CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

LEVODOPA/CARBIDOPA (DUODOPA)

(ABBVIE CORPORATION)

Indication: For the treatment of patients with advanced levodopa-responsive Parkinson's disease:

- who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of Parkinson's medicinal products, and
- for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	September 2018
Report Length:	20 Pages

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

CADTH

Abbreviations

aPD	advanced Parkinson disease
CDR	CADTH Common Drug Review
DBS	deep brain stimulation
HQO	Health Quality Ontario
HTA	health technology assessment
ICUR	incremental cost-utility ratio
LCIG	levodopa/carbidopa intestinal gel
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Parkinson disease
PEG-J	percutaneous endoscopic gastrostomy-jejunostomy
SOC	standard of care

Drug	Levodopa/Carbidopa (Duodopa)
Indication	For treatment of patients with advanced levodopa-responsive Parkinson's disease: • who do not have satisfactory control of motor fluctuations and hyper-/dyskinesia despite optimized treatment with oral therapy, and • for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration
Reimbursement Request	As per indication
Dosage Form	100 mL of gel contains 2,000 mg levodopa and 500 mg carbidopa (monohydrate)
NOC Date	1/3/2007
Manufacturer	AbbVie Corporation

Executive Summary

Background

Levodopa/carbidopa intestinal gel (Duodopa) (LCIG) is indicated for the treatment of patients with advanced levodopa-responsive Parkinson disease (PD) who do not have satisfactory control of motor fluctuations and hyper-/dyskinesia despite optimized treatment with oral therapy and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration (and who meet certain other criteria).[1] LCIG is available as a hard plastic cassette containing 100 mL of gel with 2,000 mg of levodopa and 500 mg carbidopa.[1] It is administered by infusion into the duodenum (or upper jejunum) through a permanent PEG-J tube, allowing for continuous and easily revisable dosing for patients. LCIG has a conversion from oral form at an approximately 1:1 ratio. The total dose is administered over approximately 16 hours and categorized by three individualized dosing stages: morning bolus, continuous maintenance, and extra bolus dose (if clinically indicated).[1]

At the manufacturer's marketed price of $166.00 per cassette, the annual cost is $60,590 based on a dose of one cassette per day.[1,2]

LCIG was previously reviewed by CADTH Common Drug Review (CDR) in July 2009. At that time, LCIG was indicated and reviewed for treatment of advanced Parkinson disease (aPD) in which satisfactory control of severe, disabling motor fluctuations and hyperkinesia or dyskinesia cannot be achieved with available combinations of PD medicinal products. The CADTH Canadian Expert Drug Advisory Committee (CEDAC) recommended that LCIG not be listed given the potentially high and uncertain incremental cost-utility ratio (ICUR) and the quality of the clinical evidence.[3]

As part of the 2009 submission, the manufacturer at that time (Solvay Pharma Inc.) provided a cost-utility analysis (CUA) comparing LCIG with standard of care (SOC) over a five-year period. The manufacturer requested redaction of its ICUR in the recommendation, and at that time, CDR reports were not published. As such, no information on the cost-

effectiveness from this submission is available in the public domain. The request to redact information was made prior to changes in the CDR procedure to improve transparency. The CDR appraisal noted that the primary source of uncertainty with the CUA was associated with the choice of clinical data inputs, which notably influenced the range of ICURs. The quality and effectiveness of the considered trials were uncertain due to the open-label design, high number of patient withdrawals (due to small sample size), and the patient population not being representative of those who would most likely use LCIG. CDR also highlighted the discrepancy in the daily cost of treatment between LCIG ($166 per patient per day) and oral forms of carbidopa/levodopa (less than $3 per patient per day).[3]

Approach to the Review

This review was undertaken at the request of the public drug plans participating in the CDR process, which indicated that new evidence was available to support the clinical effectiveness of levodopa/carbidopa in the treatment of PD. CDR was asked to review LCIG as per the Health Canada indication, focusing on new clinical efficacy and safety data.

The manufacturer of LCIG was invited to submit clinical and/or economic information, but was not obligated to do so. The manufacturer provided some relevant information, including previously published literature on clinical studies of LCIG, a clinical study report, and pricing information; it did not provide an economic model to support this review.

Since no economic evaluation or model was submitted, this CDR Pharmacoeconomic Report focuses on an appraisal of published literature assessing the cost-effectiveness of LCIG in patients with aPD compared with SOC therapies (including apomorphine injections) and deep drain stimulation (DBS), with a focus on the new clinical evidence in which the participating plans expressed interest for this review.

New Clinical Information Since Initial Submission

The CDR clinical review identified 20 studies from a systematic literature review that fulfilled the clinical inclusion criteria. The CDR Clinical Report focused on two of these studies in the main body of the report. A further 16 single-arm observational studies identified were not fully reported in the CDR Clinical Report due to small sample sizes and broad follow-up periods (four to 36 months). Two additional studies were summarized in the appendices. Of the four studies assessed in the CDR Clinical Report, one was a new randomized controlled trial (RCT) (Study 001/002) that had been published since the initial LCIG submission in 2009; another was an open-label extension trial (Study 003) enrolling patients from Study 001/002; the third was an open-label, non-comparative, long-term safety study (Study 004) with patients who were neither enrolled in Study 001/002 nor previously treated with LCIG via PEG-J tube; and the fourth was an open-label, long-term extension study (Study 005) with patients who had participated in Study 001/002 and one of its safety extensions, Study 003 or Study 004.

