, pp53-54, and Table 2.4, p55 of the submission.

\* Interim, unpublished, data was provided from the ELEGANCE trial during the evaluation as “Brittania 2023 Dataonfile”

6.5 The key features of the included evidence are summarised in Table 3 and Table 4.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>LECIG vs LCIG</b>					
LSM-003	11	R, OL, CO 2 days	Low for PK measures High for clinical outcomes	Advanced idiopathic PD currently treated with LCIG	PK TRS

Source: Table 2.6, p63 and Table 2.15, pp69-70 of the submission.

CO = cross-over; LCIG = levodopa/carbidopa intestinal gel; LECIG = levodopa/entacapone/carbidopa intestinal gel; OL = open label; PD = Parkinson's Disease; PK = pharmacokinetics; R = randomised; TRS = treatment response scale.

6.6 LSM-003 was a pharmacokinetic trial designed to examine systemic exposure to the compounds and metabolites of LECIG and LCIG. It was not designed to assess clinical safety or efficacy. Initial (morning) dosing of LECIG in LSM-003 was based on 80% of the individual's baseline levodopa dose (patients were all on LCIG prior to study) for the first 5 patients, then on 90% of the baseline dose for the next 6 patients.

**Table 4: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>LECIG</b>						
ELEGANCE	89	OL, MC, SA, 5 months	High	Advanced PD patients already under treatment with LECIG	"OFF"-time, UPDRS II, NMSS, PDQ-8, PDSS, Safety	Not used
<b>LCIG</b>						
GLORIA	172	OL, MC, SA 12 months	High	Advanced PD with motor fluctuations not adequately controlled by oral medication.	"OFF"-time, UPDRS II, NMSS, PDQ-8, PDSS, Safety	Not used
DUOGLOBE	195	OL, MC, SA 12 months	High	Advanced PD with motor fluctuations not adequately controlled by oral medication.	"OFF"-time, UPDRS II, NMSS, PDQ-8, PDSS, Safety	Not used

Source: Table 2.6, Table 2.7, Table 2.9, p64, Table 2.15, pp69-70 of the submission.

LECIG = levodopa/entacapone/carbidopa intestinal gel; n = number of patients; MC = multi-centre; NMSS = non-motor symptoms scale; OL = open label; PDQ = Parkinson's disease questionnaire; PDSS = Parkinson's disease sleep scale; UPDRS = Movement Disorder Society unified Parkinson's disease rating scale; R = randomised; SA = single arm.

6.7 Although all three trials included in the indirect comparison were designed to have durations in excess of 2 years, only 5 months of data were available for ELEGANCE, and 12-month data cuts were used for GLORIA and DUOGLOBE.

6.8 The outcomes listed above are those that were used in the indirect comparison. Each of the trials had several other Parkinson's disease specific outcomes that were measured.

6.9 The ESC agreed with the evaluation that the open label and single arm design of the studies in Table 4 meant that there was a high risk that bias will have affected the credibility of the outcomes measured. Furthermore, differences between the trials and the incomplete data mean that the indirect comparison has limited value. ELEGANCE required patients to already be using LECIG (for between 1 to 90 days) prior to enrolment while both DUOGLOBE and GLORIA required patients to be naïve to LCIG; the length of follow up in ELEGANCE was only 5 months while the comparator trials used 12-month data cuts; and important patient baseline data, such as previous medications, are absent.

### **Comparative effectiveness**

- 6.10 LSM-003 was a pharmacokinetic study and so the primary outcomes were measures of plasma concentrations of levodopa, carbidopa, and the metabolite, 3-O-methyldopa (3-OMD).
- 6.11 Systemic exposure to levodopa did not differ significantly between treatments (ratio of levodopa [LECIG] to levodopa [LCIG] = 1.10; 95% confidence interval [CI] 0.95, 1.17; P = 0.27). This was despite LECIG being given at a lower dose than the LCIG dose (mean levodopa dose per day: LECIG = 875mg, LCIG = 1,142mg).
- 6.12 The dose-adjusted area under the curve (AUC) 0-14h for levodopa was significantly higher (ratio 1.34; P = 0.00013) with LECIG compared to LCIG.
- 6.13 LSM-003 enrolled patients who were already receiving, and were stable on, LCIG. This may have created positive selection bias with patients being enrolled who were able to tolerate and benefit from levodopa-containing intestinal gels. This would result in the study population not being representative of the entire population specified in the proposed PBS listing and may overrepresent the efficacy of LECIG.

**Table 5: Selected pharmacokinetic parameters for LECIG and LCIG measured for 14 hours after dosing in study LSM-003**

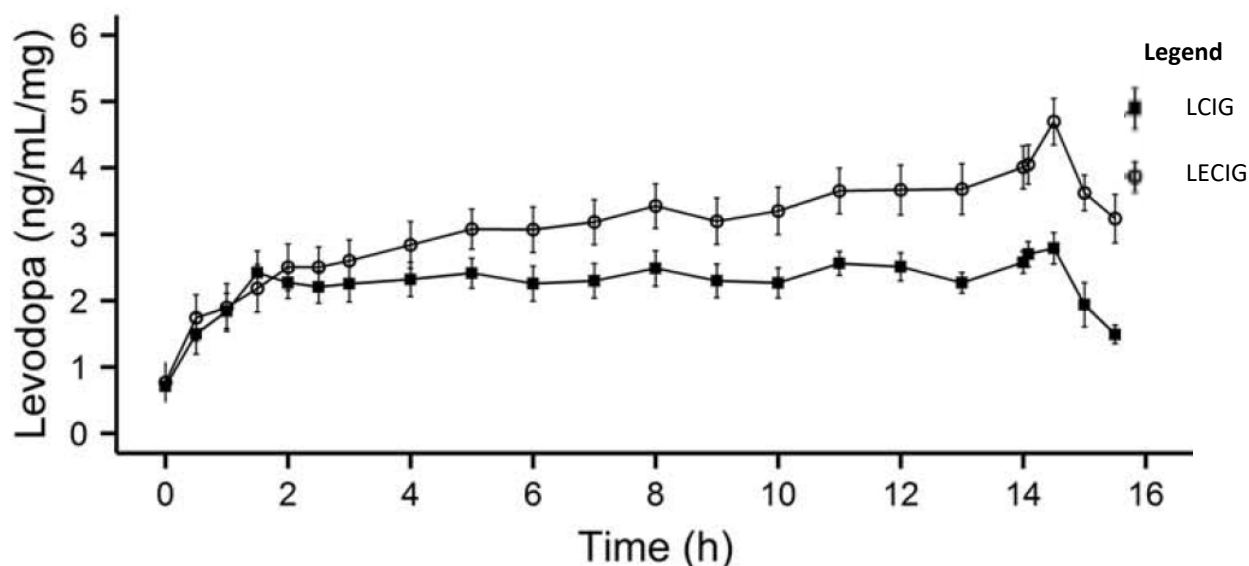
Parameter, mean (SD)	LCIG	LECIG	Ratio (95% CI)	P-value
Levodopa AUC 0–14, ng.h/mL	35,479.1 (14,693.0)	39,016.1 (17,327.6)	1.10 (0.95, 1.17)	0.27
Levodopa AUC 0–14/dose, (ng.h/mL)/mg	31.9 (9.4)	42.7 (14.1)	<b>1.34 (1.19, 1.45)</b>	<b>0.00013</b>

Source: Table 2.16, p71 of the submission.

