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Expert Review of Medical Devices

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierd20

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To cite this article: Karolina Popławska-Domaszewicz, Vinod Metta, Per Odin & K Ray Chaudhuri (08 May 2025): The device-aided intrajejunal delivery of levodopa–entacapone–carbidopa intestinal gel the treatment of Parkinson's disease: overview of efficacy and safety, Expert Review of Medical Devices, DOI: 10.1080/17434440.2025.2499153

To link to this article: https://doi.org/10.1080/17434440.2025.2499153

EXPERT REVIEW OF MEDICAL DEVICES
https://doi.org/10.1080/17434440.2025.2499153

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DEVICE PROFILE

The device-aided intrajejunal delivery of levodopa–entacapone–carbidopa intestinal gel the treatment of Parkinson's disease: overview of efficacy and safety

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ABSTRACT

Introduction: Device-aided therapies (DATs) have been developed to provide continuous drug delivery (CDD) to people with advanced Parkinson's disease (PD) whose symptoms can no longer be effectively managed with oral or transdermal therapy. Intrajejunal infusion of levodopa–carbidopa intestinal gel (LCIG), delivered via the CADD Legacy 1400 pump, is an established CDD option, while levodopa–entacapone–carbidopa intestinal gel (LECIG), delivered via the Crono LECIG pump, is a more recent addition to the range of DAT options in Europe.

Areas covered: This article explores the rationale for the development of LECIG infusion, the role of entacapone in the formulation, and the attributes and specifications of the LECIG infusion pump device. Clinical and real-world data reporting its efficacy, safety and tolerability of LECIG in advanced PD patients from a range of European centers are reviewed, with a focus on the practical benefits that a smaller, lighter and quieter device can provide for patients who wish to start treatment with intrajejunal levodopa infusion.

Expert opinion: LECIG infusion delivered via the LECIG infusion pump offers another valuable DAT option to consider for suitable people with advanced PD providing both good long-term clinical benefits and a favorable treatment experience for patients.

ARTICLE HISTORY
Received 2 December 2024
Accepted 24 April 2025

KEYWORDS
Device-aided therapy; medical device; infusion pump; advanced parkinson's disease; LECIGON; levodopa–carbidopa–entacapone

1. Introduction

Data from the Global Burden of Disease Study published in 2018 which evaluated global, regional, and country-specific epidemiological data for Parkinson's disease (PD) over the period from 1990 to 2016 found that it is the fastest growing neurological disorder worldwide [1,2]. In addition, the global burden of PD was found to have doubled from 2.5 million people in 1990 to 6.1 million in 2016. There are, however, notable variations reported in PD epidemiology dependent on geographical region, ethnicity, age (more common in older people), and sex (more common in men) [3].

PD is a complex and progressive neurological condition for which there is currently no curative, neuroprotective or disease-modifying therapy available, although the identification of such agents remains a key research priority [4,5]. Currently, the aim of PD management is to provide the best possible symptomatic treatment; however, the progressive nature of PD means that regular medication reviews are required based on the stage of the condition and presenting symptoms. Modern definition of PD describes various disease stages from early and stable disease to complex and advanced using a combination of motor, nonmotor features as well as the person's level of functional impairment [6,7].

When considering pharmacological treatment, oral levodopa therapy is recognized as the 'gold standard' and remains the most effective therapy for PD, initially providing good control of motor symptoms [8]. However, pulsatile delivery of dopamine to the brain by the oral route, which includes the gastrointestinal barrier, and erratic absorption leads to fluctuation of plasma levels and central changes in basal ganglia circuits as well as downstream epigenetic changes [9–11]. These pharmacological characteristics, alongside the ongoing progressive decline in dopaminergic neuronal capacity in the person with PD, lead to the emergence of the well-known motor and nonmotor fluctuations; dyskinesias evolve into various patterns of troublesome dyskinesias all having a major negative impact on quality of life. At this stage, a combination of levodopa with other agents, or the use of alternative formulations, to ensure patients receive a sustained delivery of levodopa is considered the best clinical practice [12–15].

Advanced PD is usually signified by inadequate control of symptoms with conventional oral therapies, including levodopa, as well as transdermal options. At this stage, a range of device-aided therapies (DATs) are available that allow the administration of continuous drug delivery (CDD) [16]. The rationale for CDD is that it provides continuous dopaminergic stimulation with the aim of achieving more stable plasma levodopa levels which in turn improve control of persistent and troublesome motor and non-motor symptoms [10,11,17–19]. Recent exploratory data also suggest that CDD with some infusion therapies may provide

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Article highlights

- Parkinson's disease (PD) is a complex and progressive neurological condition, and the fastest growing neurological disorder worldwide. While levodopa and other oral therapies can provide effective control of PD motor symptoms initially, once the disease has progressed to the advanced stage, device-aided therapies (DATs) that allow administration of continuous drug delivery are required to provide symptoms control and ensure a satisfactory quality of life.
- Currently, continuous drug delivery can be achieved by either subcutaneous, intrajejunal or intravenous (experimental) routes of administration, all of which can help overcome the limitations of oral therapy in part by mimicking continuous dopaminergic stimulation.
- Continuous intrajejunal infusion of levodopa can be given either as levodopa–carbidopa intestinal gel (LCIG), delivered via the Smith Medical CADD Legacy 1400 pump, or the substantially smaller levodopa–entacapone–carbidopa intestinal gel (LECIG), delivered via the Crono LECIG pump.
- The pump is used exclusively to administer LECIG, and a key focus of its design process was to deliver practical advantages and an improved treatment experience for patients by creating a smaller, lighter and quieter pump than the existing LCIG device.
- The inclusion of entacapone in the LECIG formulation extends the clinical benefits of LCIG allowing the administration of a reduced levodopa dose to achieve the same levodopa exposure, while also reducing levels of potentially harmful levodopa metabolites, such as 3-O-methyldopa and possibly homocysteine.
- Clinical studies suggest that LECIG is as effective as LCIG and well tolerated by PD patients, with a safety profile similar to that of LCIG infusion plus oral entacapone and patients are reporting that they prefer the reduced pump size and weight; LECIG therefore offers another useful DAT option to consider for suitable people with advanced PD who may need intrajejunal levodopa therapy.
- Alongside the good clinical efficacy of LECIG achieved with reduced levodopa dosing, the LECIG pump will make it easier for patients to use in their daily lives (in particular if they are active, frail or have limited strength and low body weight) and be more discreet to wear in social situations thus helping body image.

improvements in gait and reduce freezing of gait, effects that are independent from the improvement observed in motor symptoms [20,21]. Various national and international treatment guidelines have been published by recognized professional organizations, including the European Association of Neurology and the Movement Disorder Society, relating to patient suitability and optimal use of DATs for advanced PD [22–24].