Study 001/002 was a double-blind (DB), double-dummy, multi-centre, multinational, phase III superiority RCT comparing LCIG with immediate-release (IR) oral levodopa/carbidopa (OLC) capsules in patients with aPD having suboptimal response to current combination therapy. The CDR clinical review noted concerns of unblinding in Study 001/002 due to lower treatment compliance in the placebo group, leading to over-reporting of subjective outcomes, which may affect the overall treatment impressions. The study was relatively

short in duration (12 weeks) considering that PD therapies have a lifetime duration and overall outcomes may not be apparent until considerably later.

The CDR clinical review reported that Study 001/002 addressed the limitations of the two trials considered in the 2009 reimbursement recommendation. In Study 001/002, LCIG was considered clinically meaningful and statistically significant in reducing patients' "off" time at week 12 compared with IR OLC capsules, and was associated with significant improvement in the amount of "on" time without troublesome dyskinesia at week 12. The Unified Parkinson's Disease Rating Scale (UPDRS) Part II and the 39-Item Parkinson's Disease Questionnaire (PDQ-39) summary index score assessed PD symptoms at week 12 with statistically significant and clinically meaningful improvements in favour of LCIG.

Study 004 was an open-label, multinational, multi-centre, long-term safety study in which treatment-naive patients were administered LCIG with optimized dosing based on the their prior PD treatment before randomization in the DB study. The study evaluated the long-term safety of LCIG based on the frequency of reported adverse events (AEs) and device-related complications. Study 004 concluded with similar results to Study 001/002, with LCIG reducing the amount of "off" time for patients and increasing the amount of "on" time without troublesome dyskinesia. The key limitations of Study 004 identified by the CDR clinical review were the open-label and non-comparative nature of the study design.

The open-label extension study (Study 003) evaluated the long-term safety, efficacy, and quality of life (QoL) in patients with aPD who were enrolled in Study 001/002 and received LCIG over a 52-week period. It revealed no new safety signals after the PEG-J procedure and one year of treatment with LCIG, but the majority of patients did experience AEs relating to the PEG-J tube and its insertion. Moreover, Study 005, an ongoing long-term safety extension study, revealed no new safety signals related to patients maintaining treatment effect over the subsequent trials and through Study 005.

No comparative information was given in the outlined clinical studies (Study 001/002 and Study 004) for LCIG versus DBS. See the CDR clinical report for additional information on the clinical efficacy of LCIG.

Summary of the Published Economic Information

CDR undertook a review of published recommendations from Health Technology Assessment (HTA) agencies as well as a review of published economic evaluations based on the use of LCIG in patients with aPD who are suboptimally treated with current SOC therapies.

Health Technology Assessment Findings

CDR undertook a search of relevant HTA agency websites and grey literature to identify relevant HTA reviews that had been undertaken on LCIG for patients with aPD. The search identified six reviews undertaken by two HTA agencies.

In Australia, LCIG was reviewed by the Pharmaceutical Benefits Advisory Committee (PBAC) [4-6] three times between March 2008 and November 2010. It was initially rejected for reimbursement twice due to a high and uncertain incremental cost-effectiveness ratio and uncertainty in the clinical data. PBAC also requested that the manufacturer consider DBS as an appropriate comparator. In 2010, LCIG was listed for reimbursement under the High Specialized Drug Program (HSDP) for patients who are not adequately controlled by oral

therapy. PBAC considered a naive comparison of LCIG with DBS, but it was not well reported how DBS was considered in the economic model. PBAC did not consider information from Study 001/002 or Study 003 as part of its recommendation to list.

The Scottish Medicines Consortium (SMC)[7-9] also reviewed LCIG three times between September 2006 and November 2016. It was initially rejected twice due to insufficient clinical data, the lack of a robust economic evaluation, and a high ICUR. However, LCIG received a recommendation to list in 2016 for patients with aPD who are not eligible for DBS. SMC considered the results of Study 001/002, Study 003, and Study 004 in the 2015 and 2016 submissions, but did not appear to consider Study 005 in either appraisal. Both appraisals commented on the limitations of Study 004, with clinical data being used and included in the economic evaluation.

Additional details on these HTA reviews are provided in Appendix 4.

Findings From the Published Literature

CDR undertook a systematic review of published economic literature based on the methods identified in Appendix 2. The search identified 155 citations, of which 15 met the criteria for full text review. After full text review, two articles were identified and summarized in Appendix 3: Lowin et al. (2011) and Lowin et al. (2017). No Canadian studies were identified from the literature search; therefore, international economic evaluations that met the inclusion criteria were appraised.

Lowin et al. (2011)[10] evaluated the cost-effectiveness of LCIG compared with SOC (incorporating both oral therapies and DBS) in patients with aPD in the UK; and Lowin et al. (2017)[11] assessed LCIG and SOC (including continuous subcutaneous apomorphine injection [CSAI]) for patients with aPD with an Irish payer perspective. Lowin et al. (2011) appeared to be based on the open-label clinical trial previously assessed in the 2009 CDR submission for LCIG; the 2017 publication by Lowin et al. (2017) appeared to be based on data from a new, open-label, 54-week safety and efficacy study that had not been appraised by CDR until this review.[3,12] Both articles by Lowin et al. assessed the cost-effectiveness of LCIG versus SOC based on a local public payer perspective, not a Canadian public payer perspective. Neither published economic evaluation addressed the cost-effectiveness of LCIG compared with DBS. Lowin et al. (2017) noted that DBS was not considered the most relevant comparator due to differences in the patient groups being treated with LCIG (i.e., DBS was not recommended for patients over the age of 70 years, while LCIG patients in the studies are treated up to an older age) and the lack of direct comparative evidence for LCIG compared with DBS.[11]

Lowin et al. (2017) incorporated data from Study 004 that was assessed in the CDR clinical review. Study 004 had several limitations, including the one-arm, uncontrolled nature of the study, the open-label trial design, and patients continuing prior PD treatment during the study period. There is a lack of clarity as to how the data from Study 004 were used in the Lowin et al. (2017) and SMC models, whether previous modelling concerns have been addressed since the 2009 CDR recommendations, and what the resulting cost-effectiveness in Canada would be.