AUC = area under the curve; CI = confidence interval; LCIG = levodopa/carbidopa intestinal gel; LECIG = levodopa/entacapone/carbidopa intestinal gel; SD = standard deviation.

**Bold = statistically significant difference**

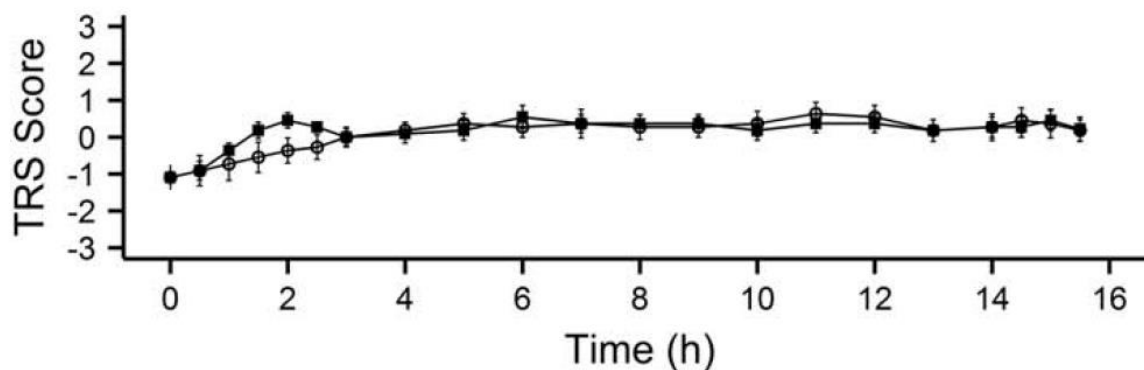
Figure 1: Mean dose-adjusted levodopa plasma concentration



Source: Figure 2-7, p72 of the submission.

LCIG = levodopa/carbidopa intestinal gel; LECIG = levodopa/entacapone/carbidopa intestinal gel.

Figure 2: Mean TRS scores



Source: Figure 2-9, p73 of the submission.

TRS = treatment response scale.

The TRS was a 7-point scale from -3 to +3 where a score of -3 to -2 corresponds to an 'OFF' period, with -3 representing severe parkinsonism, and a score of -1 to +3 corresponds to an 'ON' period, where +2 to +3 is associated with an 'ON' state with severe choreatic dyskinesia. An ideal score ranges from -1 to +1 which corresponds to an 'ON' state without dyskinesia.

6.14 A similar treatment response scale (TRS) score was observed between both study arms (no significant difference in the mean TRS score over 16 hours;  $P=0.84$ ), despite the 10-20% lower dose of LECIG administered during the study (mean levodopa dose per day: LECIG = 875 mg, LCIG = 1,142 mg; median levodopa dose per day: LECIG = 946 mg, LCIG = 1,178 mg). However, it should be noted that LSM-003 was not designed or powered to detect clinical efficacy and the small number of patients (11) and short time frame of the study are unlikely to have captured any differences in efficacy between the study drugs.

6.15 The key efficacy outcomes from the unanchored, unadjusted indirect comparison are presented in Table 6.

**Table 6: Key outcomes of the indirect comparison of LECIG (ELEGANCE) vs LCIG (GLORIA and DUOGLOBE)**

Parameter	ELEGANCE (LECIG) interim data (July 2023, approximately 5 months data)	GLORIA (LCIG) 12-month data	DUOGLOBE (LCIG) 12-month data
Mean ( $\pm$ SD) reduction in daily OFF time from baseline	-4.0 $\pm$ 3.0 hours p<0.0001 (n=64)	-4.7 $\pm$ 3.4 hours p<0.0001 (n=46)	-3.9 $\pm$ 3.6 hours p<0.001 (n=128)
Mean ( $\pm$ SD) reduction in UPDRS II scores (activities of daily living) in ON state	-5.1 $\pm$ 8.2 p=0.0002 (n=42)	-3.1 $\pm$ 8.7 p=0.0107 (n=56)	0.7 $\pm$ 7.7 NS (n=137)
Mean ( $\pm$ SD) total NMSS score decrease (improvement)	-23.6 $\pm$ 38.6 p=0.0110 (n=21)	-22.2 $\pm$ 50.6 p=0.0014 (n=59)	-23.1 $\pm$ 41.4 p<0.001 (n=123)
Mean ( $\pm$ SD) PDQ-8 summary index decrease (improvement)	-5.12* p<0.0001 (n=51)	-8.6 $\pm$ 22.6 p=0.0100 (n=50)	-9.0 $\pm$ 21.6 p<0.001 (n=135)
Mean ( $\pm$ SD) reduction in PDSS-2 scores	-8.4 $\pm$ 10.4 p<0.0001 (n=46)	Not reported	-6.5 $\pm$ 12.2 p<0.001 (n=136)

Source: Table 2.41, p98 of the submission.

LCIG = levodopa/carbidopa intestinal gel; LECIG = levodopa/entacapone/carbidopa intestinal gel; n = number of patients; NMSS = non-motor symptoms scale; PDQ Parkinson's disease questionnaire; PDSS = Parkinson's disease sleep scale; UPDRS = Movement Disorder Society unified Parkinson's disease rating scale; SD = standard deviation.

\* SD not reported.

Notes:

"Off" time is time with uncontrolled Parkinsonism measured in hours. Greater "Off" time is associated with poorly controlled Parkinson disease symptoms.

UPDRS II is a questionnaire measuring motor experiences in daily living and is scored from 0 to 52 with lower scores representing better outcomes.

NMSS is a 30-item rater-based scale to assess a wide range of non-motor symptoms across nine dimensions. Lower scores represent less severe symptoms.

PDQ-8 is a shorted version of the PDQ-39 which take one question from each domain assessed. A higher score signifies a poorer quality of life.

The PDSS-2 is used to quantify the level of sleep disruption experienced by Parkinson disease patients. A high score indicates poorer sleep quality with a total score  $\geq$  18 indicating severe sleep disturbances.

6.16 A comparable reduction in mean daily off time from baseline was observed across all the studies, indicating a benefit to symptoms for patients on both LECIG and LCIG compared to baseline. This was also seen in the comparable improvement in the non-motor symptoms scale. However, some of the outcomes reported large SDs indicating variability in the data.

6.17 Due to the differences between the trials such as different lengths of follow-up and different enrolment criteria, the absence of important background data such as previous therapies, the lack of a common comparator and adjustment for baseline differences between the single arm studies, as well as the non-blinding of subjective

outcome data, the results of this indirect comparison are unreliable and largely uninformative.