As effective symptomatic management is currently all we can offer people with PD, efforts have also been made over the years to enhance DAT options and improve drug delivery and patient acceptability. CDD can now be delivered using subcutaneous, intrajejunal and intravenous routes (Figure 1); however, the latter remains investigational and subcutaneous options are beyond the scope of this review. This article focuses on formulations that allow continuous infusion of levodopa directly into the jejunum using an ambulatory mini pump which have been developed to help overcome many of the limitations of oral therapy [15,25]. Currently, these comprise levodopa–carbidopa intestinal gel (LCIG; Duodopa, AbbVie Ltd.) infusion delivered via the CADD Legacy 1400 pump (Smith Medical, UK) [26] and most recently levodopa–entacapone–carbidopa intestinal gel (LECIG; LECIGON, LECIGIMON, Britannia Pharmaceuticals Ltd/Lobsor Pharmaceuticals) infusion delivered via the Crono LECIG pump (Canè SpA, Italy) [27,28].

Several recent reviews of CDD using LCIG infusion are available [29,30]. In this article, we review the rationale for the development of LECIG infusion for the management of advanced PD, with a particular focus on the attributes and specifications of the LECIG infusion pump device, alongside evidence for the clinical and practical benefits of LECIG in suitable patients.

2. Overview of the market

While efficacy, safety and tolerability are of critical importance when selecting a DAT for patients with advanced PD, the patient's perspectives of their treatment are critical to its success and to them continuing with the chosen therapy. With DATs, it is important that the attributes of the device provide a positive treatment experience for the patient, otherwise they may choose to discontinue what may otherwise be an effective therapy.

Following discussion of the range of suitable DAT options with their neurologist, if patients with advanced PD choose an intrajejunal levodopa infusion therapy, currently they can select either LCIG infusion or LECIG infusion. Key differences between these options relate to pump size and composition

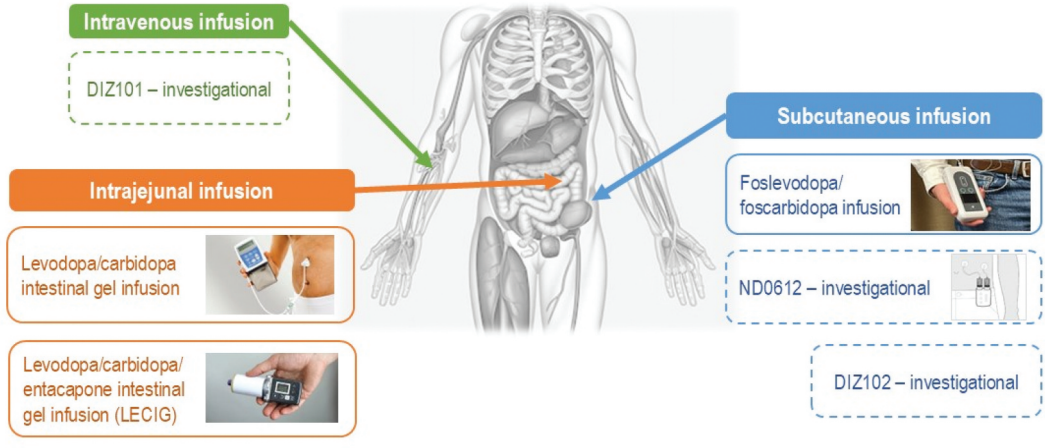


Figure 1. Methods of levodopa delivery.

of the formulation. The CADD Legacy 1400 pump used to deliver LCIG infusion is larger and heavier than the LECIG pump used to deliver LECIG infusion, and this may be an important consideration for some patients, particularly if they are frail or have low body weight.

As PD progresses and enters the advanced stages, simplification of therapy is a key aim and monotherapy with levodopa is considered ideal. Intrajejunal levodopa therapies have the potential to achieve levodopa monotherapy, and as LECIG includes the catechol-O-methyl transferase (COMT) inhibitor entacapone thereby extending the action of levodopa, monotherapy is possible. The role and clinical benefits of entacapone are discussed later in this article.

3. Introduction to the device

The LECIG infusion pump has been specifically designed for the administration of LECIG therapy and has been developed with the needs of PD patients in mind, notably the desire for a lower weight pump and smaller cartridge volume when choosing treatment with intrajejunal levodopa infusion. The LECIG pump allows treatment to be delivered efficiently and also discreetly, being a small, light and relatively quiet device.

3.1. Rationale for the development of LECIG infusion

LECIG infusion was initially developed in Uppsala, Sweden, and was approved Swedish Medical Agency in 2018 with an indication for treatment of advanced PD patients with severe motor fluctuations and hyperkinesia or dyskinesia when oral combinations of PD medication were no longer able to provide effective symptom control [31–33]. It has subsequently received marketing authorization in several other European countries, and data on clinical practice experience ar accumulating.

Several decades prior to the development of LECIG, in 1994, also in Uppsala, Sweden, LCIG infusion was developed as a DAT option for advanced PD and was approved by the European Medicines Agency in 2005. Since its initial launch, LCIG infusion has been shown in a range of pivotal randomized clinical trials, observational, retrospective and long-term registry studies to be an effective treatment option in advanced PD patients for controlling motor symptoms and improving quality of life [26,34–40]. The long-term safety and tolerability of LCIG infusion have also been confirmed in several randomized clinical trials and large open-label studies with a duration of exposure of up to four years [41,42] as well as in global registries such as DUOGLOBE [43]. Medication-related adverse events (AEs) are reported to be similar to those observed with oral levodopa/carbidopa, with the most common AEs overall being related to either the surgical procedure or device.

