EVALUATION OF THE CONTINUOUS ADMINISTRATION OF LEVODOPA/CARBIDOPA INTESTINAL GEL FOR THE TREATMENT OF ADVANCED PARKINSON'S DISEASE

Assessment Report 12-14

Health Technology Assessment Unit
(HTAU)

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Evaluation of the Continuous Administration of Levodopa/Carbidopa Intestinal Gel for the Treatment of Advanced Parkinson's Disease

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FOREWORD

The CHU de Québec's Health Technology Assessment Unit (HTAU) has as its mission to support and advise decision-makers (managers, physicians and other professionals) in making decisions regarding the best allocation of resources for implementing a health technology or intervention modality or for reviewing an existing practice.

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This report presents data compiled up to September 25, 2014 for the efficacy and safety segments using the literature search methodology that had been developed. These data are not a substitute for a clinician's judgement and do not constitute approval or a disclaimer of the treatment modality or the use of the technology under discussion.

This report does not in any way render the CHU de Québec, its personnel or the professionals liable for the contents of this report. Consequently, the authors, the CHU de Québec, the members of the working group and the members of the HTAU's Scientific Committee may not, under any circumstances, be held liable for any prejudice of any kind in connection with the use or interpretation of the said contents.

CONFLICT OF INTEREST DISCLOSURE

No conflicts of interest reported.

IN BRIEF

Parkinson's disease (PD) is a neurodegenerative disease that manifests mainly as involuntary movements, muscle stiffness and tremor. For patients with advanced Parkinson's disease, few therapeutic options are available for adequately controlling their symptoms. The continuous administration of levodopa/carbidopa intestinal gel (LCIG) via a percutaneous endoscopic gastrostomy (PEG) tube could be an approach to consider to reducing the motor fluctuations associated with the oral administration of this drug. A health technology assessment (HTA) project was undertaken at the CHU de Québec to review the evidence regarding the efficacy and safety, including the safety of its method of administration, of continuous LCIG in patients with advanced PD.

Few quality evidence was identified. However, the results of the studies included suggest that continuous LCIG could be effective in reducing the daily duration of the periods when the symptoms are not controlled by medication (off-periods) and the motor complications associated with this drug. The results also point to a possible improvement in the quality of life of patients with advanced Parkinson's disease. The analysis of the results indicates that this modality is associated with a high frequency of adverse events, although most of them are not very serious. The introduction of LCIG into the therapeutic arsenal available at the CHU de Québec for treating advanced PD would require optimizing the current practices and instituting new measures to limit the organizational and financial impact.

Upon examining all the evidence, the HTAU recommends introducing, as an innovative practice, the use of LCIG as a medication of specific necessity for managing patients who meet the diagnostic criteria for advanced Parkinson's disease, specifically, those who respond to levodopa, who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the administration of other combinations of antiparkinsonian drugs, and who do not have any clinically significant psychiatric disorders. This practice should be guided in order to document, during the first two years after its introduction, the benefits for patients, the frequency of the adverse events and their sequelae, as well as the impact on the CHU de Québec's resources and its partners. The HTAU recommends that the experience using LCIG be reviewed a year after its introduction to make any necessary adjustments to the management of patients treated with this drug and that it be reevaluated at the end of the second year to assess its usefulness as a treatment available at the CHU de Québec.

LIST OF ABBREVIATIONS AND ACRONYMS

CIILC	Continuous intestinal infusion of levodopa and carbidopa
COMT	Catechol-O-methyl transferase
DBS	Deep brain stimulation
FDA	Food and Drug Administration
HEJ	Hôpital de l'Enfant-Jésus
HTA	Health technology assessment
LCIG	Levodopa/carbidopa intestinal gel
MAO-B	Monamine oxidase B
MAUDE	Manufacturer and User Facility Device Experience
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
PEG	Percutaneous endoscopic gastrostomy
RAMQ	Régie de l'assurance maladie du Québec
RCT	Randomized controlled trial
UPDRS	Unified Parkinson's Disease Rating Scale

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SUMMARY

Introduction

According to Health Canada, the continuous administration of levodopa/carbidopa intestinal gel (LCIG) is indicated for the treatment of advanced Parkinson's disease (PD) in levodopa-responsive patients who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the available combinations of antiparkinsonians. As PD progresses over time, the pattern of motor fluctuations may be characterized by the sudden and unpredictable passage from a state where the symptoms are controlled with drugs ("on" state) to a state when they are not ("off" state). The Health Technology Assessment Unit (HTAU) was asked by Executive Office of Intensive Care, Trauma Care and Neurosciences to assess continuous LCIG in patients with advanced PD.

Decision question

Should LCIG be administered to patients at the CHU de Québec with advanced levodopa-responsive Parkinson's disease who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the available combinations of antiparkinsonians or for whom deep brain stimulation is not an option?

Assessment questions

1. How effective is continuous LCIG in alleviating involuntary motor fluctuations and improving the quality of life of patients with advanced PD?
2. What are the complications and adverse reactions associated with the method of administering LCIG?
3. If continuous LCIG proves to be effective and safe, what would be the impact of its regular use in the target population be on the CHU de Québec's resources (human and financial)?

Methodology

A search of the scientific literature was conducted in indexed databases (Medline [PubMed], Embase, Center for Reviews and Dissemination and the Cochrane Library) and the grey literature to assess the efficacy and safety, including the safety of its method of delivery, of LCIG administered for a minimum of 4 weeks in terms of involuntary motor fluctuations and quality of life compared to oral combinations of antiparkinsonians. The data search included synthesis studies, practice guidelines, randomized clinical trials (RCTs) and observational studies. Of the observational studies, only the prospective case series including at least 20 subjects were examined. The RCTs, observational studies, case series and case studies that reported a number of patients who experienced adverse reactions associated with the administration of LCIG were considered for this segment. French- and English-language publications from January 1, 2000 to September 25, 2014 were included. The bibliographies in the articles consulted were searched as well. The MAUDE and MedEffect databases were queried in search of adverse events associated with the drug's method of administration. Two evaluators independently selected, and evaluated the quality of the publications and performed the data extraction. Disagreements were resolved by involving a third evaluator.

The operational practices pertaining to the administration of LCIG were documented by means of a telephone survey involving a Quebec hospital that introduced this modality in the recent past.

The assessment was carried out in collaboration with a working group consisting of experts from the CHU de Québec. This sharing contributed to the understanding of the institution's context, to the identification of the organizational aspects to be taken into consideration, and to the generating of findings and the development of recommendations. This report was reviewed by the members of the working group. It was reviewed and approved by the HTAU's Scientific Committee.

Efficacy results

In all, 1504 publications were selected and assessed for eligibility. Those included were two practice guidelines, three expert opinions, one RCT and five prospective case series.

Original studies

The RCT of Olanow *et al*. aimed to evaluate the efficacy and safety of continuous LCIG administration via an intrajejunal percutaneous tube in adults with advanced PD presenting with off-periods that could not be controlled satisfactorily with optimized medical therapy. In all, 71 eligible patients from 26 American, German and New Zealand hospitals were randomly assigned to receive the intervention (placebo capsules + LCIG) or the comparator (levodopa/carbidopa immediate-release capsules + placebo intestinal gel). The results of this study show that after 3 months of follow-up, continuous LCIG was associated with benefits, specifically in terms of the duration of the on- and off-periods and quality of life. However, the validity of this study is limited by its short duration, a potential selection bias, and a potential conflict of interest.

The results of the five prospective case series are generally consistent with those of Olanow *et al*.'s RCT. There was similarity in the subjects' age (approximately 60 years and older) and in disease duration (12 or more years) across these studies. However, certain results suggest that the effect of the treatment was smaller for follow-ups of 24 or more months. However, given that there was no comparison group, it cannot be determined if the efficacy may have been influenced by the natural course of the disease or by other factors, such as the duration of treatment, the daily dose received or the measurement instruments used. The case series included had a number of methodological limitations, namely, the high number of subjects lost to follow-up (0 to 45%), no adjustment to the results for confounding variables, potential conflicts of interest, and the use of different measurement instruments to evaluate the efficacy of continuous LCIG. It should be noted that most of the observed losses to follow-up in the case series were due to adverse events.

Overall, the evidence for the efficacy of continuous administration of LCIG suggests that this drug could reduce the duration of OFF periods and improve the quality of life of patients with advanced PD. However, although a statistically significant decrease was observed, the clinical significance of these changes remains unknown.

Results concerning the safety of continuous LCIG administration

The search strategy for the purpose of reviewing the literature on the safety of continuous administration of LCIG yielded 2109 publications. Those included were one RCT, 25 case series and 10 case reports. These studies report the adverse events that had occurred in 895 Parkinson's patients.

The main health problems associated with the endoscopic procedure necessary for installing the gastrostomy tube were wound site infection and granulomas, which occurred in 11.4% and 4.7% of the cases, respectively. A few cases of serious adverse events, such as peritonitis (2.2%), pneumoperitoneum (2.3%) and death (0.4%) were reported with this method of administration. The frequency of these adverse events in the patients who received LCIG was comparable to that associated with installing a percutaneous endoscopic gastrostomy tube for other indications.

The adverse events associated with the tube used to administer the drug are dislocation, occlusion, kinking and knotting, leaks and accidental removal. Tube dislocation is the most common adverse event, occurring in about 1 in 5 patients. A review of the different publications concerning the safety of this practice also indicates that the same or several adverse events can occur more than once in a given patient during follow-up.

Practice guidelines and expert opinions

The practice guidelines included were of good methodological quality but arrive at divergent conclusions. One of them suggests that the duodenal administration of levodopa is probably effective in treating motor fluctuations and dyskinesia, while the other does not recommend it because of a lack of scientific evidence. Despite their methodological weaknesses, the expert opinions suggest that the continuous administration of this treatment in patients with advanced PD could be beneficial for controlling motor fluctuations.

Results of survey

The experience of the Centre hospitalier de l'Université de Montréal (CHUM)'s André Barbeau Movement Disorder Unit in terms of administering LCIG in patients with advanced PD was documented as part of this assessment report. The history of this drug's use at the clinic, the target population, and the effects and complications observed in patients treated with it were reviewed. According to the neurologist consulted, careful selection of patients likely to benefit from this treatment is key to its success. The main adverse events observed with continuous LCIG are tube dislocation and stoma infections. Currently, about 10 patients are receiving this treatment at CHUM.

Organizational impact

When planning resources for introducing this new practice at the CHU de Québec, one should anticipate a hospital stay of 5 to 7 days for each patient for installing the percutaneous endoscopic gastrostomy tube, adjusting the LCIG doses on an individual basis, and closely monitoring the patient for any complications. As well, one should plan for nurse clinician time for adjusting the medication and following the patients treated with this drug. One other element to plan for in the organization of services is the availability of gastroenterologists and of a neurologist specialized in this area. According to the working group's expert members, no additional human resources would need to be provided at the CHU de Québec afterwards, since the patients concerned are already attending the Movement Disorder Clinic at the Hôpital de l'Enfant-Jésus. The estimated number of patients who might receive this drug is around 5 per year.

As the treatment initiated in the hospital continues after discharge, the neurologist first has to obtain authorization from the Régie de l'assurance maladie du Québec (RAMQ) for coverage under the exception patient measure since LCIG is not in the RAMQ's institutional formulary. In November 2013, an agreement was concluded between AbbVie Corporation and the CHU de Québec under which the company covers the costs associated with the drug during the patient's initial hospital stay, the equipment (tubes, connectors and adapters) needed to install the PEG tube, and the pump for delivering the drug (the CADD-Legacy, model 1400) for a maximum of 24 patients. At the end of the term of this agreement, that is, one year after the initial introduction of the technology, the recurrent costs for introducing this drug at the CHU de Québec, excluding hospitalization costs and physicians' fees, would be $3316 per patient.

Discussion

Based on the data from the scientific literature on the efficacy and safety of this method of administration, the discussions with the interdisciplinary working group, the experience using LCIG elsewhere in Quebec, and the analysis of the organizational and financial impact on the CHU de Québec, the following observations can be made:

1. Despite the uncertainties, continuous LCIG seems to be an effective treatment modality in patients with advanced PD

The authors of the studies included conclude that LCIG is effective. The results of the reviewed studies suggest that this modality would be effective in reducing the duration of off-periods and the motor complications associated with the drug, and that it improves the quality of life of patients with PD. However, none of the authors assessed the clinical significance of the observed differences. In addition, the primary studies contain a number of methodological flaws, such as the limited number of study subjects, the short duration of patient follow-up (3 to 36 months), the high dropout rate, non-optimal statistical analyses, and the appearance of conflicts of interest with AbbVie Corporation. As well, the measured size and direction of the effect seem to vary according to the duration of patient follow-up, which suggests that the benefit of this treatment is more significant in studies with a short follow-up.

2. The continuous administration of LCIG via a PEG: an innovative modality but not without risks for the patient

The evidence regarding the safety of LCIG, including the safety of its method of administration, suggests that this treatment seems safe for patients. Nonetheless, despite the low incidence of serious adverse events, patients who wish to undertake this treatment would do well to familiarize themselves with the risks associated with it and with the drug's method of

administration so that they can make an informed decision.

3. Continuous administration of LCIG in patients with advanced PD at the CHU de Québec: an innovation to be guided and optimized

Considering all the uncertainties, the different elements that emerge from the evidence suggests that, for now, introducing LCIG into the therapeutic arsenal for advanced PD meets more the criteria for an innovative practice than for a standard of care. This modality meets a health need and, for patients, constitutes a new therapeutic option with positive benefits. However, the uncertainties associated with demonstrating proof of its efficacy and of the safety of its method of administration, with the potential impact of its introduction on the organization of care, and with its regulatory status in Quebec make the use of LCIG a treatment in the process of clinical maturation. Selecting patients who might benefit the most from this treatment is key to its success. Although, since a patient selection framework has been well defined by Health Canada, other criteria, such as the patient's ability to manage the pump and tubing and the size of his/her social network, should be taken into consideration as well. The preliminary data identified suggest that this innovation has little impact on a hospital's professional resources. However, the additional workload associated with following patients and managing adverse effects might be greater than expected. The net impact of this drug on patient health and the organization of health-care services is a considerable unknown, which should be documented.

Recommendation 1

It is recommended that the CHU de Québec introduce, as an innovative practice, the use of LCIG as specific necessity medication for managing patients:

- Who meet the diagnostic criteria for advanced Parkinson's disease and,
- Who respond to levodopa and,
- Who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the administration of other combinations of antiparkinsonians and,
- Who do not have any clinically significant psychiatric disorders.