Issues for Consideration

Deep brain stimulation: Feedback from the CDR-participating drug plans and the clinical expert consulted by CDR indicated that DBS is a relevant comparator for a cohort of patients with aPD who would be eligible for LCIG as well. Two reports in Canada have outlined the costs of DBS with similarities and differences in pre-, intra-, and post-operative costs. Health Quality Ontario (HQO) (2005)[13] reported a total cost ranging from C$24,420 to $28,420 (C$30,000 to $35,000 in 2018 dollars)[14] per patient from an Ontario perspective. A more recent thesis by Ng (2013)[15] from the Institute of Health Policy, Management and Evaluation calculated an overall cost of approximately C$25,428 (C$27,000 in 2018 dollars),[14] which was also reported from an Ontario perspective. No subsequent publications were associated with either report.

Treatment wastage: LCIG requires proper storage and patient accessibility to centres for the initial PEG-J tube procedure. As indicated in the product monograph,[1] the intestinal gel must be stored in a refrigerator and protected from light. Furthermore, once the cassette is taken out of the refrigerator, it must be used within 16 hours or discarded.

The clinical expert noted that the majority of patients take approximately 1,000 mg of LCIG per day. The product monograph states that the cassette is to be discarded after 16 hours; this results in approximately half of the cassette being discarded per day. This finding was consistent with the clinical trial results in the CDR clinical report. Further consideration is needed with regard to patient accessibility to treatment centres in rural or remote areas for the insertion of the PEG-J tube, pump, and any complications that may arise from the procedures. For patients who require a second LCIG cassette per day, the annual cost of LCIG could increase to approximately $120,000 per patient.

Conclusions

The economic evaluations identified as part of the review were not based on the clinical trials that form the basis of the current clinical review, as requested by participating public drug plans. Although the recent appraisals of LCIG by SMC considered data from Study 001/002 and Study 003, the economic evaluation was not based on these studies.

CDR did not identify any appropriate head-to-head or indirect comparisons assessing the comparative clinical efficacy of LCIG and DBS, although there is some question as to whether the same patient populations are likely to receive treatment with LCIG or DBS.

At the manufacturer's current marketed price of $166 per cassette of LCIG,[2] the daily drug cost is $166, resulting in an annual drug acquisition cost of approximately $61,000 (assuming a dose of one cassette per day). Additional costs may be attributable to the initial PEG-J tube insertion procedure along with physician consultations or medical testing requirements. The acquisition cost of LCIG over a one-year period appears to be greater than the procedural costs of DBS, ranging from C$27,000 to $35,000 (in 2018 dollars) while excluding other cost considerations. Costs may differ between jurisdictions when comparing DBS and LCIG. If additional costs were considered for both treatments, the magnitude of the difference in total costs between treatments may vary.

Appendix 1: Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. As deep brain stimulation was also determined to be a relevant comparator for levodopa/carbidopa intestinal gel, a summary of costs can be found in Table 1. Drug costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 1: Cost Comparison of Treatments for Advanced Parkinson Disease

Drug	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Levodopa/ Carbidopa (Duodopa)	1 mL (20 mg levodopa/ 5 mg carbidopa)	Intestinal gel (100 mL cassette)	1,162.0000 [a]	1 carton (7 per cassette)	166.00	60,590
Dopamine Agonists						
Apomorphine (Movapo)	10 mg/mL	3 mL pen	42.9520 [b]	0.2 mL to 0.6 mL pre “off” episode, maximum 2 mL daily	4.30 to 21.48	7,839 to 10,452
Oral Levodopa/Decarboxylase Inhibitor Combinations						
Levodopa/ carbidopa (generics)	100 mg/10 mg 100 mg/25 mg 250 mg/25 mg	Tablet	0.1479 0.2209 0.2466	300 mg to 1,500 mg of levodopa in three to four daily doses	0.44 to 1.48	162 to 540
	100 mg/25 mg 200 mg/50 mg	Controlled release tablet	0.3857 0.7115	200 mg to 1,600 mg of levodopa in two to four daily doses	0.77 to 5.69	282 to 2,078
Levodopa/ benserazide (Prolopa)	50 mg/12.5 mg 100 mg/25 mg 200 mg/50 mg	Capsule Capsule Capsule	0.2998 0.4936 0.8286	400 mg to 800 mg of levodopa daily in four to six doses	1.97 to 3.31	721 to 1,210
COMT Inhibitors						
Entacapone (generics)	200 mg	Tablet	0.4010	200 mg to 1,600 mg daily in multiple doses	0.40 to 3.21	146 to 1,171
Levodopa/ carbidopa/ entacapone (Stalevo)	50 mg/12.5 mg/200 mg 75 mg/18.75 mg/200 mg 100 mg/25 mg/200 mg 150 mg/37.5 mg/200 mg	Tablet	1.7371	600 mg to1600 mg of entacapone daily in multiple doses	5.21 to 13.90	1,902 to 5,072
Non-Ergolinic Dopamine Agonists						
Rotigotine (Neupro)	2 mg/24 h 4 mg/24 h 6 mg/24 h 8 mg/24 h	Patch	3.5400 6.5000 7.2702 7.2700 [c]	2 mg to16 mg daily	3.54 to 14.54	1,292 to 5,307

