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Levodopa, carbidopa monohydrate and entacapone intestinal gel for severe motor flucuations in advanced Parkinson's Disease

NIHRIO ID	31393	**NICE ID**	10681
Developer/Company	Britannia Pharmaceuticals Ltd	**UKPS ID**	660641

Licensing and market availability plans	Currently in phase I clinical development.

SUMMARY

Levodopa, carbidopa monohydrate and entacapone intestinal gel (LECIG, TRICEL, Lecigon) is in development to treat severe motor fluctuations in advanced Parkinson's disease (PD). PD is a progressive neurological disease caused by a loss of nerve cells in a particular part of the brain that results in decreased levels of the chemical messenger dopamine. This results in the motor symptoms associated with PD: tremor, slow movement, and muscle stiffness. Initially symptoms are managed with oral levodopa therapy. However, levodopa causes side-effects such as nausea or vomiting, and excessive levodopa doses result in dyskinesias (involuntary twisting hyperkinetic movements) and as PD advances, symptoms may re-emerge between doses ("wearing off").

LECIG is given through continuous infusion into the intestines and consists of levodopa, carbidopa monohydrate and entacapone. Levodopa can be converted to dopamine in the brain to supplement the low levels in PD patients and improve motor symptoms. Addition of carbidopa and entacapone prevent early breakdown of levodopa before it enters the brain, to make more available for conversion to dopamine. If licenced, LECIG would provide an additional treatment option for patients with advanced PD who are levodopa responsive and who have inadequately controlled motor fluctuations using existing medicinal products.

PROPOSED INDICATION

Treatment of advanced Parkinson's Disease (PD).[1,]

TECHNOLOGY

DESCRIPTION

Levodopa, carbidopa monohydrate and entacapone intestinal gel (Lecigon, LECIG, TRIGEL) is a medicinal product that combines the delivery of all three components: levodopa, carbidopa monohydrate and entacapone (ratio 4:1:4) to PD patients in the form of an intestinal gel for continuous infusion into the duodenum/jejunum via a portable pump.[1,2] Levodopa is a precursor of dopamine that is administered to patients with PD due to its ability to cross the blood-brain barrier (BBB).[3] Once levodopa has crossed the BBB it is metabolised to dopamine and supplements the low endogenous levels of dopamine in PD patients, resulting in improved nerve conduction and improvement in movement disorder symptoms.[4] Carbidopa is a decarboxylase inhibitor which works by preventing the breakdown of levodopa before it crosses the BBB, thus allowing lower doses of levodopa to be used causing fewer side-effects to patients such as nausea and vomiting.[5] Addition of the catechol-O-methyltransferase (COMT) inhibitor entacapone results in less conversion of levodopa to 3-Omethyldopa (3-OMD). Similarly to carbidopa, this increases the therapeutic efficacy of levodopa by increasing the levodopa plasma concentrations.[2]

In the phase I clinical trial (NCT02448914) participants are given three individually adjusted and pre-defined doses of intestinal administration of LECIG (20mg/ml levodopa, 5mg/ml carbidopa monohydrate, and 20mg/ml entacapone): a morning dose, a continuous 14 hour infusion, and extra bolus doses (if required).[1]

INNOVATION AND/OR ADVANTAGES

In advanced PD, progressive neurodegeneration and gastrointestinal impairments reduce levodopa absorption and shorten the duration of response to treatment (known as ON periods) so patients require increased doses of oral treatment to manage their symptoms. However, this means that patients experience peaks and troughs of disease activity, oscillating between OFF and ON with levodopa-induced side effects such as dyskinesia. Therefore treatments that provide continuous stimulation of levodopa are preferred for patients with advanced PD to avoid oscillating symptom control and treatment-induced side effects.[6]

Intestinal infusion of combined levodopa and carbidopa (Duodopa) provides faster absorption, comparable levodopa bioavailability and significantly reduced intra-patient variability in levodopa concentrations relative to oral administration of levodopa and carbidopa.[1,7] In tablet form, entacapone has shown to improve the bioavailability of levodopa, resulting in more preserved stability of levodopa concentrations and motor functions.[1,8]