### Comparative harms

6.18 Adverse events as reported in LSM-003 are displayed in Table 7.

**Table 7: Summary of key adverse events in trial LSM-003**

Trial ID	LECIG (n=11)	LCIG (n=11)
Total number of patients with at least one AE	6 (55%)	2 (18%)
Total number of patients with at least one AE related to study drug	3 (27%)	1 (9%)
Total number of patients with at least one AE related to study drug pump	0 (0%)	0 (0%)
Total number of patients with at least one AE related to study procedure	3 (27%)	2 (18%)
Total number of patients with at least one SAE	0 (0%)	0 (0%)
Total number of patients with at least one AE leading to discontinuation.	0 (0%)	0 (0%)

Source: Table 21, p80 of the LSM-003 CSR.

AE = adverse event; CSR = clinical study report; LCIG = levodopa/carbidopa intestinal gel; LECIG = levodopa/entacapone/carbidopa intestinal gel; n = number of patients; SAE = serious adverse event.

6.19 Although there were numerically more patients who reported at least one AE while on LECIG, the small number of patients in the trial (11) makes it difficult to quantify the risk of this occurring in the PBS target population. Rare AEs are also unlikely to have been captured. Similarly, although there were no serious AEs reported, the small number of patients and short time frame of the trial makes these data uninformative.

6.20 Additionally, as this trial enrolled patients who were already stable on LCIG, it missed the initiation stage of the intervention, which is when many AEs are observed, including AEs associated with the surgical initiation<sup>7</sup>.

6.21 Key adverse events that could be compared across the trials used in the indirect comparison are shown in Table 8.

**Table 8: Key adverse events of the indirect comparison of LECIG (ELEGANCE) vs LCIG (GLORIA and DUOGLOBE)**

AE description	ELEGANCE (N = 96)	GLORIA (N = 172)	DUOGLOBE (N = 195)
All adverse events	39 (40.6%)	75 (47.2%)	NR
Serious adverse events	22 (22.9%)	37 (23.3%)	79 (40.5)
Drug-related adverse drug reactions	11 (11.5%)	66 (41.5%)	NR
Device-related adverse drug reactions	11 (11.5%)	NR	NR
Dose increased	9 (11%)	4 (2.5%)	NR
Dose interrupted	5 (6%)	14 (8.8%)	NR
Dose reduced	9 (11%)	8 (5.0%)	NR
Drug withdrawn	2 (2.5%)	8 (5.0%)	NR

Source: Table 2.28, Table 2.30, p86, Table 2.31, p87, and Table 2.32 p88 of the submission.

LCIG = levodopa/carbidopa intestinal gel; LECIG = levodopa/entacapone/carbidopa intestinal gel; NR = not reported.

Note: The definitions of the adverse events were not provided for any of the studies in the indirect comparison.

<sup>7</sup> Rus T, Premzl M, Križnar NZ, Kramberger MG, Rajnar R, Ocepek L, et al. (2022). Adverse effects of levodopa/carbidopa intrajejunal gel treatment: A single-center long-term follow-up study. *Acta Neurologica Scandinavica*. 2022;146(5):537-44.

- 6.22 Although the rate of adverse events across ELEGANCE (LECIg), and GLORIA (LCIG) appear similar, it should be noted that data for ELEGANCE was only available for 5 months. Additionally, to be eligible for ELEGANCE patients must have been already undergoing treatment with LECIG for between 1 and 90 days and so there is the potential for AEs associated with the initiation of treatment to be missed.
- 6.23 AEs associated with the devices used in the studies included in the indirect comparison were not adequately reported. GLORIA reported device dislocation in 6 (3.8%) patients and device complications in 3 (1.9%) patients. DUOGLOBE reported device dislocation in 3 (1.5%) patients and device occlusion in 3 (1.5%) patients. The total number of device related AEs was not reported for these trials and the definitions were not provided. Additionally, the definition of Device-related adverse drug reactions was not provided for ELEGANCE. As such a comparison of AEs associated with the pumps was not possible.
- 6.24 As LECIG introduces an additional medicine (entacapone) over LCIG, patients may theoretically experience additional AEs associated with this medication such as diarrhoea or colitis.
- 6.25 After administration of LECIG or LCIG, the J-tube is flushed, delivering additional medication. In study LSM-003 it was noted that the peak concentration was observed after flushing the tube; this may be a challenge for patients who are susceptible to developing dyskinesia with small changes in dose. Given the different effective concentration of levodopa in LECIG and LCIG, there may be differences in the risk of dyskinesia in patients due to the flushing of the J-tube<sup>8</sup>.

### **Benefits/harms**

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

### **Clinical claim**

- 6.27 The submission described LECIG as non-inferior in terms of effectiveness compared to LCIG. The evaluation considered this claim was not adequately supported by the presented evidence. The key issues were:
- The key trial, LSM-003, was a pharmacokinetic trial designed to examine systemic exposure to the compounds and metabolites found in LCIG and LECIG. The trial consisted of 11 patients and was conducted over two days in a cross-over design. As such, LSM-003 was not designed to assess the clinical safety or efficacy of LECIG compared to LCIG.
  - The supporting unanchored, unadjusted indirect comparison did not resolve any of the issues from LSM-003 and was unreliable and uninformative due to

---

<sup>8</sup> Senek M, Nielsen EI, Nyholm D. (2017) Levodopa-entacapone-carbidopa intestinal gel in Parkinson's disease: A randomized crossover study. *Mov Disord.* 2017 Feb;32(2):283-6.

transitivity concerns, such as differences in eligibility criteria, different lengths of follow up, the absence of important patient data, as well as the high risk of bias due to the non-blinded subjective outcome data.

The ESC noted that the PSCR drew attention to the expected relationship between pharmacodynamics and the plasma levels of levodopa. The PSCR also drew attention to the approval of LECIG on this evidence base in multiple European countries, and the overall support from the TGA's ACM that led to registration on the ARTG. The ESC acknowledged the concerns raised by the evaluation but noted the ACM's view that efficacy can be deduced from the pharmacokinetics of levodopa, and that efficacy had strong clinical and pharmacological plausibility. Overall ESC considered the claim of non-inferior effectiveness was likely reasonable.

- 6.28 The submission described LECIG as non-inferior in terms of safety compared to LCIG. The evaluators considered this claim was not adequately supported as the design of study LSM-003 was not meant to examine clinical safety. The evaluation considered the small number of patients, the short time frame, and the fact that patients were already stable on LCIG at enrolment, thus missing AEs associated with the surgical initiation, means that the safety data from LSM-003 do not support the claim of non-inferiority. Additionally, the evaluation considered the safety data from the indirect comparison is unreliable and uninformative due to the differences between patient populations (transitivity concerns), missing data, and the high risk of biased outcome data. The ESC noted the PSCR which drew attention to the ACM's view that safety has been well characterised for oral formulations of dual and triple combination products, and for levodopa and carbidopa in the current intestinal gel product, and the view that safety can be extrapolated to a certain extent. Acknowledging the concerns raised by the evaluation, the ESC considered the claim of non-inferior safety was likely reasonable.
- 6.29 The PBAC considered that the claim of non-inferior comparative effectiveness was subject to considerable uncertainty, given the nature of the clinical evidence presented in the submission. On balance the PBAC was prepared to accept the clinical claim (see Section 7).
- 6.30 The PBAC considered that the claim of non-inferior comparative safety was likely reasonable.