This recommendation is conditional on the following:

- That patients have access to all the necessary information for making an informed and shared decision considering the expected benefits and risks of the administration of LCIG and of the other available therapeutic options (e.g., deep brain stimulation) in order to make ;

- That patients in whom this option is considered have a solid functional capacity and a well-developed social network for managing the pump and the various procedures involved in administering LCIG;
-
- That patients receiving this treatment be followed by staff (nurse clinician, physician and pharmacist) trained on the method of administering LCIG;

- That the first two years of LCIG utilization be used to document:
    - The characteristics of the treated patients;
    - The benefits for the patients;
    - The frequency of adverse events in the treated patients and their consequences for these patients and for the CHU de Québec;
    - The discontinuation rate and the reasons for discontinuation;
    - An estimate of the costs associated with installing the tube required for delivering the drug and with the subsequent visits or hospitalizations due to adverse events;
    - The impact of following patients and managing adverse events on human resources.

- That the neurologists at the Movement Disorder Clinic of the Hôpital de l'Enfant-Jésus (CHU de Québec) define

beforehand for each efficacy outcome a reference value or criteria for clinically meaningful improvement;

- That the experience using LCIG be reviewed a year after its introduction, by the neurologists at the Movement Disorder Clinic of the Hôpital de l'Enfant-Jésus (CHU de Québec) and the associated clinical/administrative team. The review should be based on the clinical and organizational data from documenting the practice and should enable one, in light of the findings, to make adjustments to the management of patients treated with this drug;

- That the experience using LCIG be reevaluated at the end of the second year in order to assess its usefulness as a treatment available at the CHU de Québec for patients with advanced Parkinson's disease compared to the use of an oral levodopa/carbidopa combination or deep brain stimulation. The decision whether to continue using this drug at the CHU de Québec should be under the responsibility of the CHU de Québec's Strategic Clinic Committee. In addition, the CHU de Québec's Pharmacology Committee should be informed of any change regarding the use of this treatment.

Recommendation 2

It is recommended that the physicians, other professionals and researchers at the CHU de Québec who are experts in Parkinson's disease join forces with the CHU de Québec Research Centre's Executive Committee to support the development of research facilities for conducting evaluative and clinical research on the management of patients with advanced Parkinson's disease.

Conclusion

A review of the evidence suggests that continuous administration of LCIG is associated with benefits, specifically in terms of involuntary motor fluctuations and the quality of life of patients with advanced PD, but that this practice is not without risks. A number of uncertainties persist, especially with regard to the clinical significance of the observed improvements, the long-term effects on the control of the disease, and the relative efficacy compared to other treatment options. The HTAU recommends, for a 2-year trial period, the introduction of LCIG at the CHU de Québec as an innovative practice for managing patients with advanced PD who meet certain clinical criteria. The continuation of the experience using LCIG beyond this period will need to be reassessed to review its usefulness as a treatment available at the CHU de Québec.

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that manifests mainly as involuntary movements, muscle stiffness and tremor [1]. These movements are due mainly to the progressive loss of dopaminergic cells. Patients with PD present with motor and non-motor symptoms, which, overall, affect their autonomy and their personal, social and professional quality of life. In patients in the advanced stage of the disease, the response to the conventional treatments may become unsatisfactory. Different treatment options may be proposed to patients, including the continuous administration of LCIG, which is administered by infusion directly into the upper small intestine by means of a portable, patient-controlled pump.

In the winter of 2014, the CHU de Québec's Pharmacology Committee recommended the use of levodopa/carbidopa intestinal gel (Duodopa™) as a specific necessity medication for the treatment of advanced levodopa-responsive PD when the control of severe, troublesome motor symptoms is unsatisfactory with the available combinations of antiparkinsonians, subject to a favourable recommendation by the Health Technology Assessment Unit (HTAU). The HTAU was therefore asked by Executive Office of Intensive Care, Trauma Care and Neurosciences to evaluate the efficacy and safety, including the safety of its method of administration, of continuous LCIG in patients with advanced PD. Usually, these are patients who no longer respond satisfactorily to the other available combinations of antiparkinsonians or in whom deep brain stimulation (DBS) is not an option.

2. DECISION QUESTION AND ASSESSMENT QUESTIONS

2.2 Decision question

Should LCIG be administered to patients at the CHU de Québec with advanced levodopa-responsive PD who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the available combinations of antiparkinsonians or in whom DBS is not an option?

2.3 Assessment questions

1. How effective is continuous LCIG in alleviating involuntary motor fluctuations and improving the quality of life of patients with advanced PD?
2. What are the complications and adverse reactions associated with the method of administering LCIG?
3. If continuous administration of LCIG proves to be effective and safe, what would the impact of its regular use in the target population be on the CHU de Québec's resources (human and financial)?

3. METHODOLOGY

3.1 Evaluation of efficacy and safety

3.1.1 Literature search

Table 1 summarizes the eligibility criteria, limits and outcomes used to conduct the literature search pertaining to the assessment questions for the efficacy and safety segments. A search was done in the indexed databases Medline (PubMed) and Embase, in those of the Centre for Reviews and Dissemination and the Cochrane Library, and in the grey literature. A search was conducted to identify systematic reviews with or without a meta-analysis and evidence-based practice guidelines. The literature search was *a priori* ranked according to the level of evidence attributed to each type of publication (Table 1). The search proceeded to the next step when there were no publications available or if their methodological quality was inadequate. The websites of health technology assessment (HTA) agencies and professional associations were visited in search of material pertaining to the assessment topic. A list of the organization websites and the databases searched is presented in Appendix 1. As well, the bibliographies in the articles were searched for further references of interest. A search for published protocols on randomized controlled trials (RCTs) and synthesis studies was performed at specialized websites (Appendix 2). The authors of the original studies were contacted as needed.

A safety evaluation was carried out using the studies included for the efficacy segment of this assessment project. As well, an additional literature search was performed in the Medline (PubMed) and Embase databases. RCTs, observational studies, case series and case studies that reported a number of patients who had experienced adverse reactions were considered for the safety segment. The search strategies used for evaluating the efficacy and safety of continuous LCIG, including the safety of its method of administration, are presented in Appendix 3. Furthermore, the MAUDE (Manufacturer in User-Friendly Device Experience) database of the US Food and Drug Administration (FDA) and Health Canada's MedEffect™ database were queried to complete the search pertaining to safety.

3.1.2 Study selection

After the search strategy was applied, publications were selected independently by two evaluators (S.L and G.A) based on the title, abstract and, if necessary, the article's original text. These two evaluators then determined if the publications met the eligibility criteria (Table 1). The opinion of a third evaluator (M.R.) was sought when there were disagreements in order to reach a consensus.

3.1.3 Evaluation of methodological quality and data extraction

The methodological quality of the studies was evaluated independently by two evaluators (S.L and G.A.) The evaluation of the systematic reviews and practice guidelines was performed using the AMSTAR [2] and AGREE II [3] checklists, respectively. The quality of the other types of publications was assessed with analytical checklists adapted from the COMPUS Adapted SIGN 50 Checklist. They were taken from the Guide méthodologique de recheche et d'analyse documentaire de l'Unité d'évaluation des technologies et de modes d'intervention en santé du Centre hospitalier universitaire du Québec (CHUQ) [4]. The opinion of a third evaluator (M.R.) was sought when there were disagreements in order to reach a consensus. Data extraction was performed by two independent evaluators (S.L. and G.A.) using a standardized form. The studies that were assessed and included are presented in Section 5.1 for the efficacy segment and in Section 5.2 for the safety segment. The list of excluded publications and the reasons for their exclusion are presented in Appendix 4.

Table 1. Eligibility criteria, limits and outcomes used

INCLUSION CRITERIA	
Population	Patients with advanced levodopa-responsive Parkinson's disease[1] who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the available combinations of antiparkinsonians
Intervention	Treatment and dosage form: levodopa/carbidopa intestinal gel Method of administration: continuous intestinal infusion into the upper small intestine by means of a portable, patient-controlled pump Dose: adjusted according to the patient's clinical status and the optimal therapeutic response Duration: a minimum of 4 weeks
Comparator	Other combinations of oral antiparkinsonians
Results	**Efficacy segment** *Primary outcome* ● Involuntary motor fluctuations, as evaluated on the basis of: ○ Off-time (tremor/stiffness) (diary, item 39 of the Unified Parkinson's Disease Rating Scale [UPDRS]) ○ On-time without troublesome motor fluctuations (diary) ○ On-time without motor fluctuations (diary) ○ Evaluation of the functional and clinical aspects of the disease (Parts III and IV of the UPDRS) *Secondary outcome* ● Quality of life, as assessed by: ○ Validated questionnaire: Parkinson's disease questionnaire - PDQ-39 or PDQ-8 (total score) ○ Validated questionnaire: UPDRS (Part II) ○ Number of hours of care provided by caregivers **Safety segment** *Outcome measures* ● Complications associated with installing the percutaneous endoscopic gastrostomy (PEG) tube (e.g., intestinal perforations, bleeding, infections and peritonitis) ● Long-term complications associated with the method of administration, (i.e., an intestinal tube) ○ Complications associated with the tube (e.g., accidental removal, leak in the device and secondary perforation) ○ Complications associated with the pump
Types of publications	I HTA reports, systematic reviews with or without a meta-analysis, and evidence-based practice guidelines II Randomized clinical trials (RCTs) III Observational studies IV Prospective case series of 20 or more patients V Case studies VI Guidelines and expert opinions
LIMITS	
Languages: French and English	**Period:** January 2000 to September 25, 2014

[1] Advanced Parkinson's disease, based on the definition used by the studies' authors.

3.2 Survey

The operational practices pertaining to continuous administration of LCIG were documented by means of a telephone survey of a Quebec university hospital that introduced this treatment modality in the recent past. The interview guide used is presented in Appendix 5.

3.3 Contextualization

The assessment was carried out in collaboration with an interdisciplinary working group. The group's composition is shown on Page iii. Its members participated in identifying the issues and aspects to be considered for the data search and in synthesizing the knowledge derived from the assessment. These discussions also contributed to the understanding of the institution's context, to the identification of the organizational aspects to be taken into consideration, and to the development of recommendations.

3.4 Review

This assessment report was reviewed by the working group's members (see "Acknowledgments" section) and was reviewed and approved by the HTAU's Scientific Committee during its meeting of November 25, 2014.

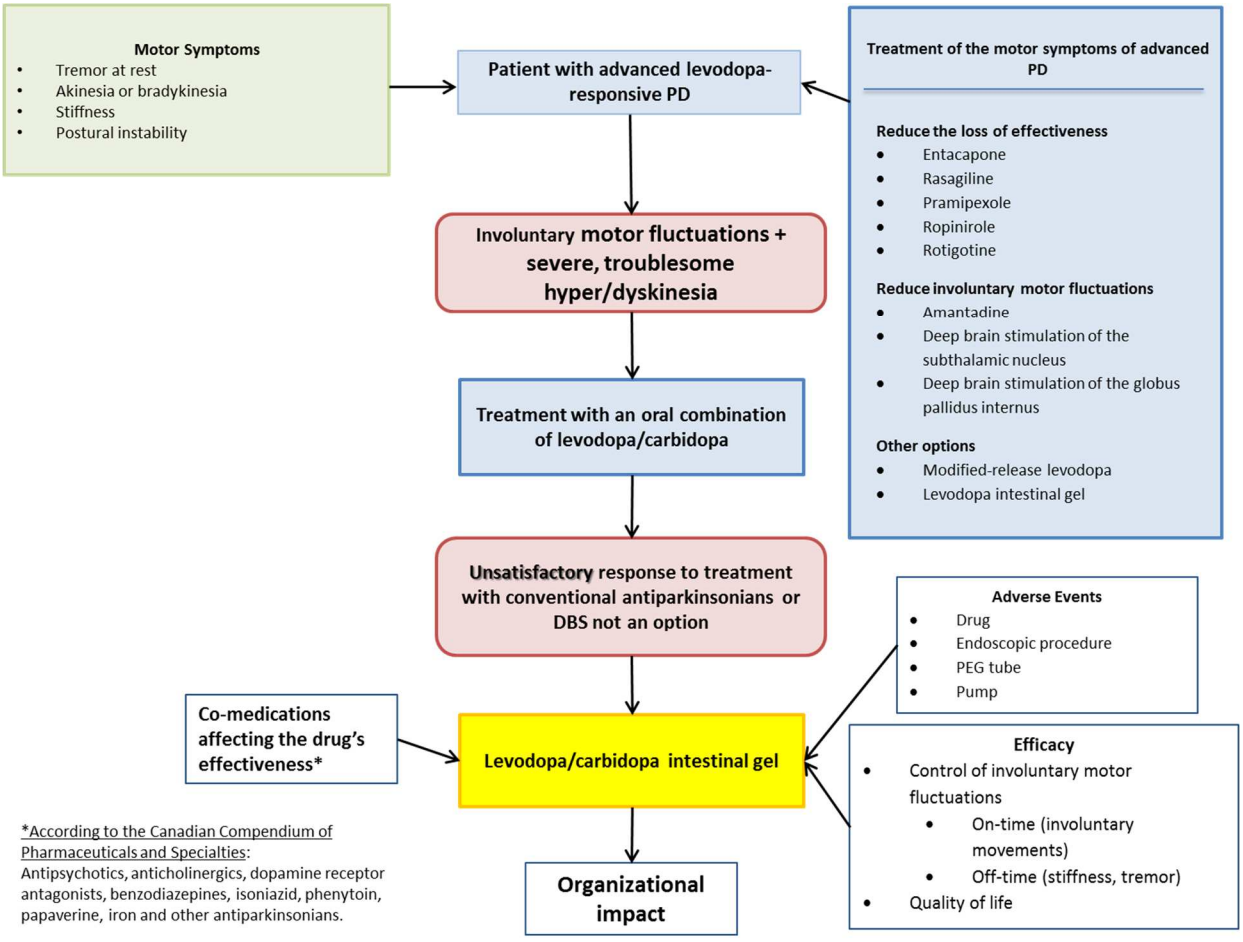
4. GENERAL INFORMATION

4.1 Parkinson's disease

According to Parkinson Society Canada, close to 100,000 Canadians have PD, including 25,000 in Quebec [1]. PD is a neurodegenerative disease that manifests mainly as motor problems. These are essentially caused by the progressive dopaminergic neuronal loss in the midbrain [7]. It is estimated that at the time of diagnosis, approximately 80% of these cells have already stopped functioning [1]. However, the loss of other neurotransmitters, such as acetylcholine, noradrenaline and serotonin, has also been linked to PD [8].

Patients with PD present with motor and non-motor symptoms, which, in general, affect their autonomy and quality of life at different levels (personal, social and professional). The most common motor symptoms of PD are tremor at rest, a slowing of movement, postural instability and muscle stiffness [1]. The non-motor symptoms of PD include various manifestations associated with mental health problems and autonomic nervous system dysfunctions (Figure 1) [1].

Figure 1. Overview of the problem - logic model



Parkinson's disease does not progress in a linear fashion, and symptom progression is more or less rapid, depending on the case, which makes it difficult to predict. Hoehn and Yahr developed a system for staging PD based on the presence of functional impairments and objective signs (Table 2) [9]. This classification scale is currently the one used most. It does, however, have certain limitations, such as the inclusion of indices that do not progress in a parallel fashion and that are sensitive to other motor fluctuations or other non-motor problems, and the use of general criteria for staging PD [8]. Thus, a given stage of the disease can lead to the inclusion of patients with different degrees of motor dysfunction. According to this scale, patients included in stages 4 and 5 are considered to be at an advanced stage of the disease [10].