Drug	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Pramipexole (generics)	0.25 mg 0.50 mg 1 mg 1.5 mg	Tablet	0.2628 0.5257[c] 0.5257 0.5257	1.5 mg to 4.5 mg in three equal doses	0.79[e] to 2.37	288 to 864
Ropinirole (generics)	0.25 mg 1 mg 2 mg 5 mg	Tablet	0.0710 0.2838 0.3122 0.8596	3 mg to 24 mg in three equal doses	0.85 to 3.75	310 to 1,369
Ergolinic Dopamine Agonists						
Bromocriptine (Generics)	2.5 mg 5 mg	tablet capsule	0.9978 1.4937	2.5 mg to 40 mg daily in two to three doses	1.00 to 11.95	364 to 4,362
MAO-B Inhibitors						
Rasagiline (Azilect)	0.5 mg 1 mg	tablet tablet	6.1285	0.5 mg to 1 mg daily	6.13	2,237
Selegiline (generics)	5 mg	tablet	0.5021	5 mg twice daily	1.00	367

COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase type B.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed March 2018), unless otherwise indicated, and do not include dispensing fees.

Note: DBS costs can be found in Appendix 4 along with a breakdown of costs determined by each report.

[a] Manufacturer's submitted price.[1,2]

[b] Manufacturer's submitted price;[16] assumes excess medication disposed of after 48 hours. Assumes at least one dose required every 48 hours.

[c] Saskatchewan formulary (March 2018).[17]

Appendix 2: Deep Brain Stimulation Reported Costs

Health Quality Ontario (HQO) (2005)[13] and Ng (2013)[15] have both reported costs associated with deep brain stimulation (DBS) treatment in Ontario. Costs are categorized into pre-, intra-, and post-operative costs for each report, with approximate overall costs reported. Fee-for-service codes from the Ontario Health Insurance Plan Schedule of Benefits and Fees were identified in each report. The total DBS cost for each report was converted to current pricing using the Bank of Canada's current inflation rate.[14]

Both estimates consider similar Ontario Health and Benefits fees regarding physician visits, assessments, and surgeries; however, there were some discrepancies between reports regarding additional assessments and operational costs. Differences in cost may vary across provinces. Based on clinical evidence from the HQO (2005) report, DBS is effective in the control of advanced Parkinson disease (aPD) symptoms for at least five years by improving motor function control, reducing the amount of "off" time spent during the waking day, and reducing medication intake. Ng (2013) reported from other publications that DBS demonstrated improvements in motor functions and reduction in medication that may be sustainable for five to 10 years.[15] Both reports indicate that the DBS device battery needs to be replaced every five years, but did not consider the additional costs of the replacement, including surgery, new battery, and physician consultations.

Table 2: Deep Brain Stimulation Reported Costs

HQO (2005)	Ng (2013)
Preoperative Costs	
• Neuropsychological assessment phase: • Specific neurocognitive assessment (FSC A185): $128 **Total expected preoperative reimbursement costs: $128**	• Neuropsychological assessment phase: • Special surgical consultation (FSC A935): $163.2 • New neurology consultation(FSC A185): $179.90 • General plastic surgery consultation (FSC A085): $123.50 • General psychiatry consultation (FSC A195): $203.40 • Repeat neurology/psychiatry (FSC A196) consultation: $86.70 • Partial neurology assessment (FSC A188): $38.40 • Diagnostic and laboratory services total: $413 **Total expected preoperative reimbursement costs: $1,208**
Intra-Operative Costs	
• Cranial functional stereotaxy procedure (FSC N124): $1,551 • Anesthetist costs (FSC N124): • 11 base units + 1 unit for each 15 minutes in first hour + 2 units per 15 minutes thereafter • 39 units: number of average units billed (2003) • $12.01 per unit fee • Total anesthetist costs: $468 **Total expected intra-operative reimbursement costs: $2,487**	• Cranial functional stereotaxy (FSC N124) procedure: $1,555.20 (quantity of 2 x 2%) = $3,712.50 • Electrophysiological assessment of movement disorder patient during functional neurosurgery (FSC G166): $284.50 • Implantation or revision of stimulation pack or leads (peripheral nerve, brain) (FSC Z823): $313.50 • Intra-operative evaluation of movement disorder patient during functional neurosurgery (FSC G267): $275.50 • Anesthetist costs (39 units) (FSC N124): $487.90 **Total expected intra-operative reimbursement costs: $5,074**
Post-Operative Costs	
• Clinical programming of DBS (FSC G547): $ 186	• Clinical programming of DBS (FSC G547): $189.40