### ***Economic analysis***

- 6.31 The submission presented a cost-minimisation approach (CMA) between LECIG and LCIG for the treatment of advanced Parkinson's Disease.
- 6.32 The key components of the CMA are presented in Table 9.

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

Component	Claim or assumption
Therapeutic claim: effectiveness	Effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Safety is assumed to be non-inferior.
Evidence base	Direct comparison of LECIG vs LCIG in a randomised, cross-over study of 11 patients (LSM-003).
Equi-effective doses	One cartridge of LECIG per day is equivalent to one cassette of LCIG per day.
Direct medicine costs	At the proposed/listed published ex-manufacturer prices, the cost per cartridge of LECIG is equivalent to the cost per cassette of LCIG.
Other costs or cost offsets	None. All other monitoring/initiation costs were assumed to be equal across the two arms.

Source: *Constructed during the evaluation*, based on Table 3.1, p106 and information provided in Section 3, pp106-112 of the submission. LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel.

6.33 The submission proposed the following equi-effective doses:

- One cartridge of LECIG (940 mg of levodopa, 235 mg of carbidopa monohydrate and 940 mg of entacapone) (in 47 mL); and
- One cassette of LCIG (2,000 mg of levodopa and 500 mg of carbidopa monohydrate) (in 100 mL).

This was based on the steady state dose-adjusted plasma levodopa concentrations observed in the LSM-003 study. The low patient numbers (n = 11) and the short observation period (one day) of LSM-003 limited the representativeness and reliability of the dose estimates. The equi-effective doses were derived on the basis that the average dose per day of levodopa for patients taking LECIG (875 mg) and for patients taking LCIG (1,142 mg) did not exceed one cartridge/cassette. The median levodopa dose per day for patients receiving LECIG was 949 mg in Study LSM-003, indicating that more than 50% of patients in the trial required more than one LECIG cartridge per day over the study period; whilst all patients treated with LCIG required only one cassette (maximum levodopa dose for LCIG reported in the trial was 1,532 mg).

6.34 The dose of levodopa per day for LCIG patients was less than the amount in one cassette of LCIG. However, as the LCIG product information (PI) states that LCIG cassettes cannot be used for more than 16 hours, a new cassette is required every day. With respect to LECIG, the PI states that the product may be used for up to 24 hours after opening and hence a second cartridge, opened later during the day, can be used for the following morning.

6.35 As data on the distribution of patients by the dose of levodopa administered was not provided in the LSM-003 clinical study report (CSR), a number of sensitivity analyses were conducted in the evaluation to explore different assumptions underpinning the equi-effective doses (Table 10).

6.36 One approach assumed 50% of patients required one cartridge of LECIG (in line with the median dose in LSM-003) and the other 50% received the maximum dose of levodopa observed in the trial (1,172 mg, equal to 1.25 [1,172/940] cartridges per day). The resulting LECIG cartridge use per day was 1.13 cartridges. The ESC noted this may be an overestimate of the levodopa dose due to assuming 50% received the

maximum dose, however countering this no wastage was assumed. Assuming 50% of patients require 2 cartridges per day rather than 1.25 increased the average number of cartridges of LECIG from 1.13 to 1.5. The ESC noted equi-effective doses of 1.5 LECIG cartridges and 1 LCIG cassette were consistent with those obtained based on the maximum recommended doses (Table 3.2.6, 5.13.COM.98, indicating 3 cartridges of LECIG and 2 cassettes of LCIG would be needed to supply maximum recommended doses) – while recognising that dosing varies considerably from patient to patient and is titrated to clinical effect – and also consistent with a sensitivity analysis referenced in the submission.

- 6.37 Another approach assumed a normal distribution (with mean of 875 mg and standard deviation (SD) of 253 mg, as reported in the LSM-003 trial) of LECIG dosing and that the first cartridge would be used entirely. The weighted number of cartridges used per day with this approximation was calculated to be 1.07. However, this is likely an underestimate, as the normal distribution assumed that 60% of patients would require one cartridge of LECIG whereas the trial-based median levodopa dose (949 mg) suggested that more than 50% of patients required more than one LECIG cartridge in LSM-003. The ESC considered this approach underestimated the levodopa dose and further no wastage for LECIG was included.
- 6.38 The submission further justified its estimated equi-effective doses of LECIG *versus* LCIG (*i.e.* one to one cartridge/cassette) by referencing three single arm studies (the ELEGANCE study for LECIG and the GLORIA and DUOGLOBE studies for LCIG). The mean LECIG levodopa dose from ELEGANCE was 924 mg on Day 1 which suggested that the ‘average’ patient only required one cartridge of LECIG. Data provided with the submission from ELEGANCE indicated that 40% of study patients required more than one cartridge of LECIG per day. Additionally, the study patients were likely to require more LECIG once they reached steady state as Day 1 represented the initial titration period. No LECIG dosing data was provided after Day 1 in the submission. Using the distribution of patients by the number of LECIG cartridges used per day in ELEGANCE (provided by the submission), the weighted number of cartridges used per day was 1.24. The PSCR provided the distribution of patients by the number of LECIG cartridges used per day in ELEGANCE for patients with an average daily infusion duration of  $\leq 18$  hours and the weighted number of cartridges used per day was 1.20. However, the ESC noted the LECIGON PI states ‘If medically justified, LECIGON can be administered up to 24 hours/day’. The PSCR argued that ELEGANCE should be used to inform the equi-effective dose, given the larger sample size in ELEGANCE than in LSM-003. The ESC noted that in the GLORIA study the dose of levodopa administered as LCIG increased from 1,304 mg at Day 1 to 1,350 mg at month 6 and 1,412 mg at month 12, and therefore the levodopa dose administered as LECIG in ELEGANCE was likely underestimated as it was the dose on Day 1.
- 6.39 The submission only provided the mean levodopa dose for LCIG patients from the GLORIA and DUOGLOBE studies. This did not consider the proportion of patients who required more than one cassette of LCIG, which might be significant as LCIG cassettes

cannot be used into the next day. A study was identified during the evaluation which presented the number of patients enrolled in the GLORIA study and in a 12-week Phase III randomised controlled trial (RCT) by their LCIG levodopa dose (categorised as  $\geq 2,000$  mg/day and  $< 2,000$  mg/day). The weighted mean number of LCIG cassettes used per day from both studies was 1.15 cassettes.<sup>9</sup>