Table 2. Progression of PD according to the Hoehn and Yahr scale

Stage	Main Clinical Manifestations
1	The symptoms are unilateral and include at least two of the following three symptoms: tremor at rest, stiffness and akinesia.
2	The symptoms start to become bilateral and can include speech problems, deformed posture and difficulty walking.
3	The bilateral symptoms worsen, and balance problems may develop. The patient's autonomy is not generally affected.
4	There is disability, but the patient's autonomy is not generally affected. Bradykinesia is more pronounced, as are motor fluctuations, if present.
5	The patient is confined to a wheelchair or bed.

Adapted from Quebec Parkinson Society [1].

Certain questionnaires for evaluating PD have been designed to permit optimal patient management. The Unified Parkinson's Disease Rating Scale (UPDRS) is one of the questionnaires used most to objectively assess the progression of PD. It consists of four parts related to non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), motor examination (Part III) and motor complications of therapy (Part IV). Each item in the questionnaire is assessed by a health professional during an interview with the patient. The lower the scores obtained on each part, the better the patient's situation is for these outcomes. The Parkinson Disease Questionnaire-39 (PDQ-39) is a 39-item, self-administered questionnaire for assessing the overall quality of life of PD patients [12]. It consists of eight scores specific to mobility, the activities of daily living, emotional well-being, psychological discomfort, social support, cognitive impairments, communication and bodily discomfort. A lower score indicates a better quality of life.

4.2 Therapeutic management of Parkinson's disease

It is important to note that no therapeutic approach can slow or stop the progression of PD. Actually, the objective of treatment is to reduce the symptoms so that the patient can attend to his/her daily activities. The most appropriate choice of treatment depends on different factors: the predominant symptoms of the disease, its stage, the adverse reactions, and the patient's preference and characteristics. There are a number of treatment strategies involving different classes of drugs, surgical procedures (e.g., DBS), physiotherapy and occupational therapy.

Currently, six classes of drugs are available in Canada [13]:

- Dopamine precursors (immediate- and modified-release levodopa in combination with carbidopa or benserazide)
- Dopamine degradation inhibitors
    - Monoamine oxidase B (MOA-B) inhibitors (rasagiline, selegiline)
    - Catechol-O-methyl transferase (COMT) inhibitors (entacapone)
- Dopaminergic agonists (pramipexole, ropinirole, bromocriptine)
- Noncompetitive N-methyl-d-aspartic acid (NMDA) receptor antagonists (amantadine)
- Anticholinergics (benztropine, ethopropazine, procyclidine, trihexyphenidyl)

According to the Canadian Neurological Sciences Federation, levodopa is presently the most effective drug for treating the symptoms of PD [7]. It is absorbed in the intestine and is transported via the bloodstream to the brain, where it is converted to dopamine [1]. In the advanced stages of the disease, the clinical response to levodopa is reduced, and the duration of its

benefits when a dose is administered may gradually shorten, which results in a loss of effectiveness [7]. Its long-term use could contribute to the development of motor fluctuations and to an on-off effect. Actually, as PD progresses, the motor fluctuations can give way to a phenomenon characterized by a sudden and unpredictable passage from a state where the symptoms are controlled with drugs (on-period) to a period where are they are not (off-period). The appearance of these motor fluctuations, involuntary movements and non-motor complications as the disease progresses requires repeated pharmacological adjustments and perhaps other treatment options. In such cases, strategies involving continuous dopaminergic stimulation may be considered.

4.2.1 Continuous administration of levodopa/carbidopa with an intestinal gel

Health Canada has authorized, subject to certain conditions, the marketing of a levodopa/carbidopa intestinal gel (Duodopa™) for the treatment of advanced PD in levodopa-responsive patients who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the available combinations of antiparkinsonians [13]. This authorization is based on the promising nature of the clinical data, which need to be confirmed by further clinical studies.

This drug is a combination of levodopa (20 mg/mL) and carbidopa (5 mg/mL) in the form of an intestinal gel. The gel is delivered directly into the duodenum by means of a portable pump [13]. Levodopa is coadministered with carbidopa, a peripheral DOPA decarboxylase inhibitor, in order to increase its bioavailability and reduce its elimination. The administration of this treatment requires the insertion of a percutaneous endoscopic gastrostomy (PEG) tube through the abdominal wall. Since LCIG is administered directly into the duodenum, its main advantage seems to be that it maintains a stable plasma levodopa concentration within the patient's optimal therapeutic range, which is not the case with the other available combinations of antiparkinsonians.

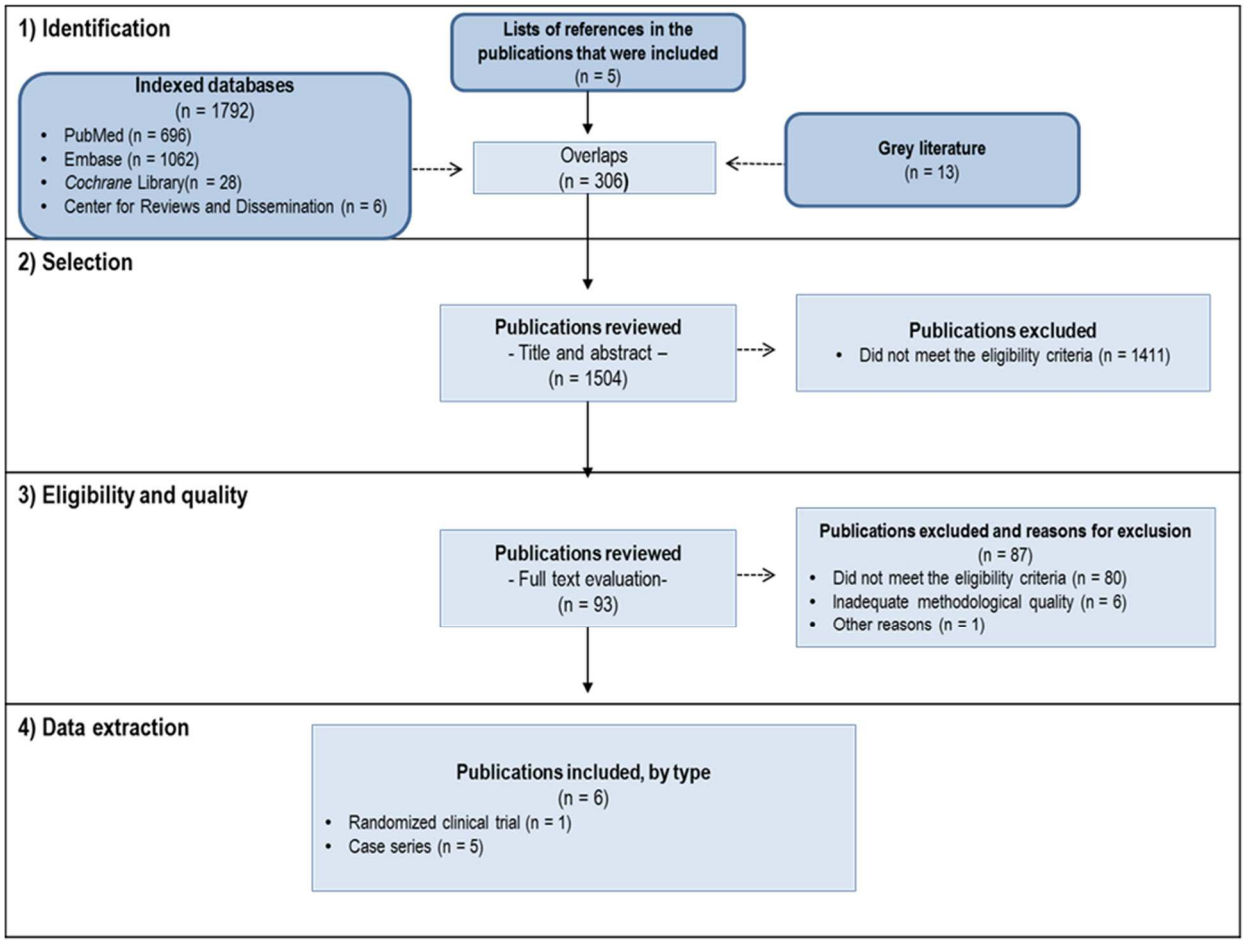
However, its use is limited by certain complications associated with the drug or its method of administration, which can lead to surgeries, hospitalizations or the discontinuation of the treatment [14]. The adverse reactions of this drug are similar to those observed with the oral form of levodopa/carbidopa. The most common serious adverse reactions of levodopa include an irregular heartbeat and changes in the patient's mental status [13]. According to the product monograph for the LCIG approved by Health Canada (Duodopa™), the endoscopic procedure performed to install the tube and the presence of the intestinal tube necessary for administering the treatment can also lead to adverse events, including tube dislocation, obstruction, kinking and knotting, abdominal pain, and wound site infection [15]. More rarely, serious complications have been observed, such as bleeding, lesions of the GI tract mucosa, inflammation of the abdominal cavity membrane (peritonitis) and pneumoperitoneum [15].

5. RESULTS

5.1 Efficacy

The search strategy for literature on the efficacy of continuous administration of LCIG led to the identification of 1504 publications. After the selection and the assessment of study eligibility, 11 publications were included [16-26]: two evidence-based clinical practice guidelines [16, 17], one RCT [18], five prospective case series [19-23] and three expert opinions [24-26]. Figure 2 shows the publication selection flowchart. The list of excluded publications and the reasons for their exclusion are presented in Appendix 4. It should be noted that the literature search led to the identification of one nonrandomized controlled study of the efficacy of continuous administration of LCIG in patients with advanced PD [27], but given its poor methodological quality, this study was not included for the purposes of this report.

Figure 2. Publication selection flowchart for the efficacy segment



5.1.1 Reviews

The scientific literature search did not yield any systematic reviews or meta-analyses of the efficacy of the administration of LCIG in patients with advanced levodopa-responsive PD who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the available combinations of antiparkinsonians or for whom DBS is not an option.

5.1.2 Randomized clinical trial

Olanow *et al.* (2014)

Olanow *et al.*'s RCT aimed to evaluate the efficacy and safety of the continuous LCIG administration via an intrajejunal percutaneous tube in adults with advanced PD with off-periods that could not be controlled satisfactorily with optimized medical therapy [18]. To participate in this study, eligible patients had to have received stable doses of levodopa for at least 4 weeks prior to enrolment in the study, have distinct on- and off-periods, and have at least 3 hours of off-time per day. The use of other antiparkinsonians was allowed during the study if the required drug doses had been stable for at least 4 weeks prior to randomization. The doses of the other antiparkinsonians had to remain stable throughout the study. The study exclusion criteria were atypical Parkinson's syndrome or secondary parkinsonism, previous neurosurgical treatment for PD, clinically significant medical, psychiatric or laboratory abnormalities in the investigators' judgement, a medical condition that could affect the absorption, distribution, metabolism or excretion of the study drug, and a contraindication to the placement of an intrajejunal percutaneous tube. Prior to study entry, eligible subjects were instructed by the investigators on the use of a home diary for recording on- and off-periods. There had to be more than 75% concordance between the results recorded by the subjects and the investigator rating, and they had to have completed their home diary more than 75% of the time.

In all, 71 eligible patients from 26 American, German and New Zealand hospitals were randomly assigned at a ratio of 1:1 to receive one of the following two treatments:

- Comparator (C): A combination of immediate-release levodopa (100 mg)/carbidopa (25 mg) capsules plus the continuous administration of a placebo intestinal gel via an intrajejunal percutaneous tube (n = 34);
- Intervention (I): Placebo capsules and the continuous administration of levodopa (20 mg/mL)/carbidopa (5 mg/mL) intestinal gel via an intrajejunal percutaneous tube (n = 37).

The treatment consisted of a morning intrajejunal bolus (5 to 10 mL) followed by continuous administration at a constant rate for the remainder of the day (approximately 16 hours). Treatment administration was stopped overnight. The medication doses were adjusted over a period of 4 weeks. The use of immediate-release levodopa/carbidopa capsules was permitted during the study if persistent off-periods occurred despite the medication. The primary outcome measure for evaluating the response to treatment was the difference in the mean duration of the off-period measured at baseline and at 12 weeks, as recorded by the subject and normalized to a 16-hour day. The main secondary outcome was the changes observed between baseline and at 12 weeks in the duration of on-time without troublesome motor fluctuations. However, other secondary outcome measures, such as the total score on Part II (activities of daily living) and Part III (motor symptoms of the disease) of the UPDRS and the overall PDQ-39 score, were assessed as well.

The study groups seemed balanced in terms of the patients' age (mean age in years: I: 63.7; C: 65.1) and the mean duration of PD (in years: I: 10.0; C: 11.8). However, in the absence of statistical tests, it cannot be determined whether or not there were any significant differences between the groups. Five subjects withdrew from the study after randomization (two in the intervention group and three in the control group). Three of these withdrawals were due to adverse events (hallucinations and psychotic disorder [n = 1], peritonitis [n = 1] and stoma dysfunction [n = 1]). The main results of this study are presented in Table 3.

Table 3. Main results concerning the changes observed between baseline and at 12 weeks with continuous LCIG administration reported in Olanow *et al.*'s RCT (2014).

	Intestinal gel Mean difference (standard error) n = 35	Immediate-release oral form Mean difference (standard error) n = 31	Difference between the treatments (95% CI)	*P*-value
Motor symptoms				
Off-time duration (hours/day)[1]	-4.04 (0.65)	-2.14 (0.66)	-1.91 (-3.05 to -0.76)	0.0015
Duration of on-time without motor fluctuations (hours/day)[1]	+3.37 (1.04)	+1.09 (1.05)	+2.28 (+0.47 to +4.09)	0.0142
Duration of on-time without troublesome motor fluctuations (hours/day)[1,2]	+4.11 (0.75)	+2.24 (0.76)	+1.86 (+0.56 to +3.17)	0.0059
Duration of on-time with troublesome motor fluctuations (hours/day)[1]	-0.11 (0.52)	-0.03 (0.52)	-0.08 (-0.98 to +0.82)	0.8574
UPDRS Part III (mean score during on- periods)	-1.5 (2.4)	-2.9 (2.4)	+1.4 (-2.8 to +5.6)	0.5020
Quality of life and activities of daily living				
PDQ-39 (mean score)	-10.9 (3.3)	-3.9 (3.2)	-7.0 (-12.6 to -1.4)	0.0155
UPDRS Part II (mean score during on- periods)	-1.8 (1.3)	+1.3 (1.3)	-3.0 (-5.3 to -0.8)	0.0086

[1] All the duration were normalized to a 16-hour day and estimated from the patient's home diary.
[2] Sum of the daily duration of on-periods without motor fluctuations and the duration of on-periods with non-troublesome motor fluctuations.