It is well recognized that COMT inhibitors, when used as adjuvant PD therapy, provide additional beneficial effects on motor function and are relatively well tolerated. A systematic review of the efficacy and safety of the available oral COMT inhibitors—entacapone, tolcapone and opicapone—concluded that entacapone and opicapone have similar efficacy when used as add-on therapy, and while tolcapone may also be effective, its use requires careful monitoring due to the possibility of acute liver failure [44]. So, while there have been three COMT inhibitors used in clinical practice, tolcapone is now largely withdrawn due to its potentially serious hepatic side effects.

Oral COMT inhibitors have been used successfully in combination with LCIG infusion in patients with advanced PD, resulting in effective motor control and a reduction in the LCIG daily dose in some cases, however they have also shown inconsistent effects which has been attributed to the gastrointestinal barrier and absorption issues [45,46], problems that can be overcome with direct intrajejunal infusion. In the GLORIA registry study that evaluated real-world use of LCIG, around 40% of patients were using oral anti-PD medications, including COMT inhibitors, at baseline, which reduced to approximately 25% after 12 months of LCIG treatment [39]. Similarly, the DUOGLOBE registry study reported that there were decreases in concomitant use of oral PD medication, most notably COMT inhibitors, within the first 6 months of LCIG treatment, and these lower levels remained steady for the next 2.5 years [43].

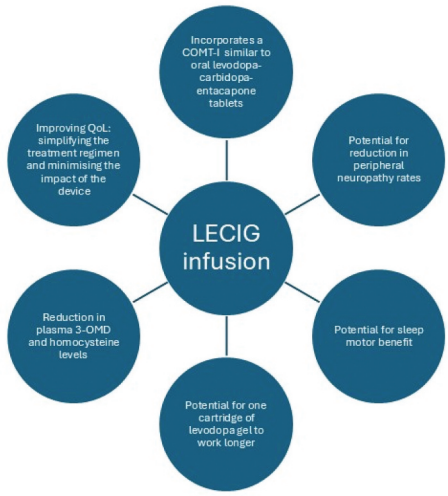
In clinical practice, combining intrajejunal levodopa with the third-generation COMT inhibitor opicapone has been attempted and appears to be effective and cost saving [46]; however, commercially, only combination of intrajejunal levodopa with entacapone is available. The LECIG formulation, which combines levodopa, carbidopa and entacapone, was developed in line with the concept used for oral Stalevo and before opicapone became commercially available.

The rationale underlying the development of LECIG was to extend the known clinical benefits of LCIG by incorporating entacapone within the formulation, thereby simplifying the overall treatment regimen as it negates the need to give oral COMT inhibitors separately (Figure 2). Another key focus of the design process for LECIG infusion was to deliver practical advantages for PD patients and a better treatment experience by way of a more user-friendly device, given that clinical experience has suggested that the bulky CADD Legacy 1400 pump is considered inconvenient and heavy by some patients, particularly those who are frail and elderly [47].

LECIG is designed to be delivered using the Crono LECIG infusion pump which is lighter than the CADD Legacy 1400 pump used to deliver LCIG [48,49], and benefits from a smaller cartridge volume. A reduced cartridge size is possible due to the presence of entacapone in the formulation, meaning that a reduced levodopa dose may be given to patients treated with LECIG to achieve the same overall levodopa exposure as LCIG.

3.2. The crono LECIG pump device

The morning dose, continuous flow rate throughout the day, and extra doses are calculated and programmed into the pump by a clinician or PD nurse. Recognizing the varying needs of individual patients, pump programming is flexible to allow infusion of LECIG at three different continuous flow rates to suit the patient's needs throughout the day. This may be particularly useful for patients who require 24-hour infusion to manage nighttime symptoms, where the flow rate can be reduced overnight. Flow rate precision is critical for consistent,



3-OMD, 3-O-methyldopa; COMT-I, catechol-O-methyl transferase inhibitor; DDCI, dopa decarboxylase inhibitor; LECIG, levodopa–carbidopa–entacapone intestinal gel; QoL, quality of life.

Figure 2. Rationale for the development of LECIG infusion.

accurate delivery of the correct dose of medication. Technical testing of the LECIG pump shows that flow rate precision is high with ± 3% of the stated dose delivered.

In terms of size and weight, the LECIG pump is substantially smaller (152 × 55 mm versus 197 × 100 mm) and lighter (230 g versus 500 g, including cartridges/syringes) than the CADD Legacy 1400 pump and uses a smaller infusion cartridge (the drug reservoir; 50 ml for LECIG versus 100 ml for LCIG) (Figure 3), all of which, as has been shown in the studies described earlier, are preferred by patients [28,50–52]. The size and weight of the CADD Legacy 1400 pump have previously been cited as drawbacks to the use of LCIG treatment with patients viewing the pump as large and heavy [47].

Technical noise tests of the pump motor undertaken using the Decibel X – Pro Sound Meter App (SkyPaw Co., Ltd., UK) have also demonstrated that the LECIG pump is quieter in use than the CADD Legacy 1400 pump (Figure 4) [53].

The overall technical specifications of the LECIG pump are shown in Table 1 [49] and details of the interface are shown in Figure 5. The LECIG pump also has Bluetooth capability, which in the future might allow healthcare teams to access usage to inform discussions with patients and adjustments to treatment if needed.