- 6.40 A summary of approaches to calculation of equi-effective doses is outlined in Table 10. These have been explored in sensitivity analyses presented in Table 12. It is noted that the submission has acknowledged that some LECIG patients would require more than one cartridge per day (whilst only needing one cassette of LCIG) and has proposed a Risk-Sharing Arrangement (RSA) to address this (see Paragraph 6.57). The ESC advised that the pricing implications of the need for more than one cartridge per day should be addressed through applying appropriate equi-effective doses in CMA.
- 6.41 The ESC noted limited data from LSM-003 were available to inform the equi-effective doses. LSM-003 was a comparative study (using a cross-over design) but had a small sample size, and despite 10-20% lower morning dosing of LECIG than LCIG, there was a dose-adjusted increase in levodopa exposure with LECIG.
- 6.42 Despite concerns about transitivity across the ELEGANCE and GLORIA studies, the ESC noted that an equi-effective dose of 1.24 LECIG cartridges to 1.15 LCIG cassettes was derived from dosing observed in large, single arm studies (as opposed to the small PK study LSM-003). The ESC noted that sensitivity analyses proposed by the evaluator based on LSM-003 resulted in higher equi-effective doses. The ESC considered that equi-effective dose estimates should ideally factor in different shelf-lives after removal from refrigeration (i.e. 16 hours for LCIG, 24 hours for LECIG, meaning some LECIG cartridges can be used the day after being started) – but that equi-effective dosing calculations based on day 1 dosing cannot do this, and there is no straight-forward way of factoring in this difference without dosing information beyond day 1. The ESC noted the preference expressed in the PSCR that ELEGANCE should be used to inform dose comparison, due to sample size considerations – but the ESC was concerned that the equi-effective dose derived from comparison of ELEGANCE and GLORIA (which would produce a 7.3% price reduction) was not reliable. The ESC considered that in this case, and given the clinical claims of non-inferior efficacy and safety against a product already on the PBS, a more conservative approach to calculation of the equi-effective dose was warranted.

---

<sup>9</sup> Zadikoff et al. (2020). Safety of Levodopa-Carbidopa Intestinal Gel Treatment in Patients with Advanced Parkinson's Disease Receiving  $\geq 2000$  mg Daily Dose of Levodopa. *Parkinson's Disease*. 2020/02/13;2020:9716317.

**Table 10: Summary of the equi-effective doses**

	LECIG dose per day	LCIG dose per day	Source	Comment
Submission's base case	One cartridge	One 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. <sup>a</sup>
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.
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.
Evaluation's sensitivity analysis	1.24 cartridges	1.15 cassette <sup>b</sup>	ELEGANCE, GLORIA and Phase III Program.	The LECIG dosing data was reflects Day 1 of treatment and levodopa doses are expected to increase once reaching steady state. The Pre-PBAC response 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 submission	1.5 cartridges	1 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: Constructed during the evaluation, based on information presented in Table 2.14, Table 3.2, Table 3.3 and Table 3.4 of the submission and Table 2 of Zadilkoff et al.<sup>9</sup>

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

<sup>a</sup> 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.

<sup>b</sup> 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).

6.43 No additional costs or cost offsets were included in the CMA as the submission indicated that both pumps (for LECIG and LCIG) would be provided for free by their respective sponsors, that monitoring and initiation costs were aligned and that the two medicines have similar safety profiles. Additionally, the LSM-003 trial did not allow for concomitant therapy containing levodopa, carbidopa or

catechol-O-methyltransferase (COMT) inhibitors and so differences in potential oral entacapone use (which may be administered with LCIG) cannot be assessed.<sup>10</sup>

- 6.44 The submission requested the same public approved ex-manufacturer price (AEMP) as LCIG (\$1,442) and acknowledged that, as LCIG has a Special Pricing Arrangement (SPA), the AEMP of LECIG using effective prices would be lower. As both products are dispensed in packs of seven cartridges/cassettes, the cost per cartridge/cassette is the same (\$206). Results of the CMA on a one-day basis are presented in Table 11.

**Table 11: 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	1
Cost per day	\$206	\$206
Difference in cost per day	\$0	

Source: Constructed during the evaluation, based on the "LECI-GON – cost-minimisation analysis" Excel workbook provided with the submission.

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

- 6.45 The submission's base case CMA shows that there are no net costs associated with LECIG over LCIG. The ESC considered that the submission's proposed equi-effective dose of 1:1 was not reasonable, and underestimated use of LECIG cartridges relative to LCIG cassettes. The ESC noted the impact of the different equi-effective doses outlined in Table 10 on the CMA in the sensitivity analyses presented in Table 12. The ESC noted the PSCR argument that the ELEGANCE trial should be used to inform the equi-effective dose. The ESC remained concerned that this approach may still be an underestimate given the dosing data in the submission and PSCR reflects Day 1 of treatment in the study and the submission has acknowledged that LECIG dosing is likely to increase after Day 1. The pre-PBAC response stated the sponsor was willing to work with the PBAC to define the equi-effective dose of LECIG and LCIG and resulting price discount in which LECIG could be listed without any additional cost to PBS.

---

<sup>10</sup> All Wales Therapeutics & Toxicology Centre. (2023). Levodopa-carbidopa-entacapone (Lecigon®) 20 mg/ml + 5 mg/ml + 20 mg/ml intestinal gel. <https://awttc.nhs.wales/files/appraisals-asar-far/appraisal-report-levodopa-carbidopa-entacapone-lecigon-4871>

**Table 12: Sensitivity analyses of CMA**

Equi-effective doses (per day)	Net cost, using the AEMP for LECIG proposed in the submission (i.e. \$1,442 per pack <sup>a</sup> )		LECIG AEMP per pack <sup>a</sup> required for net \$0	% price reduction, compared with the AEMP proposed in the submission
	Per day	Per year		
<b>Base case: 1.00 LECIG cartridge equivalent to 1.00 LCIG cassette</b>	<b>\$0</b>	<b>\$0</b>	<b>\$1,442</b>	<b>0%</b>
1.13 LECIG cartridges equivalent to 1.00 LCIG cassettes <sup>b</sup>	\$27	\$9,775	\$1,276	-11.5%
1.07 LECIG cartridges equivalent to 1.00 LCIG cassettes <sup>c</sup>	\$14	\$5,263	\$1,348	-6.5%
1.24 LECIG cartridges equivalent to 1.15 LCIG cassettes <sup>d</sup>	\$19	\$6,767	\$1,337	-7.3%
1.50 LECIG cartridges equivalent to 1.00 LCIG cassettes <sup>e</sup>	\$103	\$37,595	\$961	-33.3%

Source: Sensitivity analyses performed during the evaluation.

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

Note: partial cartridges/cassettes per day is permitted for LECIG but not for LCIG.

<sup>a</sup> For both LECIG and LCIG, each pack contains 7 cartridges/cassettes.

<sup>b</sup> Sensitivity analysis performed during the evaluation, by assuming 50% of LECIG patients use one cartridge and 50% use 1.25 cartridges, in line with the median and maximum doses reported in the LSM-003 study.

<sup>c</sup> Sensitivity analysis performed during the evaluation, by assuming a normal distribution of levodopa dosing with mean (875 mg) and SD (253 mg) sourced from the LSM-003 study

<sup>d</sup> Sensitivity analysis performed during the evaluation, based on single arm studies (ELEGANCE, GLORIA and Phase III Program). Partial LCIG cassettes are the result of weighting the distribution of cassette.

<sup>e</sup> Submission proposed this sensitivity analysis.