Overall, the results of Olanow *et al.*'s RCT indicate, after a 12-week follow-up, that compared to the immediate-release oral form, LCIG administration reduced, in a statistically significant fashion, mean daily off-time and increased mean daily on-time without motor fluctuations and without troublesome motor fluctuations. However, no significant impact was observed in terms of mean daily on-time with troublesome motor fluctuations. The reported benefits between the treatments measured from the on-/off-period data in the home diaries did not translate into a statistically significant reduction in the mean motor symptom score as evaluated by means of UPDRS Part III. However, at 12 weeks, each intervention led to statistically significant improvements in the scores on that part III of the questionnaire from the baseline scores. As for quality of life, the results of this RCT suggest that, compared to the oral form, LCIG administration was statistically associated with an improvement in the subjects' quality-of-life scores, regardless of the questionnaire used to evaluate this outcome (PDQ-39, UPDRS Part II). Based on the observed results, the authors of this RCT concluded that continuous administration of LCIG is a promising option for controlling motor complications in patients with advanced PD. However, in their view, studies are needed to determine if the continuous administration of levodopa can reduce established motor fluctuations and off-periods over a longer term.

Olanow *et al.*'s RCT is of good methodological quality. The study's authors used an appropriate randomization method and took steps to ensure the blinding of the subjects, personnel and investigators throughout the study. However, it could not be clearly determined if both groups of randomized patients were really similar at baseline, given the lack of comparative statistics. An imbalance between the groups could have led to an overestimation of the effect, since the subjects in the comparison group were, on average, older and had had PD longer. Furthermore, choosing, at the outset, participants based

on their ability to fill out a diary satisfactorily could have introduced a selection bias that limits the ability to generalize these results to other PD populations. As well, the short duration of follow-up (12 weeks) does not allow to draw any conclusions about the efficacy and safety of this long-term treatment modality, as pointed out by the authors. Although the statistical analysis was not performed according to the intent-to-treat principle, the low lost-to-follow-up rate (less than 10%) probably minimizes the impact of this factor on the observed results. Lastly, there is a potential conflict of interest in this RCT, since, in addition to funding the study, AbbVie Corporation participated in developing the design and was also responsible for the data collection, the patient follow-up, the statistical analyses and the manuscript's review.

5.1.3 Case series

After the eligibility and methodological quality assessment, five prospective case series, each involving at least 20 patients and presenting before and after measurements, were included for this assessment report [19-23, 27]. The exclusion criteria used in each of these studies are presented in Appendix 6 and their general characteristics, in Table 4. The primary objective of three of these case series was to evaluate the efficacy of continuous administration of LCIG in terms of motor symptoms and quality of life [20, 21, 23]. Although it contains some efficacy data, Fernandez *et al*.'s article reports interim results of a study of the long-term safety of the LCIG combination [22]. As for Sensi *et al*.'s study, it was aimed at identifying the predictive factors for characterizing the best candidates for this treatment [19].

Table 4. General characteristics of the selected case series concerning continuous LCIG administration in advanced Parkinson's disease

Authors (year) [Ref.] N included	n analyzed (%)	Population		Intervention (LCIG)			
		Mean age (years)	Mean time since diagnosis (years)	Type of pump	Mean levodopa dose (mg)	Duration of treatment (hrs/day)	Follow-up (months)
Caceres-Redondo *et al*. (2014) [20] n = 29	16 (55)	64.5 ± 9	14.1 ± 3.9	Portable	1671.7 ± 477	14	> 24
Fernandez *et al*. (2013) [22] n = 192	166 (86)	64.1 ± 9.1	12.4 ± 5.8	CADD-Legacy	NR	16	3
Honig *et al*. (2009) [23] n = 22	22 (100)	58.6 ± 9.1	15.3 ± 5.9	NR	2036.5 ± 850.17	19.5	6
Sensi *et al*. (2014) [19] n = 28	17 (61)	67.6 ± 6.1	15.5 ± 4.0	NR	1504 ± 540[a]	NR	24
Zibetti *et al*. (2013) [21] n = 25	17 (68)	69.9 ± 5.8	12.1 ± 4.1	CADD-Legacy	1127 ± 249	14	36

NR: not reported.

[a]Doses calculated from the mean daily volume of intestinal gel reported by the authors (75.2 ± 27 mL/day) and the levodopa concentration (20 mg/mL) in the drug (Duodopa™) [28].

5.1.3.1 Effect of continuous administration of LCIG on off-time

Four of the case series included evaluated the efficacy of continuous administration of LCIG in reducing off-time. Three of them evaluated this outcome using item 39 of the UPDRS questionnaire [19, 21], while the other used a patient diary for recording the duration of off-periods [22]. Item 39 of the UPDRS questionnaire evaluates the patient daily proportion of off-time. The results for this outcome are presented in Table 5.

Table 5. Summary of the results of the evaluation of the effect of continuous LCIG administration on off-time

Authors (year) [Ref.]	n	Follow-up (months)	Off-time		*P*-value	Difference in mean score (follow-up – baseline)[a]	Relative difference in score[b]
			Baseline	Follow-up			
Item 39 of the UPDRS questionnaire (mean scores ± standard deviations)							
Caceres-Redondo *et al*. (2014) [20]	16	> 24	58.1 ± 11.5	24.6 ± 7.2	< 0.001	- 33.5	- 57.7%
Sensi *et al*. (2014) [19]	17	24	2.3 ± 0.9	1.0 ± 0.6	< 0.00001	- 1.3	- 56.5%
Zibetti *et al*. (2013) [21]	17	36	1.6 ± 0.8	0.8 ± 0.6	< 0.01	- 0.8	- 50.0%
Diary (mean in hrs/day)							
Fernandez *et al*. (2013) [22]	166	3	6.7 ± 2.4	2.8[c]	< 0.001	- 3.9	- 58.2%

[a] Calculated by the HTAU according to the following formula: (value at follow-up - baseline value).
[b] Calculated by the HTAU according to the following formula: ([value at follow-up/baseline value] - 1) x 100.
[c] Value calculated from the results published in the original study.

Overall, the results of the case series indicate that, in comparison to the baseline values, continuous administration of LCIG for a period of 24 to 36 months statistically significantly reduced the proportion of off-time in patients with advanced PD, regardless of the evaluation method used. It should, however, be noted that mean scores, both at baseline and at follow-up, reported in the study by Caceres-Redondo *et al.* are inconsistent with those of the studies of Sensi *et al*. and Zibetti *et al*. Item 39 of the UPDRS questionnaire, which is used to assess off-time duration, offers four possible answer choices based on the proportion of such time perceived by the patient. The score varies from 0 points, if the patient has no off-time during his/her day, to 4 points, if more than 75% of his/her day is off-time. There were no data in this article from which this result could be interpreted with certainty. Its authors could not be reached for additional information about this result. Nonetheless, the relative differences in the mean score for item 39 between these studies are similar in magnitude.

5.1.3.2 Effect of continuous administration of LCIG on on-time with or without troublesome motor fluctuations

The efficacy of the continuous intestinal administration of LCIG in terms of on-time with or without motor fluctuations was evaluated by Fernandez *et al*. by means of a patient diary [22]. After a 3-month follow-up, they observed that the mean daily duration of on-time without troublesome motor fluctuations was significantly greater by 4.6 ± 3.5 hours per day with this treatment compared to baseline. As for on-time with troublesome motor fluctuations, a significant reduction of 0.6 hours per day ($p < 0.05$) was observed with this treatment.

5.1.3.3 Effect of continuous administration of LCIG on the motor symptoms of PD

The impact of continuous administration of LCIG on the motor symptoms of PD was assessed in five case series [19-23) using Part III of the UPDRS questionnaire. Motor symptoms were evaluated when the subjects were in on-periods in all the studies [19-23] and in off-periods in two of them [20, 21]. A summary of these results is presented in Table 6.

Table 6. Summary of the results of the case series on the evaluation of the impact of continuous LCIG administration on the motor symptoms of PD according to the UPDRS-III score

Authors (year) [Ref.]	n	Follow-up (months)	Motor symptom mean score		*P*-value	Difference in mean score (follow-up – baseline)[a]	Relative difference in score[b]
			Baseline	Follow-up			
Evaluation during on-periods							
Caceres-Redondo *et al.* (2014) [20]	16	> 24	27.2 ± 8.1	29.5 ± 6.4	NS	+ 2.3	+ 8.5%
Fernandez *et al.* (2013) [22]	166	3	28.4 ± 12.9[c]	20.6[d]	< 0.001	- 7.8	- 27.5%
Honig *et al.* (2009) [23]	22	6	19.1 ± 14	11.6 ± 7.2	0.002	- 7.5	- 39.3%
Sensi *et al.* (2014) [19]	17	24	35.5 ± 11.5	34.7 ± 12.4	NS	- 0.8	- 2.3%
Zibetti *et al.* (2013) [21]	17	36	23.2 ± 9.2	32.2 ± 12.6	< 0.01	+ 9	+ 38.8%
Evaluation during off-periods							
Caceres-Redondo *et al.* (2014) [20]	16	> 24	47.8 ± 8.9	45.5 ± 8.9	NS	- 2.3	- 4.8%
Zibetti *et al.* (2013) [21]	17	36	43.1 ± 13.7	48.4 ± 12.4	< 0.05	+ 5.3	+ 12.3%

NS: not significant.
[a] Calculated by the HTAU according to the following formula: (value at follow-up - baseline value).
[b] Calculated by the HTAU according to the following formula: ([value at follow-up/baseline value] - 1) x 100.
[c] Score determined from one to four hours after the administration of the morning bolus of LCIG.
[d] Value calculated from the results published in the original study.

In all case series analyzed, two of the studies found that continuous administration of LCIG was associated with a statistically significant improvement in the motor symptoms of PD [22, 23], while the results of two other did not indicate any change in these symptoms [19, 20]. The data from one of these studies suggest that continuous administration of LCIG is associated with a deterioration of the motor symptoms of PD [21]. An analysis of all the results seems to indicate that continuous administration of LCIG was associated with a statistically significant improvement in motor symptoms in the studies with a short follow-up (3 and 6 months). Furthermore, studies that did not show any benefit regarding this outcome had follow-ups of 24 months or longer.

5.1.3.4 Effect of continuous administration of LCIG on treatment-related motor complications

The motor complications associated with continuous administration of LCIG were evaluated in four case series [19-21], using Part IV of the UPDRS questionnaire as the measurement instrument. A summary of the results is presented in Table 7.

Table 7. Summary of the results of the case series on continuous LCIG administration and treatment-related motor complications according to the UPDRS-IV score

Authors (year) [Ref.]	n	Follow-up (months)	Motor complication score mean		*P*-value	Difference in mean score (follow-up – baseline)[a]	Relative difference in score[b]
			Baseline	Follow-up			
Caceres-Redondo *et al.* (2014) [20]	16	> 24	8.7 ± 2.3	6.7 ± 2.8	< 0.05	- 2.0	- 23.0 %
Honig *et al.* (2009) [23]	22	6	10.5 ± 2.9	4.5 ± 2.2	0	- 6.0	-57.1 %
Sensi *et al.* (2014) [19]	17	24	8.4 ± 2.5	4.4 ± 1.9	<0.00001	- 4.0	-47.6 %
Zibetti *et al.* (2013) [27]	17	36	8.4 ± 3.2	5.6 ± 2.8	< 0.01	- 2.8	- 33.3 %

[a] Calculated by the HTAU according to the following formula: (value at follow-up - baseline value).
[b] Calculated by the HTAU according to the following formula: ([value at follow-up/baseline value] - 1) x 100.

Globally, the results of the case series indicate that continuous administration of LCIG in patients with advanced PD was associated with a statistically significant decrease of two to six points in the mean UPDRS-IV score. These results therefore suggest that treatment-related motor complications are reduced with the use of this medication.

5.1.3.5 Effect of continuous administration of LCIG on the quality of life of patients with advanced PD

The effect of continuous administration of LCIG on the quality of life of patients with advanced PD was assessed with different instruments in case studies: the validated PDQ-39 [20-22], a short version of this questionnaire, the PDQ-8 [19, 23], or the Part II of the UPDRS questionnaire (activities of daily living) [20-22]. The results of the selected studies examining this outcome are presented in Table 8.

The results regarding quality of life as evaluated with the PDQ-39 and PDQ-8 indicate that continuous administration of LCIG was associated with a reduction in the mean score (improvement in quality of life) [19, 23]. The results were statistically significant in all these studies, regardless of the duration of follow-up. It is also noted, in Table 8, that the relative difference in the mean score measured before and after was higher with the PDQ-8, which suggests that this tool has less good specificity for determining the extent of observed changes. However, the improvement in the quality of life reported in the studies that used the PDQ-39 [20-22] did not necessarily seem to have a positive impact on the measurement of the subjects' activities of daily living as evaluated by means of the Part II of the UPDRS questionnaire (on-periods). Indeed, the results of two studies suggest deterioration at 24 and 36 months follow-up in the mean score for the evaluation of the activities of daily living [20, 21]. Furthermore, the results of Caceres-Redondo *et al.*'s study seem discordant, as they suggest a possible benefit of this medication for the activities of daily living during off-periods (-12.5%), not during on-periods (+ 13.8%) [20].

Table 8. Summary of the results of the case series on the evaluation of continuous LCIG administration and quality of life according to the score on the PDQ-39, PDQ-8 or the UPDRS Part II

Authors (year) [Ref.]	n	Follow-up (months)	Quality-of-life mean score		*P*-value	Difference in mean score (follow-up – baseline)[a]	Relative difference in score[b]
			Baseline	Follow-up			
PDQ-39							
Caceres-Redondo *et al*. (2014) [20]	16	> 24	84.2 ± 18.7	74.3 ± 21.3	< 0.05	- 9.9	- 11.8%
Fernandez *et al*. (2013) [22]	166	3	43.2 ± 14.3	32.5[c]	< 0.001	- 10.7	- 24.8%
Zibetti *et al*. (2013) [21]	17	36	59.2 ± 18.7	43.1 ± 13.9	< 0.01	- 16.1	- 27.2%
PDQ-8							
Honig *et al.* (2009) [23]	22	6	44.2 ± 18.4	20.7 ± 12.0	0.0003	-23.5	- 53.2%
Sensi et al. (2014) [19]	17	24	46.3 ± 13.7	29.9 ± 17.0	0.006	-16.4	-35.4%
UPDRS Part II (on-periods)							
Caceres-Redondo *et al.* (2014) [20]	16	> 24	14.5 ± 5.3	16.5 ± 5.0	NS	+ 2.0	+ 13.8%
Fernandez *et al.* (2013) [22]	166	3	17.0 ± 6.4	11.9[c]	< 0.001	- 5.1	- 30.0%
Zibetti *et al.* (2013) [21]	17	36	16.1 ± 7.2	20.9 ± 7.5	< 0.05	+ 4.8	+ 29.8%
UPDRS Part II (off-periods)							
Caceres-Redondo *et al.* (2014) [20]	16	> 24	27.2 ± 8.5	23.8 ± 5.9	< 0.05	- 3.4	- 12.5%
Zibetti *et al.* (2013) [21]	17	36	23.2 ± 8.5	25.3 ± 7.3	NS	+ 2.1	+ 9.1%

NS: not significant

[a] Calculated by the HTAU according to the following formula: (value at follow-up - baseline value).