HQO (2005)	Ng (2013)
• Additional implantation site (FSC G547): $158 • Electrophysiological assessment of DBS (FSC G548): $279 • Neurology consultation (FSC A185): $128 • Neurology partial Assessment (FSC A188): $25 • Neurosurgery consultation (FSC A085): $102 • Neurosurgery partial assessment (FSC A044): $27 **Total expected post-operative physician reimbursement: $2,823**	• Additional implantation site (FSC G549): $161 • Neurology partial assessment (FSC A188): $460.20 • Repeat neurology consultation (FSC A186): $86.70 • Neurosurgery partial assessment (FSC A044): $30.60 • Complex medical reassessment (FSC A181): $73.30 • Neurosurgery specific assessment (FSC A043): $60.10 • Psychiatrist (FSC C196): $107.40 **Total expected post-operative physician reimbursement: $1,169**
DBS Device Costs	
Assumption of $10,000 to $14,000 per device	Cost of device (Kinetra Medtronic DBS): • Electrode leads (quantity 2): $4,346 • Extensions (quantity 2): $1,852 • Therapy access controller (patient controller): $891.90 • Pulse generator, receiver and transmitter: $10,887 **Total cost of device: $17,977**
Estimated Total Cost	
$24,420 to $28,420 (2018 costs: $30,531 to $35,531)[14]	**$25,428 (2018 cost: $27,497)[14]**

DBS = deep brain stimulation; FSC = fee schedule code.
Note: Estimated costs inflated to 2018 Canadian dollars.[14]

CADTH Common Drug Review undertook an exploratory comparison, approximating the five-year costs for DBS and levodopa/carbidopa intestinal gel (LCIG) in Table 3. Total DBS costs over a five-year period were estimated using the HQO (2005) and Ng (2013) reports and factoring in inflation to arrive at costs in 2018 Canadian dollars using the Bank of Canada's inflation rate calculator.[14] No information was given regarding the battery replacement costs for DBS or other necessary surgical procedures after approximately five years, which may increase the total five-year cost. In addition, LCIG costs were reported using the manufacturer's submitted price per intestinal gel cassette. No information is given regarding the surgical costs of the initial percutaneous endoscopic gastrostomy-jejunostomy procedure or tube replacement arising over a five-year period, which may increase total five-year costs. Therefore, the following cost estimations may not be accurate when comparing DBS and LCIG costs for jurisdictions.

Table 3: Approximate Five-Year Costs of Deep Brain Stimulation and Levodopa/Carbidopa Intestinal Gel

DBS	LCIG
Total 5-year costs	
Total operative and device costs (per patient): $27,497 to $35,531	Cost of LCIG using 1 cassette per day (per patient): $302,950 Cost of LCIG using 2 cassettes per day(per patient): $605,900

DBS = deep brain stimulation; LCIG = levodopa/carbidopa intestinal gel.

Note: DBS costs based on 2018 Canadian dollars.[14] Future costs for LCIG were not discounted.

Appendix 3: Summary of Other HTA Reviews of Drug

The Australian Pharmaceutical Benefits Advisory Committee and Scottish Medicines Consortium have both reviewed the clinical effectiveness of levodopa/carbidopa intestinal gel (LCIG) for patients with advanced Parkinson disease on occasions (Table 4 and Table 5). Both agencies initially rejected LCIG due to high and uncertain cost-effectiveness before recommending LCIG for reimbursement in a subpopulation of patients based on acceptable cost-effectiveness and strong patient population request.

Table 4: Other Health Technology Assessment Review Findings (PBAC)

	PBAC (March 2008) [4]	PBAC (March 2009) [5]	PBAC (November 2010) [6]
Treatment	Levodopa/carbidopa monohydrate intestinal gel (20 mg/L and 5 mg/L, 100 mL)		
Price	Redacted	Redacted	Redacted
Manufacturer's results	Base case: $45,000 to $75,000 per QALY vs. SOC	Base case: $75,000 to $105,000 per QALY vs. SOC	Base case: $15,000 to $45,000 per QALY vs. SOC
Issues noted by the review group	• Did not meet HSDP listing criteria • DBS not considered comparator • Requested indication broader than trial populations in report • Uncertain clinical importance of trial results • No long-term efficacy or safety data • Concerns about AEs relating to pump and tube dislocation • Carer utilities should have been included in sensitivity analyses, not the base case • High cost of drug and potential wastage based on storage requirements	• Several issues raised previously were not addressed and remain of note, such as: the inclusion of carer utilities, the clinical importance of trial results, AE risks with pump and tubing, criteria for HSDP. • Though cost of DBS included in base case, effects were not. • Carer utilities should be included in sensitivity analysis and not base case. • Model sensitive to number of cartridges per day, transition probabilities, hospital costs, and caregiver disutilities.	• Resubmission used same model from 2009. • Carer utilities and costs included in base case. • Considered DBS as a standalone comparator rather than part of SOC group and did not incorporate DBS into base case. • Noted difficulties in comparing LCIG with DBS due to trial designs and availability of DBS.
Results of reanalyses by the review group	$105,000 to $200,000 per QALY (excluding carer burden)	$75,000 to $105,000 per QALY vs. SOC (PBAC included DBS in reanalysis, but no effect of DBS available for consideration)	$45,000 to $75,000 per QALY vs. SOC including DBS
Recommendation	Not recommended due to high and uncertain ICER.	Not recommended due to uncertainty in clinical benefits, safety concerns, and high ICER.	Recommended for listing on the HSDP.
Notable information on economic evaluation	• Manufacturer used societal perspective. • Cost inputs are based on the Australian setting. • Several issues were identified relating to economic and clinical uncertainty; and inappropriate to exclude DBS in the list of comparators.	• Similar economic model from previous report submitted by manufacturer; societal perspective adopted. • LCIG used a hospital-based medical clinic, making costs, population, and perspective irrelevant to Canada. • Not well reported how DBS was	• Economic model unchanged from 2009 submission. • Resubmission was based on a particular patient for reimbursement; therefore, not generalizable to the Canadian setting. • Not well reported how DBS considered in the PBAC

	PBAC (March 2008) [4]	PBAC (March 2009) [5]	PBAC (November 2010) [6]
		considered in the PBAC reanalysis.	reanalysis.