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

6.46 Using the published price, the drug cost per patient per year of LECIG and LCIG was estimated to be \$75,109. This was based on the proposed equi-effective doses of one LECIG cartridge and one LCIG cassette and this dose-relativity remains uncertain. The drug cost per patient per year are outlined in Table 13.

**Table 13: Drug costs/patient/year**

	LECIG			LCIG		
	LSM-003 Study	CMA	Financial estimates	LSM-003 Study	CMA	Financial estimates
Levodopa dose per day	875 mg <sup>a</sup> (one cartridge)	875 mg (one cartridge) <sup>b</sup>	≤ 940 mg or > 940 mg (one or more than one cartridge) <sup>c</sup>	1,142 mg <sup>a</sup> (one cassette)	1,142 mg (one cassette) <sup>b</sup>	≤ 2,000 mg or > 2,000 mg (one or two cassettes) <sup>c</sup>
Mean duration	1 day	NE	NE	1 day	NE	NE
Cost/patient/day	\$206	\$206 <sup>d</sup>	\$210 for patients requiring ≤ 940 mg of levodopa a day <sup>e</sup> and NE for patients requiring more <sup>f</sup>	\$206	\$206 <sup>d</sup>	\$210 for patients requiring < 2,000 mg of levodopa a day <sup>e</sup> and \$417 for patients requiring > 2,000 mg of levodopa a day <sup>g</sup>
Cost/patient/year	–	\$75,190 <sup>d</sup>	\$76,768 for patients requiring ≤ 940 mg of levodopa a day <sup>e,h</sup> and NE for patients requiring more <sup>f</sup>	–	\$75,190 <sup>d</sup>	\$76,768 for patients requiring < 2,000 mg of levodopa a day <sup>e,h</sup> and \$152,074 for patients requiring > 2,000 mg of levodopa a day <sup>g,i</sup>

Source: Constructed during the evaluation, based on the “LECIGON – cost-minimisation analysis” and the “LECIGON\_BIM Workbook” Excel workbooks provided with the submission.

CMA = cost-minimisation approach; CSR = clinical study report; DPMQ = dispensed price for maximum quantity; HSD = Highly Specialised Drug Program; NE = not estimable; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel; PBS = Pharmaceutical Benefits Scheme.

<sup>a</sup> Mean levodopa dose reported in the LSM-003 study CSR.

<sup>b</sup> The equi-effective doses were estimated based on the mean levodopa doses of LECIG and LCIG in the LSM-003 trial and assumed that all patients would require one LECIG cartridge a day or one LCIG cassette a day.

<sup>c</sup> The submission has proposed separate PBS items for patients who require a levodopa dose of ≤ 940 mg a day (one LECIG cartridge per day) and > 940 mg a day (more than one LECIG cartridge per day). This is in line with the current PBS items for LCIG which are separated based on patients requiring a levodopa dose of ≤ 2,000 mg a day (one LCIG cassette per day) and > 2,000 mg a day (two LCIG cassettes per day).

<sup>d</sup> Based on the proposed/published ex-manufacturer price of LECIG and LCIG of \$1,442 per pack (of seven cartridges/cassettes).

<sup>e</sup> Weighted DPMQ of \$5,885 (which contains 28 cartridges/cassettes). Weighted by the proposed/published DPMQs for HSD private, HSD public and General Schedule PBS items for LECIG and LCIG.

<sup>f</sup> As the second LECIG cartridge opened on a day can be used for the following the day, the number of LECIG scripts per year for patients requiring a dose of > 940 mg of levodopa per day depends on the extent of use of the second cartridge on the first day which was not estimated based on the PBS scripts data provided in the submission.

<sup>g</sup> Two cassettes required per day with a weighted DPMQ of \$11,698 (which contains 56 cartridges/cassettes). Weighted by the published DPMQs for HSD private, HSD public and General Schedule PBS items for LCIG.

<sup>h</sup> Based on the 13 scripts per year. Calculated as 365.25/(4×7) given that the maximum quantity (proposed) was four packs and each pack contains seven cartridge/cassettes, each cartridge/cassette is sufficient for one day treatment.

<sup>i</sup> 13 scripts per year (calculated as 365.25/[8×7]×2), given that the maximum quantity was eight packs and each pack contains seven cassettes, two cassettes are required each day).

### **Estimated PBS usage & financial implications**

6.47 This submission was not considered by DUSC. A market share approach was used to estimate the financial implications of listing LECIG for advanced Parkinson disease from 2023 to 2028. While it was not reasonable to assume 2023 as the first year of listing, the financial impact is not likely to change substantially by assuming 2024 as the starting year as the drug price for LECIG was determined based on a CMA.

6.48 The key data sources and parameter values used in the financial estimates are summarised in Table 14.

Table 14: Key inputs for financial estimates

Parameter		Value/Source	Comment
<b>Number of scripts</b>			
A	Number of LCIG/LECIg scripts	4% growth rate per year for total number of scripts based on 2020-2022 data for LCIG PBS items.	This methodology, based on 2 years of script data, is uncertain. Whilst it is reasonable to assume a decline in the number of maximum quantity of eight (packs) PBS scripts (due to the introduction of other PBS items) <sup>b</sup> , the trend of this reduction is difficult to determine. Additionally, the overall market may grow due to the listing of LECIG as some patients may transition earlier from prior lines of therapy due to LECIG being a more user-friendly delivery system than LCIG. <sup>c</sup>
B	Number of maximum quantity of eight (packs) LCIG/LECIg scripts <sup>a</sup>	14% decline rate per year, based on 2020-2022 data <sup>b</sup> , further justified by the majority of LCIG patients requiring a dose of less than one cassette a day.	
C	Number of maximum quantity of four (packs) LCIG/LECIg scripts <sup>a</sup>	A – B	
<b>Treatment utilisation</b>			
Uptake rate of LECIG		20% in Year 1 increasing to 50% in Year 3.	It is likely that a greater proportion of patients may uptake LECIG over LCIG as a smaller pump size, and a lower infusion volume and levodopa dose is valued by prescribers and consumers. <sup>c</sup>
LECIg script replacement		One script of LCIG is equivalent to one script of LECIG as each script contains the same number of cartridges/cassettes. Based on the equi-effective dose: one cartridge of LECIG is equivalent to one cassette of LCIG.	As raised in the economic analysis section, there are uncertainties regarding this claim. This has a substantial effect on the financial implications.

Source: Constructed during the evaluation, based on the “LECIgON\_BIM Workbook” excel workbook provided with the submission.

LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone intestinal gel; PBS = Pharmaceutical Benefits Scheme.

<sup>a</sup> The submission has requested six PBS items for LECIG for different PBS schedules (HSD private hospital, HSD public hospital and General Schedule) and each of these are separated depending on dose (< 940 mg of levodopa (one LECIG cartridge) a day or > 940 mg of levodopa a day). This was consistent with the six PBS item codes for LCIG which are based on the schedule (HSD private/public hospital or General Schedule) and dose (< 2,000 mg of levodopa (one LCIG cassette) a day or > 2,000 mg of levodopa a day) of LCIG.