3.3. The role of entacapone in LECIG infusion

Levodopa is absorbed in the small intestine via the large neutral amino acid (LNAA) transporter. In the intestinal mucosa and peripheral tissues, levodopa undergoes metabolism by two separate pathways: decarboxylation and conversion to dopamine by the enzyme dopa decarboxylase (DDC) or methylation by the enzyme COMT to 3-O-methyldopa (3-OMD) and S-adenosyl homocysteine [54–56]. Combining levodopa with agents that inhibit these metabolic steps and prevent its degradation effectively extends its half-life, ensuring that higher plasma concentrations are available to cross the blood–brain barrier and have the desired clinical effect. One of the limitations of levodopa is that in the absence of such inhibitors, its half-life is short and only ~ 30% of an oral levodopa dose reaches the systemic circulation [55]. As a consequence, in clinical practice, levodopa is always combined with a DDC inhibitor, such as

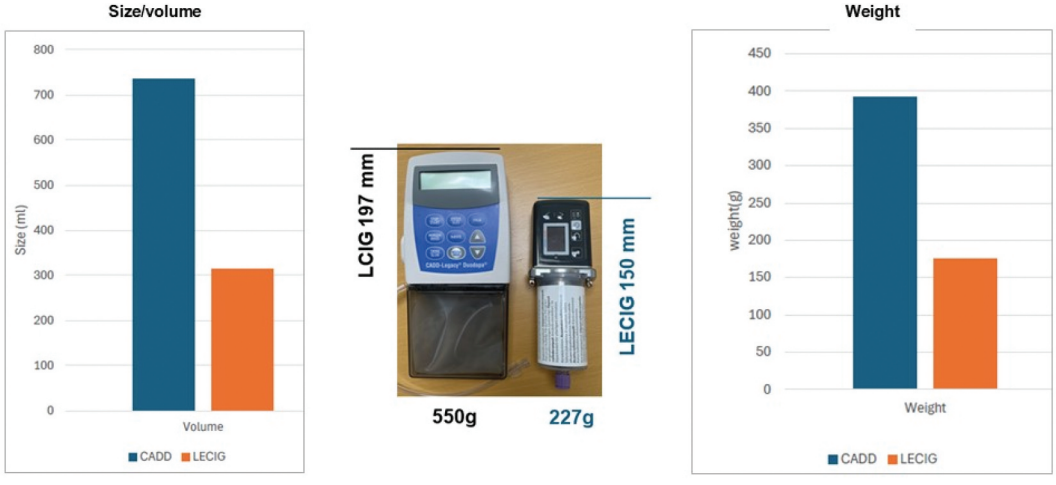


Figure 3. Size and weight of the crono LECIG infusion pump in comparison with the LCIG CADD legacy 1400 infusion pump.

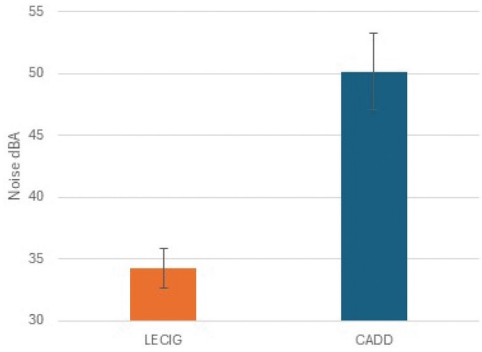


Figure 4. Results from noise recording tests using the crono LECIG infusion pump and LCIG CADD legacy 1400 infusion pump.

carbidopa, which has been shown to increase the half-life of levodopa 1.5-fold [57], or benserazide. In addition, COMT inhibitors, either entacapone, tolcapone or opicapone, can also be used to further extend the half-life of levodopa [58]. However, even in the presence of both DDI and COMT inhibitors, oral levodopa generally requires multiple daily doses to maintain effective plasma levels and adequate clinical efficacy.

The first-in-class COMT inhibitor, entacapone, was developed in the 1990s, and was approved in 2008 for use in combination with oral levodopa/carbidopa or levodopa/benserazide [59]. The addition of entacapone to the levodopa/DDI treatment regimen was able to increase the plasma availability of levodopa by ~ 35% and increase its half-life by another hour [59–62].

In clinical trials of PD patients experiencing fluctuating 'ON/OFF' symptoms and 'wearing off' of levodopa efficacy despite receiving optimal doses of oral levodopa/carbidopa, the addition of oral entacapone was found to increase 'ON' time, reduce 'OFF' time and improve quality of life measures [44,63,64]. The safety profile of adjunctive oral entacapone has been evaluated in several randomized, placebo-controlled trials which have shown it to be relatively well tolerated [65]. The most commonly reported dopaminergic adverse effects are dyskinesia and nausea, while non-dopaminergic adverse effects include diarrhea (occurring in around 10% of patients) and harmless urine discoloration.

Entacapone is now commonly administered as part of the PD treatment regimen alongside levodopa/carbidopa in a combined oral tablet. Success with this oral regimen has led to evaluation of the combination of oral entacapone with LCIG infusion therapy. In a small, short-term pilot study, oral entacapone administered at 5-hour intervals allowed a decrease in the LCIG dose by 20% while still maintaining adequate levodopa plasma levels [45]. The short half-life of entacapone when given orally necessitates the administration of multiple daily doses; however, when given as part of a continuous infusion, this is no longer an issue [60].

Another potential benefit of incorporating COMT inhibition into PD treatment regimens is that it may reduce some of the unwanted effects that arise as a result of long-term levodopa exposure. When levodopa is given alongside a DDC inhibitor but in the absence of a COMT inhibitor, metabolism of levodopa shifts toward the COMT pathway, and methylation of levodopa, rather than decarboxylation, becomes predominant. Necessary cofactors of COMT enzymes include vitamins B12, B6 and folic acid, and deficiencies of these vitamins can lead to raised homocysteine levels [66]. In addition, the metabolites of COMT

Table 1. Technical specifications of the Crono® LECIG pump based on manufacturers' information [49].