[b] Calculated by the HTAU according to the following formula: ([value at follow-up/baseline value] - 1) x 100.

[c] Value calculated from the results published in the original study.

5.1.3.6 Ongoing and unpublished studies

Four original studies whose primary objective seems to meet the eligibility criteria for this assessment in terms of population, intervention, comparator and outcome were identified (Table 9). To our knowledge, none of the results of these studies have been published yet.

Table 9. Ongoing and unpublished studies

Identifier	Study design	Funding	Primary outcomes	Secondary outcomes	Follow-up (months)	Recruitment (n patients)	Anticipated end date
NCT01747655	Comparative, prospective	AbbVie	• Activities of daily living	• Motor symptoms of PD • Complications of the medication • Quality of life	12	60	April 2015
NCT01291537	RCT	CHU de Poitiers	• Long-term efficacy	NR	NR	60	NR
NCT01754129	Prospective case series	AbbVie	• Motor complications of the medication • Off-time duration	• UPDRS-I, II and IV • Quality of life	24	150	Sept. 2015
NCT00360568	Prospective case series	AbbVie	• Long-term safety	• Off-time duration • Quality of life	12	60	Oct. 2012

5.1.4 Summary and overall appraisal of the evidence regarding the efficacy of continuous LCIG administration

In general, few studies of good methodological quality were identified for this assessment report. The evidence concerning the efficacy of the levodopa/carbidopa combination administered as an intestinal gel for the treatment of advanced PD is based on one RCT and five case series with numerous limitations. The results of these studies indicate that continuous LCIG administration via a gastrojejunal tube is associated with benefits for the treatment of advanced PD, specifically in terms of on- and off-time duration and quality of life. However, the interpretation of the results of these studies with regard to clinical validity is limited by numerous factors, including a small number of subjects, a large number of losses to follow-up, a short duration of follow-up, potential methodological biases, and potential conflicts of interest.

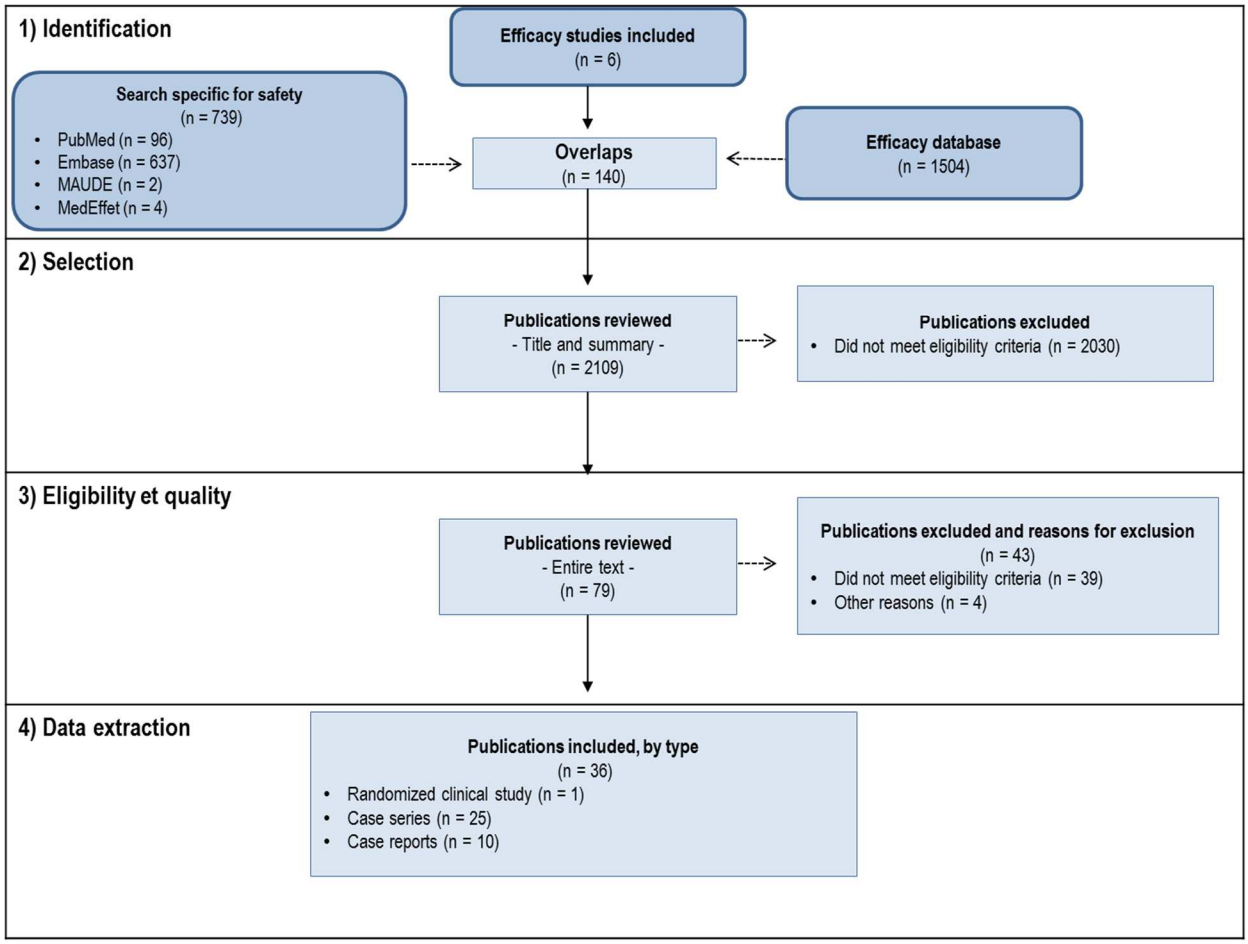
The results of the case series [19-23] are generally consistent with those of Olanow *et al.*'s RCT [18]. Although case series are a less reliable source of evidence for establishing proof, they do have the advantage of being more representative of clinical reality. These studies were similar in terms of subject age (approximately 60 years and older) and disease duration (12 years and longer). The high number of patients lost to follow-up is a significant limitation of these case series, which, in addition to other factors, may have biased the results in favour of this treatment. As well, most of the observed losses to follow-up in these case series were due to adverse events. Furthermore, in these studies, no statistical adjustment was made to the results for the confounding variables. It is also noted that one of these case series was industry-funded [22] and that four of them reported potential conflicts of interest declared by the authors [19, 20, 22, 23]. In Olanow *et al.*'s RCT, AbbVie Corporation participated in developing the study design and was responsible for the data collection, the patient follow-up, the statistical analyses and the manuscript's review. Different inclusion and exclusion criteria were used in these studies. For example, in three case series, a minimal response to levodopa had to have been demonstrated in order for a patient to be eligible for this study [21-23]. However, despite this clinical heterogeneity, secondary or atypical PD symptoms, or clinically significant psychiatric disorders were common subject exclusion criteria. Another source of heterogeneity observed resided in the use of different measurement instruments to evaluate the efficacy of Duodopa™, which limits the ability to pool, if only qualitatively, the results of the different studies to examine them as a whole. The results show, for example, significant differences in diary-evaluated on- and off-time duration, while a mitigated impact on the motor symptoms of the disease was reported with the Part III of the UPDRS questionnaire. The use of a diary enables patients to record more precisely, to the nearest half-hour, daily changes in symptoms during on- and off-periods, while the use of the UPDRS

questionnaire mainly provides a qualitative estimate of the observed changes in motor capacities. The duration of follow-up is another heterogeneity factor between the studies. Most of the studies point to a positive short-term effect of continuous LCIG administration on the symptoms of the disease. However, from the available data, no statement can be made about this treatment's long-term efficacy. Some results suggest that the effect of this treatment would be smaller for follow-ups of 24 months or longer. However, given the absence of a comparison group, it is not possible to determine whether its efficacy is influenced by the natural course of the disease or by other factors, such as the duration of treatment, the daily dose received or the measurement instruments used.

5.2 Safety

The search strategy for the purpose of reviewing the literature on the safety of continuous LCIG yielded 2109 publications. After the selection and eligibility assessment process, 36 publications were included: one RCT [18], 25 case series [19 20, 22, 29-51] and 10 case reports [50, 52-60]. Figure 3 shows the publication selection flowchart. The list of excluded publications and the reasons for their exclusion are presented in Appendix 4.

Figure 3. Publication selection flowchart for the safety segment



These studies reviewed the adverse events that had occurred in a total of 895 patients treated with LCIG, 320 of whom were in four of the studies included for the efficacy segment [18-20, 22]. A list of the adverse events associated with the endoscopic procedure or the equipment used to administer the treatment (pump and tube), together with the overall proportion of patients in whom these events were reported, is presented in Table 10. Frequencies of adverse events associated with the endoscopic procedure required for installing the tube ranging from 0.1 to 11.4% were noted. Few cases of serious adverse events, such as peritonitis (2.2%), pneumoperitoneum (2.3%) or death (0.4%), were reported. Frequencies of adverse effects associated with the equipment used to administer the drug ranging from 0.1 to 14.6% were reported as well. The most frequent adverse events are tube dislocation, occlusion, kinking, knotting and leakage, and accidental tube removal.

According to the product monograph for an LCIG approved by Health Canada (Duodopa™), the adverse events associated with the endoscopic procedure or the use of the tube for administering this drug, including adverse events such as nausea, abdominal pain and flatulence, were reported in 73.7% (n = 291) of the 395 patients who had received this treatment in clinical trials [15]. The most frequent adverse events associated with the endoscopic procedure required for installing the

tube were the same as those noted in the studies included for this report, namely, wound site infection (21.0%) and granulomas (18.2%). A slightly higher prevalence of serious adverse reactions is reported in the product monograph, such as peritonitis (3.0%) and pneumoperitoneum (6.1%), compared to those indicated in Table 10. The product monograph does not mention death. In addition, fewer cases of tube dislocation (2.5%), occlusion, kinking or knotting (1.5%) are reported in the pharmaceutical product monograph than were noted when reviewing the publications on the drug's safety. On the whole, 3.5 % of the patients had experienced at least one adverse event associated with the endoscopic procedure or the use of the tube that led to the discontinuation of the treatment.

5.2.1 Summary and overall appraisal of the evidence regarding the safety of continuous LCIG

The analysis of the research results on the safety of continuous LCIG gel suggests that this treatment is associated with a relatively high frequency of adverse events, although the vast majority of them are mild. The main problems reported with regard to the endoscopic procedure required for installing the tube are wound site infections and granulomas, which occurred in 11.4% and 4.7% of the cases, respectively. Those associated with the equipment for administering the drug include tube dislocation, occlusion, kinking, knotting and leakage, and accidental tube removal. Tube dislocation is the adverse event reported most often, with a prevalence of about 1 in 5 patients. The review of the different publications pertaining to the safety of this practice also indicates that one or more adverse events can occur more than once in a given patient during follow-up. This is especially the case for the adverse events associated with the equipment for administering the drug. In the total population included in the efficacy studies, the most frequent adverse events were generally the same as those observed in the total population in the studies included for the safety segment and those reported in the pharmaceutical product monograph. One of the main limitations of the product monograph is, though, that the reported adverse events cannot be linked to specific studies, although a list of references is available at the end of the monograph.

The adverse events associated with the endoscopic procedure are mostly mild to moderate and are representative of those generally associated with PEG tube placement for other indications, such as enteral feeding [63]. In effect, overall, complication rates ranging from 4 to 23.8% following the installation of a PEG tube for various other indications are generally noted in the literature. Three to 4% of patients experience major complications (e.g., bleeding, peritonitis and death), while minor complications are more common, occurring in 7.4 to 20.0% of cases (e.g., ileus, peristomal infections, leaks, gastric ulcers, and accidental tube removal) [61]. These frequencies of minor and major complications are comparable to those observed in the included studies on the safety of continuous administration of LCIG. In addition, in the studies included for this report, the mortality rate attributable to PEG tube placement was 0.4%. This rate is similar to the mortality rates generally reported for PEG tube placement for other indications, which vary from 0 to 2.1% [61].

Table 10: Adverse events reported in the included publications concerning safety

Adverse events	Cases reported in all the studies (n = 895)		Cases reported in four of the studies included for the efficacy segment (n = 320)
	n studies (Ref.)	Prevalence n (%)	Prevalence n (%)
Adverse events associated with the endoscopic procedure required to install the tube			
Wound site infection	13 [18-20, 22, 34, 35, 40, 41, 44, 47, 51]	102 (11.4)	43 (13.4)
Granulomas	4 [19, 20, 22, 49]	42 (4.7)	36 (11.3)
Peritonitis	8 [18, 19, 22, 29, 34, 37, 38, 47]	20 (2.2)	10 (3.1)
Pneumoperitoneum	5 [18, 20, 22, 39, 46]	21 (2.3)	18 (5.6)
Phlegmon (inflammation)	3 [20, 34, 40]	13 (1.5)	2 (0.6)
Perforation (intestinal, gastric, hepatic)	6 [37-39, 46, 48, 52]	6 (0.7)	----
Intestinal volvulus, ileus, intestinal obstruction	3 [39, 58, 59]	4 (0.4)	----
Duodenal ulcer	4 [19, 39, 46, 53]	5 (0.6)	1 (0.3)
Death	3 [19, 42, 46]	4 (0.4)	2 (0.6)
Bleeding (intestinal, stoma)	1 [39]	2 (0.2)	----
Hyperthermia	2 [35, 48]	2 (0.2)	----
Cardiac arrest	1 [34]	1 (0.1)	----
Adverse events associated with continuous LCIG administration via a PEG tube			
Tube-related			
Tube dislocation	18 [18-20, 22, 30, 32, 34-38, 40-44, 46, 49]	131 (14.6)	37 (11.6)
Tube occlusion, kinking and knotting	20 [18-20, 29-31, 33-38, 40-42, 46, 47, 49, 54]	76 (8.5)	16 (5.0)
Tube leakage	8 [18, 29, 34, 35, 38, 40, 44, 48]	52 (5.8)	3 (0.9)
Accidental removal of the tube or gel cassette	10 [18, 19, 29, 34, 35, 38, 41, 43, 45, 55]	40 (4.5)	3 (0.9)
Tube reinsertion	7 [30, 37, 39, 46, 47, 51, 55]	33 (3.7)	----
Tube replacement	6 [29, 31, 38, 42, 46, 47]	11 (1.2)	----
Tube detachment	1 [52]	2 (0.2)	
Recurrent pancreatitis	1 [53]	1 (0.1)	----
Severe gastroesophageal reflux	1 [38]	1 (0.1)	----
Jejunal incarceration of the tube	1 [41]	1 (0.1)	----
Erosion of the esophagus, ventricle or duodenum caused by the tube	1 [47]	1 (0.1)	----
Cholecystitis	1 [55]	1 (0.1)	----
Other			
Pump failure	9 [18, 19, 44, 47, 48, 56, 57, 60]	39 (4.4)	12 (3.8)

5.3 Clinical practice guidelines and expert opinions

After the assessment of eligibility and methodological quality, two practice guidelines were included for this assessment report [16, 17]. The main recommendations pertaining to the use of LCIG in these guidelines are presented in Table 11.