<sup>b</sup> Due to new LCIG PBS codes added in 2020 (for one cassette a day LCIG doses) the submission considered PBS script data prior to this date would not be appropriate. *This was reasonable.*

<sup>c</sup> Öthman M, Widman E, Nygren I, Nyholm D (2021). Initial Experience of the Levodopa–Entacapone–Carbidopa Intestinal Gel in Clinical Practice. *Journal of Personalized Medicine*. 11(4):254.

6.49 The submission has assumed separate markets for LECIG/LCIG PBS items relating to a maximum quantity of four packs *versus* eight packs<sup>11</sup>. The submission’s financial analysis assumes that the PBS items with a maximum quantity of four (packs) are for patients who require a levodopa dose of less than 940 mg for LECIG (one cartridge) or less than 2,000 mg for LCIG (one cassette) per day. The PBS items with a maximum quantity of eight (packs) are for patients who require a greater levodopa dose per day. For both LECIG and LCIG, there are one set of three PBS codes for a maximum quantity of four packs (Highly Specialised Drugs Program (HSD) – Private hospital, HSD – Public

<sup>11</sup> For both LECIG and LCIG, each pack contains seven cartridges/cassettes.

hospital, and General Schedule) and another set of three PBS codes for a maximum quantity of 8 packs (for the same PBS schedules).

- 6.50 The growth rate of the total number of scripts (including both maximum quantities) and the rate of decline of the number of scripts with a maximum quantity of eight packs was estimated based on the PBS script data for all six LCIG PBS codes from 2020 to 2022. The submission considered utilisation data prior to 2020 as inappropriate, given new LCIG PBS items (for a maximum quantity of four (packs) scripts) were added in 2020. The evaluation considered this appears reasonable. The submission has assumed only those eligible for LCIG would be eligible for LECIG and hence did not expect any further market growth due to the listing of LECIG. The evaluation considered this may not be reasonable. As the LECIG pump is a more user-friendly deliver system,<sup>12</sup> patients may transition earlier from prior lines of therapy, increasing the total LECIG market size, noting that the insertion of a PEG-J tube is a major decision for clinicians and patients.
- 6.51 The LECIG market share was assumed to be 20% in Year 1, increasing to 50% in Years 3-6. The ESC considered it is likely that a greater proportion of patients may choose LECIG over LCIG as providers and consumers value the smaller pump size, lower infusion volume and levodopa dose associated with LECIG.<sup>12</sup>
- 6.52 Each LECIG script was assumed to be equivalent to a LCIG script (as each pack contains seven cartridges/cassettes and as per the proposed equi-effective doses of one LECIG cartridge *versus* one LCIG cassette). The full dispensed price for maximum quantity (DPMQ) was applied to each script. This assumed the distribution of scripts by PBS schedule (HSD Private, HSD Public and General Schedule) was the same as what was observed for LCIG in 2022, for both a maximum quantity of four scripts and a maximum quantity of eight scripts.
- 6.53 The net financial implications for the RPBS/PBS are presented in Table 15. While the estimated \$0 net cost to PBS/RPBS was consistent with the CMA, the financial analysis did not take into account potential differences in concomitant therapy as noted previously (e.g. oral entacapone use with LCIG).<sup>10</sup> This may change the financial impact.
- 6.54 The submission expected that the listing of LECIG will have no cost implications to the MBS. While this was consistent with the CMA, if the market size increases due LECIG, this would increase the number of initiation surgeries which may have MBS implications.

---

<sup>12</sup> Öthman M, Widman E, Nygren I, Nyholm D (2021). Initial Experience of the Levodopa–Entacapone–Carbidopa Intestinal Gel in Clinical Practice. *Journal of Personalized Medicine*. 11(4):254.

Table 15: Estimated use and financial implications

	2023	2024	2025	2026	2027	2028
<b>Projected number of advanced Parkinson's disease intestinal gel market</b>						
Maximum quantity of four (packs) scripts <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Maximum quantity of eight (packs) scripts <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Market share of LECIG	20%	30%	40%	50%	50%	50%
Maximum quantity of four (packs) LECIG scripts <sup>b</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Maximum quantity of eight (packs) LECIG scripts <sup>c</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Estimated financial implications of LECIG</b>						
Maximum quantity of four (packs) LECIG scripts costs, less copayments <sup>d,e</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Maximum quantity of eight (packs) LECIG scripts costs, less copayments <sup>d,f</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Estimated cost savings due to reduction in LCIG scripts</b>						
Maximum quantity of four (packs) LCIG scripts cost savings, less copayments <sup>d,e</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Maximum quantity of eight (packs) LCIG scripts cost savings, less copayments <sup>d,f</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net financial implications to the RPBS/PBS</b>						
<b>Total</b>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>

Source: Constructed during the evaluation, based on the "LECIGON\_BIM Workbook" excel workbook provided with the submission.

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; RPBS = Repatriation Pharmaceutical Benefits Scheme.

<sup>a</sup> Growth rate/decline rate per year based on average annual growth rate of LCIG utilisation from 2020 – 2022 for all six PBS items: 11910W, 11913B, 11919H (maximum quantity of four (packs) items) and 9744W, 9743 and T8970D (maximum quantity of eight (packs) items). Maximum quantity of four (packs) scripts are for patients who require one cartridge/cassette of LECIG/LCIG a day. Maximum quantity of eight (packs) scripts are for patients who require more than one cartridge/cassette of LECIG/LCIG a day.

<sup>b</sup> Maximum quantity of four (packs) scripts are for patients who require a levodopa dose of < 940 mg a day (i.e. one cartridge of LECIG). There are three different maximum quantity of four PBS items depending on PBS schedule (HSD private hospital, HSD public hospital, and General Schedule). This is aligned with the current LCIG PBS items (11910W, 11913B and 11919H).

<sup>c</sup> Maximum quantity of eight (packs) scripts are for patients who require a levodopa dose of > 940 mg a day (i.e. more than one cartridge of LECIG). There are three different maximum quantity of eight PBS items depending on PBS schedule (HSD private hospital, HSD public hospital, and General Schedule). This is aligned with the current LCIG PBS items (9744W, 9743 and T8970D).

<sup>d</sup> 4% of scripts were related to the RPBS, based on 2022 LCIG utilisation data. Weighted copayments of \$3.46 and \$10.16 were applied to RPBS and PBS scripts, respectively.

<sup>e</sup> The full DPMQs were applied to each script based on the following proportions: 18% HSD private (\$5,816), 2% HSD public (\$5,768) and 80% General Schedule (\$5,903). Based on LCIG utilisation data in 2022.

<sup>f</sup> The full DPMQs were applied to each script based on the following proportions: 10% HSD private (\$11,584), 1% HSD public (\$11,536) and 89% General Schedule (\$11,698). Based on LCIG utilisation data in 2022.

The redacted values correspond to the following ranges:

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

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

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

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

6.55 The submission did not present any sensitivity analyses for the financial estimates. This was not reasonable given uncertainty regarding the equi-effective doses. Sensitivity analyses using the dispensed prices could not be easily tested during the evaluation due to the different mark-ups applied to different PBS items (by dispensing setting and by maximum quantity). Hence the ex-manufacturer price per cartridge/cassette (\$206) and the alternative equi-effective doses (outlined in Table 10) were used to estimate the net financial implications of listing LECIG, see Table 16.