Technical characteristic	Specification
Pump dimension	84 × 55 × 42 mm.
Weight	139 g (including battery).
User interface	Colour OLED display 96 × 64pixels. 6 buttons —The buttons perform a dedicated function: BOLUS, UNDO, START/STOP, MENU/OK, UP, DOWN. The interface is menu driven for easy navigation to all pump functions and information. The menu language can be chosen when ordering the device.
Battery	Lithium CR 123A 3 V.
Battery life	Approximately 90 infusions.
Single-use reservoir	Dedicated reservoir with a 50 ml capacity.
Quantities that can be administered	50 ml.
Shot volume	20 microliters (shot = quantity administered for every rotation of the motor).
Flow rate precision	± 3%
Occlusion pressure	4.7 ± 1.5 bar
Setting parameters	Clock; flow rate; end infusion alarm; extra dose; morning dose
Keyboard lock levels	It is possible to lock the settings of the pump: OFF: no restriction; ON: allows only switching on and off and dose delivery. When switched ON, the display shows the lock symbol.
Range	Flow rate: F1: 0–20 ml/hour; F2: 0–20 ml/hour; F3: 0–20 ml/hour in 0.1 ml/hour increments.
Reading the number of infusions performed	It is possible to display the number of infusions performed.
Resetting the number of infusions	It is possible to reset the number of infusions performed.
Visualization when switched ON	The display continuously shows a colored progress bar, the operating mode, the time remaining until the end of infusion (updated every minute), the flow rate set and the residual volume inside the syringe.
Safety system	Connection and locking of the syringe. 10 different error messages (visual and acoustic) depending on the type of problem identified by the pump safety systems. Occlusion message and battery exhausted message. Indications of how to correct the error are also shown.
Data storage	The plunger position remains in memory even if the device is left without battery while set to OFF or STOP.
Motor	Coreless DC motor, the rotation of which is controlled by an infrared system.
Electronic circuit	Has two microcontrollers for increased safety.
Protection degree	IP 42.
Advancement system	Made of metal. The force on the piston is axial.
Events data	Allows storage of up to 2,944 events.

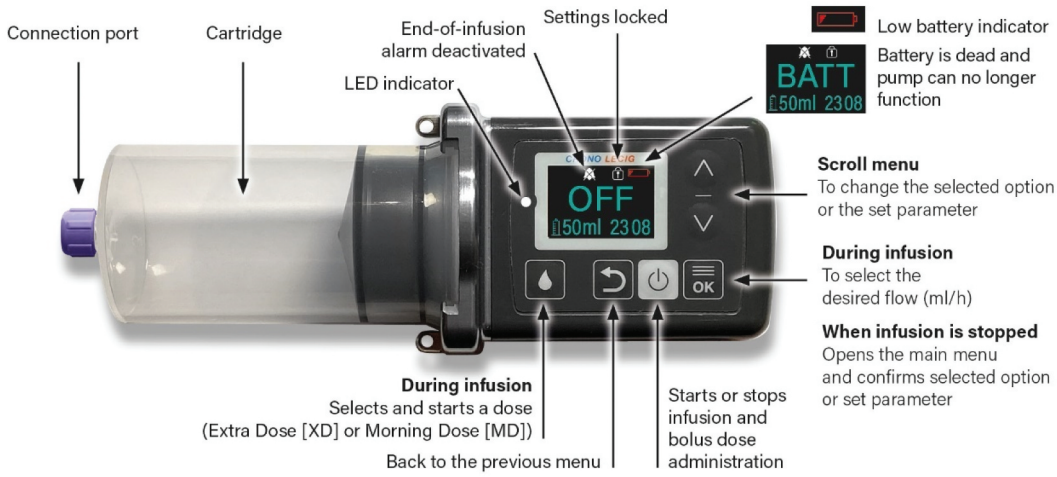


Figure 5. The crono LECIG infusion pump interface.

metabolism of levodopa are eventually converted into homocysteine, again, contributing to raised homocysteine levels. Increased concentration of these levodopa metabolites, specifically homocysteine, is thought to be associated with an increased risk of developing peripheral neuropathy in patients with PD, although the evidence is not definitive [33,67]. However, a multicenter study of 197 PD patients in which 144 were exposed to levodopa for >3 years while 53 simultaneously received entacapone for ≥18 months showed that the presence of entacapone appeared to have a protective effect against the development of levodopa-induced peripheral neuropathy [68].

COMT also exists in several forms and the presence of Val158Met (rs4680) in exon 4 of the COMT enzyme leads to three types of enzyme activity: high activity (COMT 'GG' (Val/Val)), intermediate activity (COMT 'GA' (Val/Met)), and low activity (COMT 'AA' (Met/Met) [69,70]. Reports suggest that in PD patients with Val/Val carriers of COMT may respond more favorably to entacapone, with prolonged ON time compared to those with Met/Met carriers and therefore, pharmacogenetic principles may also guide use of COMT inhibition in the future [71].

4. Clinical profile and post-marketing findings

4.1. Data from pre-approval studies

The possibility of achieving adequate clinical efficacy using a reduced levodopa dose when treating with LECIG was demonstrated in a small, randomized, open-label crossover pharmacokinetic study of 11 patients comparing levodopa levels when administered as LECIG infusion or as LCIG infusion [27]. The bioavailability of levodopa over a 14-hour infusion was higher with LECIG compared with LCIG. In addition, treatment response scale (TRS) scores did not differ significantly between treatment groups, suggesting that plasma levodopa concentrations achieved with LECIG are therapeutically effective despite using a reduced levodopa dose [27]. In addition, the study reported a slower decline of levodopa concentration after disconnecting the LECIG pump in the evening compared with LCIG which may be beneficial for those patients who experience symptoms indicating end-of-day wearing off of their usual medication effect [27]. However, while data suggest LECIG can provide similar levodopa bioavailability to LCIG, it should be noted that the pre-approval study included only 11 participants and as such should be considered as a proof-of-concept study. Further larger data collection studies addressing pharmacokinetic properties of LECIG are warranted. Similarly, there are no robust head-to-head comparative trials of LCIG and LECIG to confirm efficacy and tolerability findings, although the ongoing ELEGANCE registry will provide valuable information on real-world use of LECIG [72].

A subsequent population pharmacokinetics modeling study using data from the previous 11 patients showed the continuous flow rate of levodopa dose can be decreased by approximately 35% when using LECIG compared with LCIG, while still maintaining stable and clinically effective levodopa levels [73]. Notably, the observed stability seemed to occur without accumulation of levodopa and the resulting risk of dyskinesias, which can be observed with oral entacapone [73].

Peripheral neuropathy has been reported in PD patients receiving prolonged treatment with oral or intestinal infusion of levodopa [67,74]. This increased risk of peripheral neuropathy is thought to be linked to duration of levodopa exposure, the use of high doses of levodopa and, as previously discussed, high plasma levels of the levodopa metabolite homocysteine [75–78]. Although it needs to be confirmed in robust clinical trials, it seems logical that using the minimal effective dose of levodopa is likely to achieve the best long-term patient outcomes. In the Senek et al. 11-patient study, it was found that on switching from LCIG to LECIG, plasma levels of the levodopa metabolite 3-OMD decreased by 35% (Senek et al., 2017). Conversely, when switching from LECIG to LCIG, they increased by 22%.