Table 11. Recommendations regarding continuous LCIG administration in patients with advanced PD

Organization (year) [Ref.]	Objectives of the guideline	Recommendations	Scientific evidence
Movement Disorder Society (2011) [16]	Treatment of the motor symptoms of PD	• The data suggest that the duodenal infusion of levodopa is probably effective for treating motor fluctuations and dyskinesia	• 1 RCT [45]
Scottish Intercollegiate Guidelines Network (2010) [17]	Diagnosis and pharmacological management of PD	• There are not enough data supporting the routine use of intraduodenal levodopa • Intraduodenal levodopa administration is not recommended	• 1 RCT [45] • 3 OSs [35, 44, 62]

RCT: randomized clinical trial; OS: observational study

As well, three expert opinions were identified through the literature search. These publications are of low methodological quality and are based on data that do not seem to be from a systematic scientific literature search. The possibility of a conflict of interest should be considered in two of these expert opinions [24-26]. The methods for developing the recommendations are not spelled out in the publications identified. The main conclusions of these expert opinions are presented in Table 12.

Table 12. Conclusions regarding continuous LCIG administration in patients with advanced PD according to the expert opinions

Authors (year) (Ref.)	Objectives of the expert opinion	Number of experts involved	Conclusions regarding continuous LCIG administration	Scientific evidence
Volkmann *et al.* (2013) [24]	Appropriate therapies for treating the motor symptoms of advanced PD	24	• Benefit for controlling motor fluctuations. Because of a lack of formal data, no firm conclusions can be stated.	• 1 RCT [18]
Kulisevsky *et al.* (2013) [25]	Indications for therapeutic measures for managing advanced PD	16	• Effective in controlling motor fluctuations. Could probably reduce troublesome motor fluctuations. • Despite the complications associated with the infusion device, continuous LCIG administration is generally well tolerated.	• 2 RCTs [18, 63] • 10 OSs [23, 31, 34, 35, 47, 51, 64-68]
Oertel *et al.* (2011) [26]	Modality for controlling the motor complications of advanced PD	20	• May help stabilize patients with motor fluctuations associated with PD or treatment-related motor fluctuations.	• 2 RCTs [45, 63] • 3 OSs [31, 34, 35]

RCT: randomized clinical trial; OS: observational study

5.3.1 Overall appraisal of the clinical practice guidelines

The different evidence-based clinical practice guidelines, which are based on similar scientific evidence (one RCT and three observational studies), arrive at divergent conclusions. One of them suggests that duodenal levodopa infusion is probably effective for treating motor fluctuations and dyskinesia, while the other does not recommend it because of insufficient scientific evidence. These two clinical practice guidelines are of good methodological quality, and their objectives are specific and relevant to the problem examined in this report. Furthermore, despite certain methodological weaknesses, the quality of the literature search used for these practice guidelines was satisfactory. The recommendations issued by these organizations are clear and easily identifiable, and they are based mainly on the results of one RCT [45] and three

observational studies [35, 44, 62]. This evidence was identified during the literature search process but was not included in this report because they do not fulfill the report eligibility criteria. However, the Movement Disorder Society's clinical practice guideline lacks information about its external review process and says little about the aspect of the applicability of the recommendations issued and its editorial independence [16]. Also to be noted are potential conflicts of interest, since the authors of this guideline declare certain ties with companies marketing LCIG (Abbott and Solvay). Despite their methodological weaknesses, the expert opinions identified suggest that the continuous administration of this treatment in patients with advanced PD might be beneficial for controlling motor fluctuations.

In short, it emerges from the analysis of the clinical practice recommendations and the expert opinions that continuous LCIG administration in patients with advanced PD could potentially confer a positive benefit by reducing involuntary motor fluctuations. However, the scope of this recommendation is limited by the number, the designs and the quality of the studies on which it is based.

5.4 The André Barbeau Movement Disorder Unit's experience

The experience of the André Barbeau Movement Disorder Unit of the Centre hospitalier de l'Université de Montréal (CHUM) regarding the administration of LCIG gel in patients with advanced PD was documented as part of this assessment report. An interview concerning the history of the use of this drug at this clinic, the target population and the effects and complications observed in patients treated with it was conducted by means of a conference call with a neurologist who works in this care unit. A summary of this discussion is presented in Table 13.

Table 13. Summary of the discussion concerning different organizational aspects of the use of LCIG in CHUM's Barbeau Movement Disorder Unit

Aspect discussed	Summary of discussion
History of use	• This treatment was first introduced 4 years ago in the context of a clinical study involving a small number of subjects. • It became official a year and a half ago (the spring of 2013).
Target population and intervention	• Proper selection of patients likely to benefit from this treatment is the key to its success. • Cases involving patients likely to receive this treatment are discussed during a multidisciplinary meeting. • Eligible patients are identified by means of an in-house protocol. The target population has characteristics similar to candidates for neurosurgery or deep brain stimulation. A discussion is initiated with the patient so that he/she can choose the treatment that would be the most appropriate, based on the risks and benefits of each. • Patients who opt for LCIG are seen at the outpatient clinic or during a hospital stay for the purpose of assessing their response to treatment administered via a nasogastric tube. This response is evaluated by measuring their on-periods. • If the response to treatment is positive, the patient is hospitalized for the installation of a PEG tube by a gastroenterologist. Once the tube has been installed, the patient remains in hospital so that the dose can be adjusted. In all, he/she remains in hospital for 3 days. • Patients are seen periodically at an outpatient clinic by a nurse specifically trained to follow patients on this treatment. • Presently, about 10 patients are on LCIG (Duodopa™). It is administered under the Régie de l'assurance maladie du Québec (RAMQ)'s exception patient measure.
Observed effects	• According to the neurologist contacted, continuous LCIG is effective, and the observed benefits outweigh the risks involved. • Improvements in quality of life have been observed.
Observed complications	• Adverse events following the administration of LCIG are often observed. They are mainly associated with tube dislocation or the gastrostomy and stoma infections. • There have been cases of peritonitis and treatment discontinuation. • This drug's safety profile is similar to that observed for the oral form of levodopa. • The complication rate seems to decrease over time as the gastroenterologists' learning curve improves. • Patients who experience adverse events are managed by the nurse dedicated to the follow-up of LCIG-treated patients or are referred to a gastroenterologist. The cost of managing the adverse events is borne by the hospital. • Increased workload for the neurologist.

5.5 Brief assessment of the potential impact of introducing LCIG at the CHU de Québec

A hospital stay of 5 to 7 days should be planned for each patient in order to initiate treatment with LCIG. The purpose of this stay is to install a PEG tube, adjust the doses on an individual basis, and closely monitor the patient for any complications. Prior to tube insertion by gastrostomy, all patients are tested for a positive clinical response to the administration of LCIG via a temporary nasoduodenal tube. The doses are adjusted by a nurse according to the patient's clinical status. At the

beginning, hospitalizing patients would be the best method for introducing this new practice at the CHU de Québec.

5.5.1 Human resources

Introducing LCIG into the therapeutic arsenal for PD involves adding a nursing resource, specifically, a nurse clinician, for adjusting the LCIG and following patients who receive this drug. AbbVie Corporation, a company that markets an LCIG, is responsible for providing the initial training to the hospital personnel who will be charged with managing and ensuring the follow-up of patients receiving this treatment [69]. This training should be provided not only to the nursing staff in the Neurological Sciences Unit and the Endoscopy Room, but also to the pharmacists, liaison nurses, emergency room personnel, and primary care partners outside the CHU de Québec (local community service centres and family physicians) who are likely to care for these patients when practicing their profession. The nurse clinician participates, together with the medical team, in adjusting the dose of the medication to be administered according to the patient's clinical status. In addition, a gastroenterologist should be involved in the installation of the PEG tube. The neurologist works closely with the gastroenterologist in monitoring the patient for adverse events associated with the endoscopic procedure for installing the tube and with the system for administering the drug.

Overall, according to the experts in the CHU de Québec's working group, no additional human resources would need to be provided afterwards for managing the patients on this drug, who are already being seen at the Hôpital de l'Enfant-Jésus (HEJ)'s Movement Disorder Clinic. The estimated number of patients who might receive this drug is around 5 per year. The actual workload for following the patients and managing the adverse events is not known at this time.

5.5.2 Financial resources

Since treatment started in hospital continues after discharge the patient, the neurologist must first obtain authorization from the RAMQ for coverage of LCIG under the exception patient measure. This measure permits coverage, by the public prescription drug insurance plan, of drugs that are not on the *List of Medications* or the list of exception drugs and that are prescribed for therapeutic indications that are not on either list [70]. These drugs must be specifically and exceptionally necessary for the insured individual. It should be noted that the daily cost of LCIG ($166) is higher than that of the available oral combinations of levodopa and carbidopa (less than $3) [71].

The recurrent costs associated with the addition of a nurse clinician vary from $43,865 to $78,171 a year, based on the current collective agreement. In November 2013, an agreement was concluded between AbbVie Corporation and the CHU de Québec. The agreement provides for the coverage of the costs associated with the medication during the initial hospital stay, the equipment (tubes, connectors and adapters) required to install the PEG tube, and the pump for administering the drug (CADD-Legacy, model 1400) for a maximum of 24 patients. Under this agreement, AbbVie agrees to assume responsibility for the pump's maintenance and repair while it is being used by the patient and to replace it if it is damaged or becomes unusable. However, at the end of the term of this agreement, that is, one year after the initial introduction of the technology, the recurrent costs for introducing this drug at the CHU de Québec, excluding hospitalization costs and physicians' fees, would be $3316 per patient [74]. This cost does not include the expenses relating to the patient's in-hospital accommodation, the equipment necessary for managing the patient during his/her hospital stay, the management of adverse events, or physicians' fees. It should be noted that a portion of the cost of the initial adjustment of the LCIG dose attributable to hospitalization could be reduced in the future with the possible management of CHU de Québec patients on an outpatient basis.

5.5.3 Patients and natural caregivers

According to AbbVie Corporation, administering LCIG to patients with advanced PD could lead to a reduction in hospitalization costs and treatment costs and enable patients to reintegrate into the job market [72]. Positive effects on patients' quality of life are reported in the studies reviewed for this assessment report, although their clinical significance cannot be determined. As for caregivers, two of the case series identified suggest that administering LCIG in patients with PD did not have a significant impact on the caregivers' quality of life [19], burden or state of mind [20].

6. DISCUSSION

Managing advanced PD is a clinical challenge, and the available therapeutic options for controlling involuntary motor fluctuations are limited to a few possible choices for maintaining an acceptable quality of life for these patients. This report presents the most exhaustive picture possible of the available evidence regarding one of these options, the administration of levodopa/carbidopa intestinal gel in patients with advanced PD whose response to the other combinations of antiparkinsonians is no longer satisfactory.

The following observations can be made from the data in the scientific literature on the efficacy and safety of this method of administration, discussions with the interdisciplinary working group, the experience using LCIG elsewhere in Quebec, and the analysis of the organizational and financial impact on the CHU de Québec :

1. Despite the uncertainties, continuous LCIG administration seems to be an effective therapeutic option in patients with advanced PD

Only a few of the publications identified with the search strategy used for this assessment report were eligible and of good methodological quality. The efficacy evidence is based mainly on one RCT [18], five prospective case series [19-23], two clinical practice guidelines [16, 17] and the opinions of three panels of experts in the treatment of PD [24-26]. Regardless of the type of designs used in the studies considered, the authors concluded that LCIG is efficacious. The results of the studies reviewed suggest that this intervention would be effective in reducing the duration of off-periods and the motor complications associated with this drug, and that it improves the quality of life of patients with PD [18-23]. Two studies suggest that continuous LCIG administration could lead to a benefit in terms of the duration of on-periods without motor fluctuations [18, 22] but that it has little impact on the duration of on-periods with troublesome motor fluctuations. The literature data also suggest that continuous LCIG administration does not have a significant impact on caregiver burden or quality of life [19, 20]. The practice guidelines and expert opinions recognize that continuous LCIG administration could be effective for treating patients with advanced PD, but some moderate their conclusion because of the poor quality of the available evidence.

The benefits of LCIG observed in the studies reviewed were statistically significant. However, none of their authors assessed the clinical significance of the observed differences in the scores measured by the questionnaires or in on- or off-time duration. Based on data at 6 months in two studies of the efficacy of ropinirole monotherapy for the treatment of patients with stage 1 to 3 PD (Hoehn and Yahr scale), some authors have suggested that a difference of five points in the score of the Part III of the UPDRS questionnaire might constitute a clinically meaningful difference [73]. Assuming that these data apply to a population of patients with advanced PD, the differences in the scores reported in the studies of Fernandez *et al*., Honig *et al*. and Zibetti *et al*. could be considered clinically meaningful [21-23]. As for the duration of off-time, as evaluated by means of a home diary in levodopa-treated patients, one study suggests that, after 6 months of follow-up, a difference of one hour could prove to be clinically meaningful in patients who have had a minimal response to levodopa [74]. Given the limits to generalizing the results of this study, the reduction in off-time duration observed in Olanow *et al*.'s and Fernandez *et al*.'s studies could be clinically meaningful [18, 22]. As for the other parameters, such as the evaluation of quality of life or the duration of on-time with or without troublesome motor fluctuations, no minimal difference in term of duration or score was suggested to be clinically meaningful. Consequently, we cannot comment on the clinical significance of the differences in these outcomes observed in the included studies. However, regardless of the measurement instrument used (PDQ-39 or PDQ-8), a significant improvement in the subjects' quality of life was observed. The size of the effect on quality of life varied according to the questionnaire used. Although it is a shortened version of the PDQ-39, the PDQ-8 is more sensitive to fluctuations because of the number of statements evaluated. Indeed, the UPDRS questionnaire assesses the impact of different symptoms, motor and non-motor, on the patient's functional quality of life. However, a positive correlation between the PDQ-39 and the Part II of the UPDRS questionnaire was found in the literature (Spearman correlation: 0.753; $p = 0.01$) [75].