However, the PSCR does confirm the sponsor’s expectation that prices can be aligned after taking into account the additional cartridges needed for LECIG, so that listing should result in zero financial impact to the PBS. If the equi-effective dosing in practice differs from that assumed in the evaluation, there is a risk of financial impact to the PBS as demonstrated in Table 16.

**Table 16: Sensitivity analyses performed during the evaluation of the net financial impact to the RPBS/PBS**

	2023	2024	2025	2026	2027	2028	Total
<b>Base case: 1.00 cartridge of LECIG to 1.00 cassette of LCIG)</b>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
1.13 cartridges of LECIG to 1.00 cassette of LCIG <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>
1.07 cartridges of LECIG to 1.00 cassette of LCIG <sup>b</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
1.24 cartridges of LECIG to 1.15 cassette of LCIG <sup>c</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
1.50 cartridges of LECIG to 1.00 cassette of LCIG <sup>d</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>

Source: Constructed during the evaluation, based on the “LECIGON\_BIM Workbook” excel workbook provided with the submission and Table 10 and Table 12.

AEMP = approved ex-manufacturer price; CMA = cost-minimisation approach; LCIG = levodopa, carbidopa monohydrate intestinal gel; LECIG = levodopa, carbidopa monohydrate and entacapone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Note: equi-effective doses sourced from Table 10 and each cartridge/cassette was assumed to cost \$206 (AEMP per cartridge/cassette). Results indicate net financial implications before dispensing fees and patient copayments.

<sup>a</sup> Assuming 50% of LECIG patients use one cartridge and 50% use 1.25 cartridges, in line with the median and maximum doses reported in the LSM-003 study.

<sup>b</sup> Assuming a normal distribution of levodopa dose with mean (875 mg) and SD (253 mg) sourced from the LSM-003 study

<sup>c</sup> Cartridge use based on single arm studies (ELEGANCE, GLORIA and Phase III Program). Partial LCIG cassettes are the result of weighting the distribution of cassette.

<sup>d</sup> Submission proposed this equi-effective dose as a sensitivity analysis.

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> \$50 million to < \$60 million

## Quality Use of Medicines

6.56 No information was provided in the submission. A pilot study, identified during the evaluation, has reported that patients value LECIG as it is a more user-friendly delivery system than LCIG and prefer the smaller pump size.<sup>12</sup> Additionally, as LECIG cartridges have a smaller volume and have a longer shelf life once opened (24 hours vs 16 hours for LCIG), this may result in less medicine product wastage.

## Financial Management – Risk Sharing Arrangements

6.57 The submission has acknowledged that a certain proportion of LECIG patients would require more than one cartridge per day and this would result in additional costs to the PBS. To address this, the submission has stated that the sponsor is open to an RSA to cover additional costs as a result of listing LECIG on the PBS. As discussed, there is clinical evidence which showed that a non-trivial proportion of patients required more than one cartridge of LECIG per day whilst only needing one cassette of LCIG.

Additionally, the evaluation considered an RSA may reduce the impact of market growth due to patients transitioning earlier from prior lines of therapy for LECIG due to its ease of use (as discussed previously); however, the size of this population is expected to be minimal. The ESC advised that the need for more than one cartridge per day should be addressed through appropriate equi-effective dosing calculations which would flow through to a reduced price per cartridge, for LECIG relative to LCIG. The ESC noted the PSCR stated the sponsor expected to align the price of LECIG and LCIG considering additional cartridge needs for LECIG. The ESC also noted that the PSCR stated the sponsor was aware LCIG is currently subject to an RSA and expects that similar parameters are applied to LECIG.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of levodopa with carbidopa and entacapone, intestinal gel (LECIG), in patients with advanced idiopathic Parkinson disease with severe motor fluctuations despite optimised alternative pharmacological treatment. The PBAC was concerned that limitations in the submission's clinical evidence raised uncertainties about clinical claims of non-inferior efficacy and safety vs LCIG. While, on balance, the PBAC was prepared to accept those clinical claims as reasonable, listing was not recommended because of uncertainty about appropriate equi-effective dosing.
- 7.2 The PBAC considered the primary reason for this outcome was due to the economic evaluation provided.
- 7.3 The PBAC advised that, given PBS listing of levodopa/carbidopa intestinal gel (LCIG) after PBAC recommendation in 2010, there was no clear unmet clinical need for another levodopa-containing intestinal gel formulation, although the use of a smaller infusion pump with LECIG was noted. The PBAC also noted the rationale for addition of a catechol-O-methyltransferase (COMT) inhibitor to LCIG in patients with severe and fluctuating symptoms.
- 7.4 The PBAC accepted the proposed clinical place of LECIG as an alternative to LCIG, and considered LCIG an appropriate comparator.
- 7.5 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. 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 (see paragraph 6.14). 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. 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.

- 7.6 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.
- 7.7 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 (see paragraph 6.27) and concluded that the clinical claim was likely reasonable.
- 7.8 Given the short study duration and small sample size in Study LSM-003, the PBAC acknowledged that the safety outcomes were difficult to interpret (see paragraph 6.28). However, the PBAC agreed with the ESC that the claim of non-inferior comparative safety was likely reasonable.
- 7.9 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) (see paragraph 6.33). 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 (see paragraph 6.45). The PBAC noted the impact of the different equi-effective doses outlined in Table 10 on the CMA in the sensitivity analyses presented in Table 12. The PBAC noted the PSCR argument for using the ELEGANCE trial to inform dose comparison with LCIG, given its larger sample size than Study LSM-003. 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 (see paragraph 6.42). The PBAC noted the pre-PBAC response indicated the sponsor was willing to work with the PBAC to define the equi-effective dose. 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.
- 7.10 The PBAC did not accept the financial estimates presented in Table 15 as it did not accept the equi-effective dosing assumptions on which they were based. The PBAC noted the impact on the financial estimates of variations in the equi-effective dosing

utilised (Table 16). The PBAC considered that revised financial estimates based on a more conservative approach to calculation of the equi-effective dose were required.

- 7.11 The PBAC noted the sponsor's willingness to negotiate participation in a RSA and agreed that this would be a necessary step if the PBAC recommended listing of LECIG after any re-submission.
- 7.12 The PBAC considered that the outstanding issues could be resolved in a simple resubmission for LECIG using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- 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 (see paragraph 6.12), so equi-effective dosing should be much closer to 2 LECIG cartridges: 1 LCIG cassette.
  - Recalculation of the financial implications using the revised LECIG price.
  - Proposal of a risk-share arrangement that sufficiently mitigates financial risk to the PBS of any utilisation of LECIG cartridges beyond that estimated in the re-submission base-case.
- 7.13 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.
- 7.14 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**

STADA Pharmaceuticals Australia Pty Ltd appreciates the opportunity to resubmit via the early re-entry pathway and is committed to working with the PBAC to bring levodopa with carbidopa and entacapone intestinal gel (LECIG), to Australian patients with advanced Parkinson disease, in a timely manner.