4.2. Data from post-approval studies

Data accumulated to date suggest that LECIG is well tolerated by patients, with no serious or unexpected adverse events and a safety profile in line with clinical reports of LCIG infusion plus oral entacapone [27,28,50–52,72,79].

Several European countries where LECIG is now available have reported their clinical practice experience of its use (Table 2) with generally positive reports of efficacy and tolerability, and patients

stating that they prefer the smaller, lighter LECIG pump compared with LCIG device [28,50–52,72,79,80].

A valuable addition to the evidence base for LECIG will be provided by the results of the ELEGANCE study (NCT05043103), an ongoing non-interventional observational study that is gathering real-world data on long-term efficacy, safety and patient-reported outcomes following LECIG treatment from 13 European countries. Results from an interim analysis of 167 patients are currently are now available [72], and it is anticipated that the final outcomes will help inform clinical decision-making when selecting DAT options.

4.3. Suitable candidates for LECIG infusion

Every person with Parkinson's presents with a specific clinical picture, and many endophenotypes have been described and

Table 2. Overview of studies reporting outcomes of real-world clinical practice use of LECIG.

Author, year, study description & participants	Overview of key results
Öthman M et al, 2021 [28] • Observational study • 24 patients undergoing LECIG treatment • 12 patients switched from LCIG • Follow-up: One year	**LECIG dosing**: Continuous infusion rate with LECIG: 76% of previous LCIG dose. **Patients' perceptions of treatment**: Most patients who had not used levodopa infusion before ($n = 10$) perceived that their symptoms had improved (70%). • Questionnaire responses on patient-perceived ability to perform daily activities, and quality of life after starting LECIG ($n = 21$): most patients reported improvement in the ability to perform daily activities and in their self-rated quality of life. • Among those who switched from LCIG ($n = 12$), the most common perception of the effect of LECIG on PD symptoms was that there was no change (45%). • A majority of patients previously treated with LCIG regarded the new pump to be improved both with respect to user-friendliness and in terms of changing cassette/syringe; all patients thought the pump size was improved.
Szász JA et al, 2024 [51] • Retrospective analysis • 74 advanced PD patients undergoing LECIG treatment • Data from 12 tertiary centers in Romania • Follow-up: Observations made during LECIG titration period	**OFF time**: LECIG treatment significantly reduced daily OFF time versus baseline from 5.7 hours/day to 1.7 hours per day ($p < 0.01$). **Dyskinesias**: The duration and severity of peak-dose dyskinesia and the occurrence of diphasic dyskinesia were significantly reduced compared with baseline values; paired profiles for the duration of mild/moderate dyskinesia and severe dyskinesia showed significant reductions in mean values with LECIG treatment compared with baseline **Other treatment effects**: Improvements were observed in Hoehn and Yahr Scale scores; significant reduction in the use of concomitant oral medications.
Viljaharju V et al, 2024 [50] • Retrospective analysis • 30 consecutive PD patients treated between 2020 and 2022 at Helsinki University Hospital, Finland • Follow-up: 6 months	**Change in medication**: Significant increase in LEDD from baseline to 6 months of LECIG treatment (1,230 mg vs. 1,570 mg, $p = 0.001$. **LECIG monotherapy**: At discharge 19% of patients used LECIG monotherapy without concomitant antiparkinsonian medications; this figure was 16% at 6 months. **Adverse events**: Similar to those seen with LCIG. P**atients' perceptions**: Patients preferred the small pump system of LECIG versus LCIG.
Atanasova-Ivanova KA et al, 2023 [52] • Observational study • 5 patients treated with LECIG at St Naum University Hospital, Sofia, Bulgaria • Folow-up: One year	**Motor efficacy**: All patients showed improvements in motor function (assessed using MDS-UPDRS) versus oral levodopa. **Dyskinesias**: No patient experienced an increase in the dyskinesias. **Quality of life (assessed using PDQ-8) and sleep problems**: Both improved. **Polyneuropathy**: No evidence of levodopa-induced polyneuropathy after one year of follow-up. **Tolerability**: Generally well tolerated; the most common adverse effects were diarrhea and weight loss (in one patient who had existing *Helicobacter pylori* infection).
Öthman M et al, 2024 [79] • Retrospective analysis • 24 patients undergoing LECIG treatment • Four-year follow-up of the 24 patients reported in Öthman et al., 2021 (above).	**Continuation of treatment**: 11/24 patients (45%) were still receiving LECIG treatment at four years of follow-up. **Discontinuations**: • 5/24 (21%) patients discontinued LECIG during the first 6 weeks due to adverse effects (3: diarrhea; 1: hallucinations; 1: preexisting leg edema) • 8/24 (33%) patients died over the study period (considered unrelated to LECIG treatment; expected mortality rate for this population) **Health-related quality of life**: Scores measured using validated scales (PDQ-8, EuroQol 5D) were relatively good for those who remained on treatment.
Santos-García D et al, 2025 [80] • Observational study • 73 patients from 21 Spanish centers • Follow-up: 6 months	**OFF time**: Significant decrease in mean daily OFF time from 5.2 hours/day (pre-LECIG) to 1.9 hours/day (post-LECIG; $p < 0.0001$). **Global improvement**: Observed in > 85% of patients. **LEDD**: No significant change observed from baseline to 6 months. **Adverse events**: 34 patients (46.6%) had at least one treatment- or device-related adverse event a **Discontinuations**: Five patients (6.8%) discontinued LECIG.
Weiss D et al, 2025 [72] • European observational, non-interventional registry study: ELEGANCE (NCT05043103) • Interim analysis of 167 patients from 37 centers • Follow-up: One year	**OFF time**: Mean daily OFF time hours substantially reduced by 3.47 hours from baseline (5.15 hours) at V2 (3–6 months of treatment). **Discontinuations**: Three patients from this analysis set (1.8%) discontinued LECIG treatment. **Adverse events**: Most adverse events were related to the procedure or the device. **Quality of life (assessed using PDQ-8) and sleep (assessed using PDSS-2)**: Both improved from baseline. **Patient perceptions of device**: Patient-reported satisfaction with the LECIG pump was high for all parameters assessed.