AE = adverse event; DBS = deep brain stimulation; HSDP = highly specialized drug program; ICER = incremental cost-effectiveness ratio; LCIG = levodopa/carbidopa intestinal gel; PBAC = Pharmaceutical Benefits Advisory Committee; SOC = standard of care; QALY = quality-adjusted life-year; vs. = versus.
Note: PBAC approved LCIG for revised reimbursement criteria in November 2016.[18]
All PBAC stated prices are reported in Australian Dollars ($) at the time of the submission.
1 AUD = 0.924 CAD in March 2008.[19]
1 AUD = 0.840 CAD in March 2009.[19]
1 AUD = 1.001 CAD in November 2010.[19]

Table 5: Other Health Technology Assessment Review Findings (Scottish Medicines Consortium)

	SMC (September 2006) [9]	SMC (November 2015) [8]	SMC (November 2016) [7]
Treatment	LCIG (20 mg/L and 5 mg/L)		
Price	Redacted	Redacted	Redacted
Manufacturer's results	• £76,000 per QALY vs. SOC	• ICER with PAS, LCIG vs. SOC: £46,000 • DSAs and PSA indicated model most sensitive to health state costs and number of gel cassettes.	• ICER without PAS comparing LCIG with SOC: £58,250 • DSAs and PSA indicated model most sensitive to health state costs and number of gel cassettes.
Issues noted by the review group	• Uncertainty around utility mapping exercise • Resultant QoL estimates creating high ICER.	• ICER is high • Lack of robust head-to-head studies or indirect comparisons • Patients on SOC assumed to follow natural history (no tx benefit) • Initial LCIG treatment effect maintained over model duration • Assume LCIG patients achieve 50% reduction in "off" progression over duration of the model • Results were sensitive to health state costs and utility values	• Same limitations noted as per 2015 submission. • Additionally, apomorphine use was underestimated.
Results of reanalyses by the review group	• £94,000 per QALY	Not well reported (may range from £50,000 to £130,000 per QALY; uncertain whether with or without PAS)	Not well reported (may range from £60,000 to £80,000 per QALY without PAS)
Recommendation	Not recommended due to unsatisfactory cost-effectiveness.	Not recommended. The economic analysis was not robust. Insufficient treatment costs in relation to health benefits.	Recommended for patients who are not eligible for DBS.
Notable information on economic evaluation	• CUA was based on a 5-year Markov model with yearly cycles comparing LCIG with SOC. • Health states were defined by time in "off" state for treatment arms.	• CUA was based on a 20-year Markov model comparing LCIG with SOC. • Model consisted of 25 health states with one death state.	• Same structure as 2015 submission. • Analysis specific to patients not eligible for DBS.

	SMC (September 2006) [9]	SMC (November 2015) [8]	SMC (November 2016) [7]
	• Clinical data did truly represent overall patient population. • Efficacy data rely on 3 weeks of treatment and may not reflect the overall proportion of patients who can respond to LCIG. • Clinical data were from small, open-label studies of LCIG. • Not cost-effective or limited data on the clinical effectiveness of LCIG as well as maintenance and safety concerns regarding the intestinal gel pump.	• Lack of robust, direct head-to-head studies was used to compare LCIG with SOC. • Clinical data were from single-arm study of LCIG (Study 004). • Results were sensitive to health state costs used in the model. • LCIG has orphan drug status in Scotland; accepting greater uncertainty in the economic analysis. • Analysis focused on patients not suitable for DBS.	

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DBS = deep brain stimulation; DSA = deterministic sensitivity analysis; ICER = incremental cost-effectiveness ratio; LCIG = levodopa/carbidopa intestinal gel; NG = nasal gastric; PAS = patient access scheme; PEG = percutaneous endoscopic gastrostomy; PSA = probabilistic sensitivity analysis; SMC = Scottish Medicines Consortium; SOC = standard of care; QoL = quality of life; tx = treatment; UPDRS = Unified Parkinson's Disease Rating Scale; vs. = versus.

Note: All SMC stated prices are reported in British pounds (£) at the time of the submission.

1 GBP = 2.105 CAD in September 2009.[19]

1 GBP = 2.017 CAD in November 2015.[19]

1 GBP = 1.673 CAD in November 2016.[19]

Appendix 4: Summary of the Literature Search

Methodology

CADTH Common Drug Review undertook a review of the economic literature for the use of Duodopa for patients with advanced Parkinson disease.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Duodopa, carbidopa and levodopa.

Methodological filters were applied to limit retrieval to economic studies. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on March 1, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on July 18, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free).

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Inclusion Criteria

Inclusion criteria were created to identify literature articles that contained economic evaluations comparing levodopa/carbidopa with standard of care and deep brain stimulation:

- Patients with advanced Parkinson disease
- Administration of levodopa/carbidopa
- Relevant comparators (standard of care and deep brain stimulation)
- Performed an economic evaluation
- Published 2009 or later

The inclusion criteria did not restrict for articles focused on the Canadian setting due to the expected paucity of relevant studies.