The primary studies evaluating the efficacy of LCIG administration had a number of methodological flaws, such as the limited number of study subjects, the short duration of patient follow-up (three to 36 months), the high dropout rate, suboptimal statistical analyses, and the appearance of conflicts of interest with AbbVie Corporation. This company was involved in the majority of the studies identified, and one cannot rule out the possibility that its involvement may have influenced the results

in a positive direction. For example, in the case of Olanow *et al*.'s RCT, the company was involved in developing the study, in the data collection, in the patient follow-up and in the statistical analysis of the results, in addition to having funded the study and reviewed the article manuscript. The authors of the case series, too, report conflicts of interest with AbbVie Corporation. A selection bias in the patient inclusion procedure for these studies cannot be totally ruled out either. The standard initial procedure for evaluating LCIG involves first measuring the patient's response to the drug when administered via a nasoduodenal tube. Consequently, only patients who tolerate this procedure and who have an adequate response to the drug will be given the option of continuing the treatment via a PEG tube. In addition to this consideration is another factor in Olanow *et al*.'s RCT: the pre-randomization assessment of the patient's diligence in filling out his/her diary and the concordance of the data with those of the evaluating physician [18]. In Zibetti *et al*.'s case series, an initial response to levodopa, defined as a decrease of at least 33% in the baseline UPDRS-III score, was a prerequisite for study entry [21]. As well, there were significant dropout rates ranging from 32 to 45% in three of the case series included [19-21] in this report. This leads one to suspect that there was an attrition bias, which can result in an overestimation of the drug's effect. All of these factors may have influenced the results in favour of this treatment, but they also cast doubt on the ability to generalize these results to a larger population of patients with advanced PD. However, the authors are critical in their conclusions, and a number of them state that larger studies should be conducted.

Although the clinical validity of the instrument is not questioned, but the direction and magnitude of the effect on the motor symptoms of PD evaluated using the Part III of the UPDRS questionnaire varied from study to study in the case series that were examined. This could be due, in part, to the very nature of this instrument, which, unlike a home diary, is more of a qualitative than quantitative evaluation measure of improvement in the symptoms of the disease during on-periods. This part of the questionnaire includes several items, including the assessment of posture, stiffness, tremor and dyskinesia, which can vary according to other concomitant medical issues, such as stroke, osteoarthritis or orthopedic problems, issues that affect this instrument's sensitivity. The effect size and direction measured by the UPDRS-III score also varied according to the duration of patient follow-up, which suggests that the benefit of this treatment was more significant in the studies with a short follow-up [22, 23]. Without the results of a long prospective study with an LCIG-treated comparison group, it is not possible to determine if this difference persists or diminishes over time due to the drug's inefficacy (e.g., tolerance or absorption problem) or to disease progression. For now, it does not seem that these questions can be answered.

2. Continuous LCIG administration via a PEG tube: an innovative modality but not without risks for the patient

Although this assessment report does not examine the adverse events associated with LCIG, it is recognized that its safety profile is similar to that of levodopa [69]. The adverse events most commonly associated with the administration of levodopa include irregular heartbeat, a sensation of vertigo or a loss of consciousness while standing, and a change in mental status, such as hallucinations or depression [69].

A PEG tube has to be installed in order to administer LCIG. Although this endoscopic procedure is often performed in a clinical setting, this surgical procedure is associated with adverse events at the wound site, such as stoma infections and the development of granulomas. In rare cases, the procedure can cause peritonitis or pneumoperitoneum, which can have serious consequences for the patient's health. Adverse events have also been reported rather frequently with the tube used to administer the drug. In brief, they are tube dislocation, occlusion, kinking, knotting and leakage, and even accidental removal of the tube or the gel cassette. The incidence of these adverse events in patients treated with LCIG is similar to that generally observed with this type of procedure for other medical indications [61], and some adverse events can occur more than once in a given patient. Although they are not serious, they can make managing these patients in hospital more complicated (surgery, hospitalization and medication) and, for the patient, result in frequent trips and consequently reduce the quality of his/her care experience. The rate of adverse events associated with the administration of LCIG in the studies had a direct impact on the patients' adherence to the treatment. Indeed, approximately 60% of the subjects who dropped out of the studies did so because of adverse events.

In brief, the evidence concerning the safety of LCIG, including the safety of its method of administration, suggests that this treatment seems safe for patients. Nonetheless, despite the low frequency of serious adverse events, patients wishing to undertake this treatment would do well to familiarize themselves with the risks associated with it and with its method of administration, so that they can make an informed decision.

3. Continuous LCIG administration in patients with advanced PD at the CHU de Québec: an innovation to be guided and optimized

In light of the available evidence, is the administration of LCIG in patients with advanced PD a practice to be encouraged? Considering all the uncertainties about this, the different elements that emerge from the evidence suggest that, for now, introducing LCIG into the therapeutic arsenal for advanced PD meets more the criteria for an innovative practice rather than a standard of care. Indeed, this treatment modality meets a health need, and for patients, constitutes a new therapeutic option with positive benefits. However, given the uncertainties associated with demonstrating proof of the efficacy of this treatment and of the safety of its method of administration, with the potential impact of its introduction on the organization of care, and with its regulatory status in Quebec, LCIG corresponds to the notion of a treatment in the middle of the process of clinical maturation, thus paving the way to new avenues of research. For example, the positioning of this treatment modality in the therapeutic arsenal and the care trajectory for PD remains to be determined, since few comparative studies between LCIG and the other treatment options for advanced PD (e.g., DBS) are available.

In a product monograph for one LCIG, Health Canada defines a framework for guiding the selection of patients with advanced PD who are potential candidates for this treatment [2]. Selecting patients who might benefit the most from this treatment is essential, given the high dropout rates due to adverse reactions observed in the studies identified. Consequently, criteria beyond those indicated by Health Canada should be looked at in order to guide the introduction of this innovative practice into the health-care system. For example, the patient's ability to manage the pump and tubing and the size of his/her social network are important criteria to be taken into consideration when selecting patients likely to benefit from this treatment. The scientific literature reviewed seems to indicate that in addition to not achieving satisfactory control of motor fluctuations with the use of conventional antiparkinsonians, the population for whom LCIG is intended should not have any clinically significant psychiatric disorders. According to the expert consulted at CHUM's André Barbeau Movement Disorder Unit, the target population may be substantially the same as that eligible for deep brain stimulation. However, the movement disorder neurologists involved in our expert group for this report are of a somewhat different opinion in this regard. They indicated that eligible patients might be those in whom deep brain stimulation is not an option for reasons such as an advanced stage, the presence of a significant cognitive impairment, the presence of uncontrolled psychiatric symptoms or the refusal to consider DBS as a treatment[1]. In addition, in light of the available safety evidence, it seems essential that patients have access to all the necessary information for making an informed decision about the choice of treatment, in order to ensure long-term adherence.

Furthermore, the actual impact of this therapy on internal human resources is unknown, even if the preliminary data identified suggest that introducing this innovation would have little impact. Nonetheless, the current discussions converge toward the addition of a nurse clinician to ensure an appropriate follow-up of these patients. In addition, the workload that the follow-up of these patients and the management of adverse events might represent is another element that needs to be documented to better assesses the impact on resources. Training will be required for the nursing staff in the Neurological Sciences Unit and the Endoscopy Room, the other members of the CHU de Québec's staff (pharmacists, follow-up nurses, gastroenterologists, ostomy nurses, liaison nurses and emergency personnel) and also for other primary care health professionals who provide care to these patients. Putting in place the resources dedicated to following patients receiving this treatment is necessary. As well, since the administration of this drug involves installing a PEG tube, the availability of a gastroenterology team is essential for managing patients who might experience adverse events associated with the installation of the tube or with the tube per se.

The net impact generated by the administration of this new medication on patient health and the organization of health-care services (the potential gains through this modality, the financial impact, etc.) is unknown and substantial and should be therefore documented within the context of introducing an innovative practice. Indeed, introducing a new pharmacological therapy often leads to changes, which can be significant, in the way certain services are provided, used and organized [76].

In short, introducing LCIG for the treatment of advanced PD into the available therapeutic arsenal at the CHU de Québec will require optimizing the current practices, but also instituting new measures to limit the organizational and financial impact to

[1] E-mail communication between S.L and Dr. Mélanie Langlois, a neurologist at the CHU de Québec, on August 25, 2014.

ensure that this treatment constitutes the best option for the patient's benefit. The planned agreement with AbbVie Corporation for the first year of use of this innovation will provide an opportunity to document the impact of this method of administering LCIG on patients and the organization of health care and services. This in-field evaluation of this practice could provide a better assessment of the actual impact of introducing this treatment at the CHU de Québec. However, this business tie must at no time be considered an argument in favour of deciding to introduce this option into the therapeutic arsenal. This decision must be based above all on an analysis of the benefits and risks for patients.

7. RECOMMENDATIONS

Recommendation 1

Considering that:

- The CHU de Québec should achieve the highest standards of quality by incorporating an assessment of the usefulness, efficacy, quality and safety of all the procedures available to its patients;
- The therapeutic options are limited for patients with advanced Parkinson's disease who present with involuntary motor fluctuations that are not controlled satisfactorily with standard combinations of antiparkinsonians;
- An LCIG has been approved by Health Canada for the treatment of patients with advanced PD, but it is not listed in the RAMQ's institutional formulary;
- Despite the relative uncertainties regarding the available evidence, the administration of LCIG could constitute an effective and safe innovation for controlling involuntary motor fluctuations and improving the quality of life of patients with advanced Parkinson's disease.
- The method of administering LCIG is associated with adverse events, which must be taken into consideration when the patient decides whether or not to start this treatment;
- Defining the eligibility criteria is key to the success of this therapy, especially because of the high dropout rates noted, the adverse reactions and the patient's ability to manage the method of administration;
- It is relevant to document the experience administering LCIG in patients with advanced PD in order to generate proof and support decisions;
- The decision whether or not to introduce this innovative practice must not be supported simply by the fact that the costs pertaining to this treatment would be covered, for a set period, by a company that markets this drug.

It is recommended that the CHU de Québec introduce, as an innovative practice, the use of LCIG as a specific necessity medication for managing patients:

- **Who meet the diagnostic criteria for advanced Parkinson's disease and,**
- **Who respond to levodopa and,**
- **Who do not achieve satisfactory control of severe, troublesome motor fluctuations and hyper/dyskinesia with the administration of other combinations of antiparkinsonians and,**
- **Who do not have any clinically significant psychiatric disorders.**

This recommendation is conditional on the following:

- That patients have access to all the necessary information for making an informed and shared decision considering the expected benefits and risks of the administration of LCIG and of the other available therapeutic options (e.g., deep brain stimulation) in order to make;
- That patients in whom this treatment is being considered have a solid functional capacity and a well-developed social network for managing the pump and the various procedures involved in administering LCIG;
- That patients receiving this treatment be followed by staff (nurse clinician, physician and pharmacist) trained on the method of administering LCIG;
- That the first two years of LCIG utilization be used to document:
    - The characteristics of the treated patients;
    - The benefits for the patients;
        - Proposed follow-up outcomes:
            - ✓ The duration of on- and off-periods (diary)
            - ✓ Motor symptoms and motor complications associated with the drug (scores on Parts III and IV of the UPDRS)
            - ✓ Quality of life (PDQ-8)

- The frequency of adverse events in the treated patients and their consequences for these patients and the CHU de Québec
  - Proposed follow-up outcomes:
    - ✓ All adverse events requiring a hospital visit
    - ✓ The frequency of serious adverse events (peritonitis, pneumoperitoneum)
    - ✓ The number of hospital visits per patient due to adverse events
    - ✓ Health professionals involved in managing each adverse reaction (nurse clinicians, ostomy nurses, gastroenterologists, neurologists)
- The discontinuation rate and the reasons for discontinuation;
- An estimate of the costs associated with installing the tube required for administering the drug and with the subsequent visit or hospitalization episodes related to adverse events;
- The impact of following patients and managing adverse events on human resources.

- That the neurologists at the Movement Disorder Clinic of the Hôpital de l'Enfant-Jésus (CHU de Québec) define beforehand for each efficacy outcome a reference value or criteria for a clinically meaningful improvement;

- That the experience using LCIG be reviewed a year after its introduction, by the neurologists at the Movement Disorder Clinic of the Hôpital de l'Enfant-Jésus (CHU de Québec) and the associated clinical/administrative team. The review should be based on the clinical and organizational data from documenting the practice and should enable one, in light of the findings, to make adjustments to the management of patients treated with this drug;

- That the experience using LCIG be reevaluated at the end of the second year to review its usefulness as a treatment available at the CHU de Québec for patients with advanced Parkinson's disease compared to the use of an oral levodopa/carbidopa combination or deep brain stimulation. The decision whether to continue using this drug at the CHU de Québec should be under the responsibility of the CHU de Québec's Strategic Clinic Committee. In addition, the CHU de Québec's Pharmacology Committee should be informed of any change regarding the use of this treatment.

Recommendation 2

Considering that:

- Efficacy and safety evidence for LCIG should be supported by other evidence;
- Few studies enable one to properly position the administration of LCIG in the therapeutic arsenal for adequately managing patients with advanced PD;
- There are few studies enabling one to determine if the administration of LCIG is a pharmacoeconomically efficient and cost-effective option;
- The CHU de Québec should stand out among the best by achieving superior academic levels in its specialties and subspecialties.

It is recommended that the physicians, other professionals and researchers at the CHU de Québec who are experts in Parkinson's disease join forces with the CHU de Québec Research Centre's Executive Committee to support the development of research facilities for conducting evaluative and clinical research on the management of patients with advanced Parkinson's disease.

8. CONCLUSION

The objective of this report was to assess the efficacy and safety of levodopa/carbidopa intestinal gel, including the safety of its method of administration, and the organizational impact of its use in patients with advanced PD.

A review of the evidence suggests that continuous LCIG administration is associated with benefits, specifically in terms of involuntary motor fluctuations and the quality of life of patients with advanced PD. However, a number of uncertainties persist regarding the administration of LCIG, especially as to the clinical significance of the observed improvements, the long-term effects on the control of the disease, and its efficacy compared to other treatment options. This assessment also indicates that the administration of LCIG gel via a PEG tube is not without risks. The adverse health effects associated with its method of administration should be taken into account when the patient decides whether or not to start this treatment.

Given the current state of the evidence, the HTAU recommends the introduction of LCIG at the CHU de Québec as an innovative practice for managing patients with advanced PD who meet certain clinical criteria. This practice must be guided in order to document, during the first two years after it is introduced, the benefits for patients, the frequency of adverse events and their repercussion, and the impact on the CHU de Québec's resources. The decision whether to continue using LCIG should be reevaluated by the interested stakeholders in order to review its usefulness as a treatment available at the CHU de Québec. Given the innovative nature of this treatment modality and the uncertainties, the HTAU also recommends encouraging clinical research to improve knowledge regarding its positioning in the therapeutic arsenal for advanced PD.