LCIG, levodopa–carbidopa intestinal gel; LECIG, levodopa–entacapone–carbidopa intestinal gel; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PDQ-8, Parkinson's Disease Quality of Life Questionnaire, 8-item; PDSS-2, Parkinson's Disease Sleep Scale 2.

therefore the need for a personalized approach to treatment cannot be overstated [81]. More recently, a combination of phenotypes and personalized treatments has been described as part of a stepped-care strategy for PD [82]. The attributes of each of the available DATs for the management of advanced PD in terms of both clinical efficacy and safety, and practical utility, need to be considered when making treatment decisions considering the patient's preferences and personal circumstances.

In the case of LECIG, it is indicated for the treatment of patients with advanced PD who have severe motor fluctuations and hyperkinesia or dyskinesia when available oral combinations of PD medicinal products have not given satisfactory results [83]. Since the LECIG trigel includes entacapone in the formulation, it can help simplify the (often complex) PD treatment regimen and reduce the overall number of oral tablets that need to be taken. A regimen that is as simple as possible is important in this patient population who may also be taking multiple medications for PD as well as other concomitant conditions, or who may have impaired cognition.

From a practical and pragmatic standpoint, we feel that the overall reductions in size, weight and noise of the LECIG pump will make it easier for patients to carry and more discreet to wear in social situations and this may particularly appeal to active and working patients as well as younger female patients. Also, the small, light LECIG pump makes it particularly suitable for those who are frail, those with a low body weight, or who would experience shoulder pain with daily use of a larger device. In terms of noise levels, humans perceive decibel levels logarithmically, meaning that an increase of approximately 10 dB is often perceived as a doubling of loudness. Thus, the differences recorded between the LECIG pump and CADD Legacy 1400 pump can be considered as substantial. The LECIG pump noise level (34.3 dB) is only slightly above the background noise level (by 4.3 dB), suggesting that it is likely to blend in with the environmental noise levels.

Flexibility of dosing is a valuable attribute when delivering a drug continuously. The flow rate of the LECIG pump can be easily programmed and adjusted, so patients who tend to accumulate levodopa across the day and become dyskinetic in the evenings can use a lower infusion rate in the afternoon [28], or where 24-hour infusion is desired with lower dose levels overnight.

As discussed, some data suggest that entacapone may have a protective effect against the development of with peripheral neuropathy [68], so continuous infusion of entacapone with LECIG may be helpful in PD patients at particular risk of neuropathy, although this needs to be confirmed in clinical studies.

There is a potential for improvement in nocturnal sleep with LECIG infusion based on available data from LCIG [43] as well as emerging data from foslevodopa/foscarbidopa 24-hour subcutaneous infusion [84]. Addition of entacapone may extend levodopa action through the night and specific studies in this regard with LECIG infusion are warranted.

While LECIG has shown good efficacy and tolerability in studies to date, it also has certain limitations. In terms of concerns for clinicians and patients, not all advanced PD patients will be suitable candidates for LECIG infusion. Those with known entacapone intolerance, for example, should not commence treatment with LECIG. There will undoubtedly be a 'learning curve' for any patients switching from oral or transdermal therapies to LECIG, while they become familiar with handling the new device. However, it is acknowledged that the smaller pump and control buttons may be difficult to handle by some patients if they have dexterity issues and dose adjustments may be complicated, so they may in fact prefer a larger pump device. As the PEG-J insertion process is the same for LECIG and LCIG, they are both likely to be associated with the same level of procedure-related issues. Rates of dyskinesia with any potential adverse effects due to long-term infusion of entacapone is something that needs to be carefully monitored in LECIG-treated patients and will hopefully be addressed when the full results of the ELEGANCE registry database are available [72].

In terms of device limitations, although the pump allows the patient to use different flow rates at different time, they are not automated and require programming by the healthcare team. While the pump has Bluetooth enabled, this is not yet fully functional yet, but in the future may allow information to be exchanged with the healthcare team to better inform treatment decisions.

5. Alternative devices

In terms of different forms of levodopa infusion therapy, the only competing option for intrajejunal delivery currently is LCIG infusion delivered using the CADD Legacy 1400 pump which is larger and heavier than the pump used to deliver LECIG infusion. LECIG also benefits from inclusion of entacapone within the gel formulation, thereby simplifying the overall treatment regimen. A recent addition to the range of levodopa infusion options is subcutaneous foslevodopa/foscarbidopa which is intended to be administered over 24 hours, also using an ambulatory mini-pump. Foslevodopa/foscarbidopa infusion has shown benefits in reducing OFF time and improving motor function, with monotherapy being possible in around 30% of PD patients [16,18]. However, infusion site issues can be a problem with erythema (27%), local site pain (26%), cellulitis (19%) and skin edema (12%) being reported after 12 months of treatment in the pivotal Phase III trial [85].

6. Conclusions

A pragmatic and personalized approach to PD management in the advanced stage is essential and LECIG infusion offers yet another valuable DAT option to consider for suitable people with advanced PD. The relative potential advantages of the LECIG pump as well as the combination of levodopa and entacapone given as continuous infusion have already been discussed in detail. In addition, patient preference is key, with some studies suggesting that patients prefer the smaller, easy-to-use pump that delivers LECIG which meets the central premise that PD patients should be at the center of all therapeutic decisions. Accumulated clinical evidence to date suggests LECIG infusion achieves good clinical efficacy in terms of

symptom management with a reduced levodopa dose, while having a similar safety and tolerability profile to LCIG infusion. The design of the LECIG pump, being smaller, lighter and quieter than the CADD Legacy 1400 pump, can provide practical benefits for PD patients in their daily lives, particularly if they are active, frail or have limited strength and low bodyweight, as well as being discreet to wear. LECIG is a relatively new DAT option, having entered the market in Sweden in 2018, so real-world data collection is ongoing with the aim of establishing its long-term clinical impacts, in particular the effect of continuous entacapone infusion.