Appendix 5: Summary of Published Economic Evaluations

From the literature search, two economic evaluations[10,11] were identified comparing levodopa/carbidopa intestinal gel with standard of care (including deep brain stimulation). They are summarized in Table 6. The articles do not take a Canadian public payer perspective; therefore, they may not be generalizable to a Canadian context.

Table 6: Summary of Published Economic Evaluation: Lowin Et Al.

<table>
<tr><th></th><th>Lowin et al. (September 2011)</th><th>Lowin et al. (October 2017)</th></tr>
<tr><td>Independence of investigators</td><td>Received consultancy fees from manufacturer</td><td>Received consultancy fees from manufacturer</td></tr>
<tr><td>Economic evaluation</td><td>CUA</td><td>CUA</td></tr>
<tr><td>Setting</td><td>UK</td><td>Ireland</td></tr>
<tr><td>Perspective</td><td>Public payer perspective</td><td>Public payer perspective</td></tr>
<tr><td>Patient population</td><td>Starting cohort: aPD with H & Y 3, 4, or 5 and experiencing “off”: ≥ 50%.</td><td>Starting cohort: aPD with H & Y 3, 4, or 5 and experiencing OFF ≥ 50%.</td></tr>
<tr><td>Treatments</td><td>LCIG vs. SOC (best available oral treatment)</td><td>LCIG vs SOC (best available oral treatment). Median age = 64.</td></tr>
<tr><td>Time horizon</td><td>Lifetime. 6-month cycle length.</td><td>20 years</td></tr>
<tr><td>Study design</td><td>• Markov model based on model for Sweden. 13 health states: “Off” stages (0% to 25%, 26% to 50%, 51% to 75%, 76% to 100%) combined with H & Y stages (3 to 5), death. Assume patients transition to adjacent or worse “off” stage, can only move to worse H & Y state.
• LCIG costs £77/day/patient (90:10 split 1:2 cassettes).</td><td>• Markov model based on previous model from UK, 26 health states: H & Y scale combine with “off” time (0% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%), death.
• Costs and outcomes discounted: 4% DSA and PSA.
• Unit cost of LCIG cassette: €106.75/patient (assumes 90% of patients require one cassette [unit] per day).</td></tr>
<tr><td>Data inputs</td><td>• Clinical data based on two small, published studies about LCIG (Eggert et al., Antonini et al.).
• Rates and device-related AEs based on clinical trial.
• Medical resource use from expert opinion and clinical trial.
• Health state costs from observational study.
• Health utilities based on observational data.</td><td>• Clinical data based on a single-arm study of LCIG (Study 004) and a retrospective review of Swedish medical records.
• Resource use, costs from Lowin (2011).
• Direct medical and non-medical resource costs based on data set observations.
• Health utilities based on pooled data sets from published studies.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>LCIG</th><th>SOC</th><th>Incr.</th></tr>
<tr><td>Costs</td><td>£201,192</td><td>£161,548</td><td>£39,644</td></tr>
<tr><td>QALYs</td><td>1.88</td><td>0.78</td><td>0.30</td></tr>
<tr><td>ICER</td><td></td><td></td><td>£36,024</td></tr>
</table>
DSA findings: £32,127 to £66,421. Sensitive to treatment duration (duration of LCIG), clinical benefits (short- vs. long-term assumptions of LCIG), and cohort definitions (including patients with lower “off” time).
</td><td>
<table>
<tr><th></th><th>LCIG</th><th>SOC</th><th>Incr.</th></tr>
<tr><td>Costs</td><td>€537,687</td><td>€514,037</td><td>€23,650</td></tr>
<tr><td>QALYs</td><td>4.37</td><td>3.49</td><td>0.88</td></tr>
<tr><td>ICER</td><td></td><td></td><td>€26,944</td></tr>
</table>
• LCIG cost-effective at WTP threshold of €45,000
• DSA and PSA findings: Sensitive to discontinuation and long-term benefit assumptions, health state costs.
</td></tr>
<tr><td>Limitations identified</td><td>• High degree of uncertainty for key model parameters due to small sample size. Identified in DSA.</td><td>• Costing uncertain, limited data.
• Uncertain treatment duration and switch to SOC; assumption patients switch to oral therapy ~5 years.</td></tr>
</table>

	Lowin et al. (September 2011)	Lowin et al. (October 2017)
	• Limited data and robustness of available sources. • Use of unpublished sources, reducing credibility and relevancy of findings. • LCIG was truncated at 5 y and assumed patients revert to SOC after 5 y.	• Lack of robust long-term data. • Short follow-up (12 months); LCIG-naive patients. • Did not state if AE incorporated. • Clinical data based on open-label studies and few patients (n = 65).

aPD = advanced Parkinson disease; AE = adverse event; CUA = cost-utility analysis; DSA = deterministic sensitivity analysis; H & Y = Hoehn and Yahr scale; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LCIG = levodopa/carbidopa intestinal gel; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus; WTP = willingness to pay; y = year.
Note: 1 GBP = 1.579 CAD in September 2011;[19] 1 EUR = 1.479 CAD in October 2017.[19]