APPENDICES

Appendix 1 – List of organizations, professional associations and databases considered for the gray literature search

Acronym	Name	Country (province)	Website	Search result
Keywords **English websites:** Duodopa, levodopa-carbidopa, gel **French websites:** Duodopa, lévodopa-carbidopa, gel				
General websites visited				
AFSSPS	Agence française de sécurité sanitaire des produits de santé	France	www.afssaps.fr/	0
AHRQ	Agency for Healthcare Research and Quality	United States	http://www.ahrq.gov/	1
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical	Australia	http://www.surgeons.org/racs/research- and-audit/asernip-s	0
AHTA	Adelaïde Health Technology Assessment	Australia	http://www.adelaide.edu.au/ahta/	0
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada	http://www.cadth.ca/fr	0
CEBM	Center for Evidence-based Medicine	United Kingdom	http://www.cebm.net/	0
CEDIT	Comité d'évaluation et de diffusion des innovations technologiques	France	http://cedit.aphp.fr/	0
DACEHTA	Danish Centre for Health Technology Assessment	Denmark	http://www.sst.dk/English.aspx	2
DETMIS - CHUM	HTA Division of the Centre hospitalier de l'Université de Montréal	Canada (Quebec)	http://www.chumontreal.qc.ca/patients-et-soins/a-propos-du-chum/les- directions/detmis	0
HAS	Haute Autorité de Santé	France	http://www.has-sante.fr/portail/jcms/fc_1249601/fr/evaluati on-recommandation	3
HIQA	Health Information and Quality Authority	Ireland	http://www.hiqa.ie/	0
HSAC	Health Services Assessment Collaboration	New Zealand	http://www.healthsac.net/aboutus/aboutus. htm	0
ICER	Institute for Clinical and Economic Review (ICER)	United States	www.icer-review.org	0
ICES	Institute for Clinical Evaluative Sciences	Canada (Ontario)	http://www.ices.on.ca/	0
IHE	Institute for Health Economics	Canada (Alberta)	http://www.ihe.ca/	0
INESSS	Institut national d'excellence en santé et en services sociaux	Canada (Quebec)	http://www.inesss.qc.ca/	1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im	Germany	www.iqwig.de	0
KCE	Belgian Healthcare Knowledge Centre	Belgium	http://www.kce.fgov.be/	0
MHRA	Medicines and Healthcare products Regulatory Agency	United Kingdom	www.mhra.gov.uk/index.htm	1
MSAC	Medical Services Advisory Committee	Australia	http://www.msac.gov.au/	0

Acronym	Name	Country (province)	Website	Search result
NGC	National Guidelines Clearinghouse	United States	http://www.guidelines.gov/	3
NICE	National Institute for Health and Care Excellence	United Kingdom	http://www.nice.org.uk/	0
NIHR HTA	National Institute for Health Research Health Technology Assessment Programme	United Kingdom	http://www.nets.nihr.ac.uk/programmes/hta	0
NIHW (formerly FINOHTA)	National Institute for Health and Welfare	Finland	http://www.thl.fi/en_US/web/en	0
NPSA	National Patient Safety Agency	United Kingdom	www.npsa.nhs.uk/	0
NZHTA	New Zealand Health Technology Assessment	New Zealand	http://www.otago.ac.nz/christchurch/research/nzhta/	0
OHTAC	Ontario Health Technology Advisory Committee	Canada (Ontario)	http://www.health.gov.on.ca/english/providers/program/ohtac/ohtac_mn.html	0
SCIRP	Scientific Research Publishing (Open Access)	United States	http://www.scirp.org/	0
SIGN	Scottish Intercollegiate Guidelines Network	Scotland	http://www.sign.ac.uk	1
TAU-MUHC	Technology Assessment Unit, McGill University Health Centre	Canada (Quebec)	http://www.mcgill.ca/tau/	0
THETA	Toronto Health Economics and Technology Assessment	Canada (Ontario)	http://theta.utoronto.ca/	0
UETMIS (CHUS)	HTA Unit, Centre hospitalier universitaire de Sherbrooke	Canada (Quebec)	http://www.chus.qc.ca/volet-academique-ruis/evaluation-des-technologies/	0
UETMIS (CHUSJ)	HTA Unit, CHU Sainte-Justine	Canada (Quebec)	http://www.chu-sainte-justine.org/Pro/micro-portails.aspx?AxeID=16	0
VATAP	Veterans Affairs Technology Assessment Program (VATAP)	United States	http://www.va.gov/vatap/	0
WHO	World Health Organization	International	http://www.who.int/fr/	0
WSHCA-HTAP	Washington State Healthcare Authority – Health Technology Assessment Program	United States	http://www.hta.hca.wa.gov/	0
Websites of professional organizations and associations specific to the topic				
NEUROLOGY				
AAN	American Academy of Neurology	United States	https://www.aan.com/	1
ABN	Association of British Neurologists	England	http://www.theabn.org/Home.aspx	0
ANQ	Association des neurologues du Québec	Canada (Quebec)	http://www.anq.qc.ca/	0
ANLLF	Association des neurologues libéraux de langue française	France	http://anllf.org/	0
ANS	Australasian Neuroscience Society	Australia	http://www.ans.org.au/	0
APDA	American Parkinson Disease Association	United States	http://www.apdaparkinson.org/	0
BNA	British Neuroscience Association	England	http://www.bna.org.uk/	0

Acronym	Name	Country (province)	Website	Search result
CNSF	Canadian Neurological Sciences Federation	Canada	http://www.mybrainmatters.ca/fr/organisation/canadian-neurological-sciences- federation-french	0
Acronym	Name	Country (province)	Website	Search result
MDS	International Parkinson and Movement Disorder Society	International	http://www.movementdisorders.org/	1
PSC	Parkinson Society Canada	Canada	http://www.parkinson.ca/site/c.kgLNIWOD	0
WFN	World Federation of Neurology	International	http://www.wfneurology.org/	0
GASTROENTEROLOGY				
ACG	American College of Gastroenterology	United States	http://gi.org/	0
AGA	American Gastroenterological Association	United States	http://www.gastro.org	0
AGEQ	Association des gastro-entérologues du Québec	Quebec	http://www.ageq.qc.ca/	0
ASGE	American Society for Gastrointestinal Endoscopy	United States	http://www.asge.org/	0
BSG	British Society of gastroenterology	United Kingdom	http://www.bsg.org.uk/	0
CAG	Canadian Association of Gastroenterology	Canada	http://www.cag-acg.org/	0
GESA	Gastroenterological Society of Australia	Australia	http://www.gesa.org.au/	0
UEG	United European gastroenterology	Europe	http://www.ueg.eu/	0
WGO	World Gastroenterology Organisation	International	http://www.worldgastroenterology.org/	0
Websites of government agencies				
CDC	Centers for Disease Control and Prevention	United States	www.cdc.gov	0
HC	Health Canada	Canada	http://www.hc-sc.gc.ca/index-fra.php	2
			NUMBER OF DOCUMENTS IDENTIFIED	16
			NUMBER OF OVERLAPS	3
			NUMBER OF PUBLICATIONS SELECTED	13

Last search conducted on September 25, 2014.

APPENDIX 2. Results of the search for published protocols

Name	Organization	Website	Search result (n)
Synthesis studies **Keyword:** Duodopa			
PROSPERO	Center for Reviews and Dissemination	http://www.crd.york.ac.uk/prospero/	0
Cochrane	The Cochrane Library	www.thecochranelibrary.com	0
RCT **Keywords:** apnea and postoperative, apnoea and postoperative			
	U.S. National Institute for Health Research	http://www.Clinicaltrials.gov	4
	Current Controlled Trials Ltd.	http:///www.controlled-trials.com	0
		NUMBER OF DOCUMENTS IDENTIFIED	4

Last search conducted on September 25, 2014.

APPENDIX 3. Search strategies used to evaluate the efficacy and safety, including the safety of its method of administration, of continuous LCIG

EFFICACY SEGMENT

PubMed

Search	Strategie
#1:	"antiparkinson agents"[MeSH Terms] OR "antiparkinson agents" OR "levodopa"[MeSH Terms] OR levodopa OR "carbidopa"[MeSH Terms] OR carbidopa OR "carbidopa, levodopa drug combination" OR "carbidopa levodopa" OR "Duodopa" OR "modified-release levodopa" OR "LCIG"
#2:	"infusion pumps"[MeSH Terms] OR "infusion pumps, implantable"[MeSH Terms] OR "Infusions, Parenteral" OR gel OR infusion OR
#3:	#1 and #2
#4:	#3 + Limits: starting January 1, 2000; Languages: French and English

- 696 publications identified.
- Search conducted on September 25, 2014.

Embase

Search	Strategie
#1:	'antiparkinson agent'/exp OR 'antiparkinson agent' OR 'levodopa'/exp OR levodopa OR 'carbidopa'/exp OR 'carbidopa' OR 'carbidopa plus levodopa'/exp OR 'carbidopa plus levodopa' OR 'Duodopa' OR 'modified-release levodopa' OR 'LCIG'
#2:	'infusion pump'/exp OR 'infusion pump' OR 'intraduodenal drug administration'/exp OR 'intraduodenal drug administration' OR 'gel'/exp OR 'gel' OR 'infusion'/exp OR 'infusion' OR 'intestinal' OR 'jejunal' OR 'intrajejunal' OR 'duodenal' OR 'intraduodenal'/exp OR
#3:	#1 AND #2 AND ([article]/lim OR [article in press]/lim) AND ([english]/lim OR [french]/lim) AND [embase]/lim AND [2000-2014]/py

- 1062 publications identified.
- Search conducted on September 25, 2014.

Cochrane Library

Search	Strategie
#1:	MeSH descriptor: [Antiparkinson Agents] explode all trees
#2:	MeSH descriptor: [Levodopa] explode all trees
#3:	MeSH descriptor: [Carbidopa] explode all trees
#4:	"antiparkinson agents" or levodopa or carbidopa or "carbidopa, levodopa drug combination" or "carbidopa levodopa" or Duodopa o "modified-release levodopa" or LCIG
#5:	#1 OR #2 OR #3 OR #4
#6:	MeSH descriptor: [Infusion Pumps] explode all trees
#7:	MeSH descriptor: [Infusion Pumps, Implantable] explode all trees
#8:	"Infusions, Parenteral" or "infusion pump*" or gel or infusion or intestinal or jejunal or intrajejunal or duodenal or intraduodenal or PEG* or pump* or CADD
#9:	#6 or #7 or #8
#10:	#5 and #9 + Limit: Starting January 1, 2000; Cochrane review, other reviews and technology assessment reports only

- 28 publications identified.
- Search conducted on September 25, 2014.

Center for Reviews and Dissemination

Search	Strategies
#1:	MeSH DESCRIPTOR Antiparkinson Agents EXPLODE ALL TREES
#2:	MeSH DESCRIPTOR Levodopa EXPLODE ALL TREES
#3:	MeSH DESCRIPTOR Carbidopa EXPLODE ALL TREES
#4:	("antiparkinson agents" or levodopa or carbidopa or "carbidopa, levodopa drug combination" or "carbidopa levodopa" or Duodopa or "modified-release levodopa" or LCIG)
#5:	#1 OR #2 OR #3 OR #4
#6:	MeSH DESCRIPTOR Infusion Pumps EXPLODE ALL TREES
#7:	MeSH DESCRIPTOR Infusion Pumps, Implantable EXPLODE ALL TREES
#8:	("Infusions, Parenteral" or "infusion pump*" or gel or infusion or intestinal or jejunal or intrajejunal or duodenal or intraduodenal or PEG*
#9:	#6 OR #7 OR #8
#10:	#5 AND #9 + Limit starting January 1, 2000

- 6 publications identified.
- Search conducted on September 25, 2014.

SAFETY SEGMENT

PubMed

Search	Strategie
#1:	("carbidopa, levodopa drug combination" OR "carbidopa levodopa" OR "Duodopa" OR "modified-release levodopa" OR LCIG) AND ("adverse effects" [Subheading] OR "adverse effect*" OR "adverse event*" OR "negative effect*" OR safety OR "side
#2:	#1 + Limites: à partir du 1 janvier 2000, Langues: français et anglais

- 96 documents identified.
- Search conducted on September 25, 2014.

Embase

Search	Strategies
#1:	('carbidopa plus levodopa'/exp OR 'carbidopa plus levodopa' OR Duodopa OR 'modified-release levodopa' OR LCIG) AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'adverse event' OR 'drug safety'/exp OR 'drug safety' OR 'side effect'/exp OR 'side effect')
#2:	#1 AND ([article]/lim OR [article in press]/lim) AND ([english]/lim OR [french]/lim) AND [embase]/lim AND [2000-2014]/py

- 637 publications identified.
- Search conducted on September 25, 2014.

APPENDIX 4. List of the excluded publications and reasons for exclusion

EFFICACY

Did not meet the eligibility criteria

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- Cenci MA, Ohlin KE, Odin P. Current options and future possibilities for the treatment of dyskinesia and motor fluctuations in Parkinson's disease. CNS & Neurological Disorders - Drug Targets. 2011;10(6):670-84.
- Chan DKY. Adjuvant treatment to levodopa in patients with motor complications. Focus on Parkinson's Disease. 2012; 23(1):10-5.
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Other reasons

Population included in one of the studies selected (Zibetti et al., 2013)

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Other reasons

Results reported as a number of events rather than as a number of patients

- Antonini A, Odin P, Opiano L, Tomantschger V, Pacchetti C, Pickut B, et al. Effect and safety of duodenal levodopa infusion in advanced Parkinson's disease: a retrospective multicenter outcome assessment in patient routine care. Journal of neural transmission (Vienna, Austria: 1996). 2013;120(11):1553-8.
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No adverse events associated with the method of administering the drug

- MedEffet Canada, Canada Vigilance Adverse Reaction Online Database. Adverse Reaction Report #000544766. 2013

Population included in one of the studies included (Zibetti et al., 2013)

- Zibetti M, Merola A, Artusi CA, Rizzi L, Angrisano S, Reggio D, et al. Levodopa/carbidopa intestinal gel infusion in advanced Parkinson's disease: A 7-year experience. European Journal of Neurology. 2014;21(2):312-8.

APPENDIX 5. Interview guide used for the André Barbeau Movement Disorder Clinic (CHUM) to document the operational practices pertaining to the administration of Duodopa™

1. History of the use of Duodopa™
    a. When was it introduced?
    b. What led to the introduction of this drug?
    c. How was Duodopa™ introduced at the hospital?

2. Who is given Duodopa™?
    a. How are eligible patients selected?
    b. What is the length and objective of the patients' hospital stay?
    c. How many patients are being followed and for how long have they been followed?

3. Observed effects
    a. What changes have you observed in patients on Duodopa™?
    b. How and by whom are patients followed (organizational aspects)?

4. Have you observed any complications?
    a. Rate?
    b. What complications?
    c. Have there been any serious complications?
    d. How are these complications managed?

5. Do you know any other neurologists, elsewhere in Quebec, who prescribe Duodopa™ to their patients?

criteria used in the selected case series

ondary or typical nptoms of PD	History of neurosurgery for PD	Clinically significant medical problems	Clinically significant psychiatric problems	Conditions interfering with the availability, absorption or metabolism of the drug	Contraindication to installing a PEG tube	Patient or caregiver difficulty handling the pump	Respons e rate to levodopa < 33%
x		x	x				
x	x		x	x	x		
x			x			x	
x		x	x			x	
x			x				x

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