7. Expert opinion

The use of advanced therapies for Parkinson's disease (PD) has been a complex area of clinical management for some time, with uncertainties surrounding the diagnosis of advanced PD, the use and definition of the term 'advanced' as well as the availability and optimal use of the therapeutic options. Since the late 1990s, so-called advanced therapies, firstly deep brain stimulation (DBS) using stereotactic brain surgery followed by device-aided subcutaneous apomorphine infusion and intrajejunal levodopa–carbidopa infusion (LCIG; Duodopa), have been used successfully worldwide for treatment of advanced PD. More recently, however, two further options have become available to add to the armory of advanced therapies, namely subcutaneous levodopa infusion using a combination of the prodrugs foslevodopa and foscarbidopa (ProDuodopa) and levodopa–entacapone–carbidopa intestinal gel (LECIG; LECIGON). The exact place of these new therapies within the current treatment paradigm remains to be confirmed, but certainly subcutaneous foslevodopa/foscarbidopa offers a robust 24-hour treatment option for those choosing to have subcutaneous therapy, while intrajejunal LECIG seems a logical option to offer to patients suitable for intrajejunal therapy.

For a long time, there has been debate about the use of COMT inhibitors earlier in clinical practice for the treatment of PD as, physiologically, while COMT inhibition extends the clinical effect of levodopa dose, COMT activity also generates the inactive metabolite 3-O-methyldopa (3-OMD) in addition to potentially harmful homocysteine. In LECIG, the addition of entacapone to the levodopa gel formulation increases the bioavailability of levodopa, allowing a lower dose to be given. This offers theoretical advantages of less 3-OMD production, while the presence of entacapone may also reduce serum homocysteine levels which is suggested may be associated with the development of peripheral neuropathy. The use of COMT inhibition with intrajejunal levodopa was initially attempted in clinical practice by combining LCIG with oral entacapone or opicapone. However, the combination of intrajejunal levodopa with oral COMT inhibition leads to unpredictable clinical effects since oral therapies are subject to all gastrointestinal barriers that are often exacerbated in advanced PD. Incorporating entacapone into the intestinal gel avoids these issues and makes continuous COMT inhibition, as offered by LECIG, a real-life strategy. Treatment guidelines for PD in the future would need to include clear indications for management of advanced and early advanced PD with subcutaneous levodopa therapy as well as intrajejunal levodopa-entacapone gel therapy.

Clinical trials data from small pivotal studies and also real-life data collection from several European countries all suggest sustained clinical benefits of LECIG therapy and a real patient preference for using the small, accurate and less noisy LECIG pump. The licensing of LECIG infusion in many European countries has therefore opened up another clinical therapeutic option for people with advanced PD. Further studies with LECIG infusion in real-life settings are required to ascertain its beneficial effects and tolerability with long-term use, and also patient experience of using the LECIG pump.

In future, there are likely to be debates about the use of LECIG preferentially over LCIG and also whether there are specific indications for each of these two formulations, thus refining personalized therapy options for advanced PD. A key unmet need in PD is management of disabling nonmotor symptoms of PD. Key gaps in the management of sleep dysfunction, early morning off-related nonmotor issues, pain and insomnia remain, as well as issues related to cognitive and neuropsychiatric problems [86]. It is envisaged that with the advent of new advanced therapies and technology such as the LECIG device, pumps will be more efficient delivering 24-hour therapy in addition to being programmable (lower doses at night). It is also expected that therapies will also gather valuable evidence base for management of specific nonmotor issues such as sleep dysfunction, early morning akinesia, pain, sleep maintenance insomnia and nonmotor fluctuations so that advanced therapy becomes truly modern and capable of personalized delivery of care.

Funding

Editorial assistance in the development of the manuscript was funded by provided by Britannia Pharmaceuticals Ltd.

Declaration of interest

K. Popławska-Domaszewicz has received honoraria for participating in sponsored academic symposia and Advisory Boards organized by Britannia Pharmaceuticals Ltd., Stada, AbbVie, Woerwag Pharma and has received academic support from GKC and Altoida. V. Metta has received grants from Britannia, Indonesia Government, Dubai Health Authority, AbbVie and has spoken at sponsored symposia organized by AbbVie, Stada, and Britannia Pharmaceuticals Ltd. He is official advisor to Parkinson's UAE and visiting Professor at SRM University Hospital, India. P. Odin has participated in recent Advisory Boards organized by AbbVie, GKC, Bial, Lobsor, Nordic Infucare, Stada, Zambon, Britannia Pharmaceuticals Ltd; he has received honoraria for recent lectures from AbbVie, Britannia Pharmaceuticals Ltd., Zambon, Bial, MDS; recent academic grants: Swedish Parkinson foundation, Faculty of Medicine at Lund University, Southern Swedish Health Care Region, Swedish Parkinson Academy, SRA Multipark, Åhlens Foundation. K.R. Chaudhuri is Editor in chief of JPM (Movement Disorders section), Nature Parkinson's Journal (Founder Editor). He has participated in recent Advisory Boards organized by AbbVie, UCB, GKC, Bial, Cynapsus, Lobsor, Stada, Zambon, Profile Pharma, Synovion, Roche, Therevance, Scion, Britannia Pharmaceuticals Ltd., Acadia, 4D Pharma; Advisory Boards over two years ago: Medtronic; he has received honoraria for recent lectures from AbbVie, Britannia Pharmaceuticals Ltd., UCB, Zambon, Novartis, Boehringer Ingelheim, Bial, Kyowa Kirin, SK Pharma, Scion, GKC, MDS, EAN; recent grants (Investigator Initiated): Bial; grants (Investigator Initiated) over two years ago: Britannia Pharmaceuticals Ltd., AbbVie, UCB, GKC; recent academic grants: EU Horizon 2020, Parkinson's UK, NIHR, Parkinson's Foundation, Wellcome Trust; academic grants over two years ago: Kirby Laing Foundation, MRC, MDS (MDS NMS Project); royalties or licenses (ongoing): Oxford (book), Cambridge publishers (book), MAPI institute (KPPS, PDSS 2); payment for expert testimony: GMC, NICE, NIHR.

Reviewer disclosure

Peer reviewers in this manuscript have no relevant financial relationships or otherwise to disclose.

Acknowledgments

Editorial assistance in the development of the manuscript was provided by Dr Karen Wolstencroft.

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