References

1. [Pr]Duodopa® (levodopa/carbidopa intestinal gel): intestinal gel (1 mL contains 20 mg levodopa and 5 mg carbidopa monohydrate) [product monograph]. St. Laurent (QC): AbbVie Corporation; 2017 Apr 27.
2. AbbVie response to February 6, 2018 CDR request for additional information regarding the Duodopa CDR review: Duodopa pricing information[**CONFIDENTIAL** additional manufacturer's information]. St-Laurent (QC): AbbVie; 2018 Feb.
3. CEDAC final recommendation and reconsideration and reasons for recommendation: *levodopa/carbidopa (Duodopa™ - Solvay Pharma Inc.)* [Internet]. Ottawa: CADTH; 2009. [cited 2018 Apr 24]. Available from: https://cadth.ca/sites/default/files/cdr/complete/cdr_complete_Duodopa_July_24_2009.pdf
4. Pharmaceutical Benefit Advisory Committee. Public summary document: levodopa with carbidopa, intestinal gel, 20 mg-5 mg per mL, Duodopa® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2008 Mar. [cited 2018 Apr 24]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2008-03/pbac-psd-levodopa%20with%20carbidopa-mar08.pdf
5. Pharmaceutical Benefit Advisory Committee. Public summary document: levodopa with carbidopa monohydrate, intestinal gel, 20 mg - 5 mg (base) per mL, 100 mL, Duodopa® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2009 Mar. [cited 2018 Apr 24]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2009-03/Levodopa_with_Carbidopa_Solvay_PSD_7-5_2009-03_FinaL.pdf
6. Pharmaceutical Benefit Advisory Committee. Public summary document: levodopa with carbidopa (as monohydrate), intestinal gel, 20 mg - 5 mg (base) per mL, 100 mL, Duodopa® [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2010 Nov. [cited 2018 Apr 24]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2010-11/Levodopa_Carbidopa_DUODOPA_Abbott_Australasia_PSD_2010-11_7-7_FINAL.pdf
7. Re-submission: co-careldopa (levodopa 20mg/mL and carbidopa monohydrate 5mg/mL) intestinal gel (Duodopa®) [Internet]. Glasgow: Scottish Medicines Consortium; 2016 May 6. [cited 2018 Apr 24]. (SMC advice; no. 316/06). Available from: https://www.scottishmedicines.org.uk/media/1491/dad_co-careldopa_2nd_resubmission_final_may_2016_for_website.pdf
8. Re-submission: co-careldopa (levodopa 20mg/mL and carbidopa monohydrate 5mg/mL) intestinal gel (Duodopa®) [Internet]. Glasgow: Scottish Medicines Consortium; 2015 Nov 6. [cited 2018 Apr 24]. (SMC advice; no. 316/06). Available from: https://www.scottishmedicines.org.uk/files/advice/co-careldopa__Duodopa__Resubmission_FINAL_Nov_2015_for_website.pdf
9. Co-careldopa intestinal gel, 20mg/5mg levodopa/carbidopa per ml for continuous intestinal infusion, (Duodopa®) No. (316/06) [Internet]. Glasgow: Scottish Medicines Consortium; 2006 Sep 8. [cited 2018 Apr 24]. Available from: https://www.scottishmedicines.org.uk/files/co-careldopa_intestinal_gel_Duodopa_316_06.pdf
10. Lowin J, Bergman A, Chaudhuri KR, Findley LJ, Roeder C, Schifflers M, et al. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. J Med Econ. 2011;14(5):584-93.
11. Lowin J, Sail K, Baj R, Jalundhwala YJ, Marshall TS, Konwea H, et al. The cost-effectiveness of levodopa/carbidopa intestinal gel compared to standard care in advanced Parkinson's disease. J Med Econ. 2017 Nov;20(11):1207-15.
12. AbbVie. Levodopa-Carbidopa intestinal Ggel open-label study in advanced Parkinson's disease. 2006 Jun 9 [cited 2018 Apr 24]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 -. Available from: https://clinicaltrials.gov/ct2/show/study/NCT00335153 NLM Identifier: NCT00335153.
13. Medical Advisory Secretariat. Deep brain stimulation for Parkinson's disease and other movement disorders; an evidence-based analysis. Ontario Health Technology Assessment series [Internet]. 2005 [cited 2018 Apr 24];5(2). Available from: http://www.hqontario.ca/Portals/0/Documents/evidence/reports/rev_dbs_030105.pdf
14. Inflation calculator [Internet]. Ottawa: Bank of Canada; 2018. [cited 2018 May 9]. Available from: https://www.bankofcanada.ca/rates/related/inflation-calculator/
15. Ng VW. The costs and benefits of deep brain stimulation surgery for patients with Parkinson's disease at different stages of severity - an initial exploration [Internet]. Toronto (ON): University of Toronto; 2013. [cited 2018 Apr 24]. Available from: https://tspace.library.utoronto.ca/bitstream/1807/35659/2/Ng_Vivian_WM_20136_MSc_thesis.pdf
16. CADTH Common Drug Review pharmacoeconomic review report: apomorphine (Movapo) [Internet]. Ottawa: CADTH; 2018 Feb. [cited 2018 Apr 26]. Available from: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0527_Movapo_PE_Report.pdf
17. Drug Plan and Extended Benefits Branch. Saskatchewan online formulary database [Internet]. Regina (SK): Government of Saskatchewan; 2018. [cited 2018 Apr 24]. Available from: http://formulary.drugplan.health.gov.sk.ca/
18. Pharmaceutical Benefit Advisory Committee. November 2016 PBAC meeting - positive recommendations [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2016. [cited 2018 May 2]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2016-11/positive-recommendations-2016-11.pdf
19. Exchange rates [Internet]. Ottawa: Bank of Canada; 2018. [cited 2018 May 9]. Available from: https://www.bankofcanada.ca/rates/exchange/