The combination of levodopa-carbidopa intestinal gel (LCIG) infusion with oral entacapone is already licenced for PD disease patients with end of dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment. The combination of all products (levodopa, carbidopa, and entacapone) administered as an intestinal gel, however, does not have Marketing Authorisation in the EU/UK.[9,10] Development of a levodopa, carbidopa, entacapone intestinal gel was thought to optimise delivery of levodopa in the treatment of advanced PD.[11,7] Additionally, levodopa, carbidopa and entacapone intestinal gel

is delivered via a pump that is approximately half the size and half the weight of the LCIG pump which is a significant patient-centred improvement for a patient population who experience impaired physical functioning.[12,13]

Results from the phase I crossover trial (NCT02448914) suggest that the required levodopa dose can be successfully reduced with continuous infusion of levodopa, carbidopa monohydrate and entacapone intestinal gel, without lowering levodopa exposure relative to LCIG.[2] In a real-world study of 24 patients who were treated with Lecigon, 15 of whom switched from or previously received LCIG, the efficacy and safety of Lecigon was as expected and patients with previous experience with the LCIG pump indicated that they preferred the size and usability of the Lecigon pump.[14]

In addition, levodopa, carbidopa and entacapone intestinal gel is delivered via a pump that is approximately half the size and half the weight of the LCIG pump. This is a significant patient-centred improvement for a patient population who experience impaired physical functioning.[12,13]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination of levodopa, carbidopa and entacapone intestinal gel infusion does not have Marketing Authorisation in the EU/UK for any indication.

The combination of levodopa-carbidopa intestinal gel (LCIG) infusion with oral entacapone is already licenced in the UK for PD disease and end of dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment.[9,10]

The very common drug-related adverse effects (experienced by ≥ 10% of patients) associated with LCIG infusion are weight decrease, anxiety, depression, insomnia, orthostatic hypotension, dyskinesia, nausea, constipation and falls.[10]

The very common device and procedure related adverse effects from intestinal infusion of LCIG are postoperative wound infection, abdominal pain, excessive granulation tissue, complications of the device insertion, incision site injury or complications.[10]

PATIENT GROUP

DISEASE BACKGROUND

PD is a progressive neurodegenerative disease, characterised by progressive degeneration of the dopaminergic system due to a loss of nerve cells in part of the brain called the substantia nigra. Dopamine plays a vital role in regulating the movement of the body as it is the chemical messenger (neurotransmitter) that transmits messages between nerves that control muscle movements.[15,16] A reduction in dopamine is responsible for the motor symptoms of PD which include bradykinesia (slow movement), rigidity, tremor and postural instability.[16,17] It is not known exactly what causes the loss of dopaminergic nerve cells associated with PD but it is believed to be a combination of genetic changes and environmental factors such as the pesticides and herbicides used in farming; traffic; or industrial pollution.[18] The biggest risk factor for developing PD is advancing age; with the average age of onset being 60 years old. Men are also more likely to develop PD than women.[17]

Early-stage symptoms of PD are managed with oral levodopa treatment. However, as the disease progresses, symptoms are no longer well controlled by oral medication and the symptoms re-emerge or worsen usually around 3-4 hours after a dose of levodopa.[17,19] This phenomenon is called "wearing off" where the control of motor and non-motor symptoms fluctuate, occurring more frequently and with less predictably.[19] The main factor leading to the development of motor fluctuations is the gradual loss of dopaminergic cells over time in PD, meaning that the level of dopamine in the patient's brain becomes increasingly dependent on the availability of levodopa in the blood.[19] OFF periods also become more common in advanced PD due to the development of gastric complications that reduce the capacity for levodopa absorption and therefore shorted the duration of response to oral medication.[11] Wearing off can occur at any time after the initial 'honeymoon period' of starting levodopa treatment, but most commonly develops five or more years after the onset of motor symptoms and happens more frequently as PD progresses.[19] The associated motor and non-motor symptoms of advanced PD can complicate the basic activities of daily living such as bathing, dressing, eating, sleeping and walking.[20]

CLINICAL NEED AND BURDEN OF DISEASE

PD is the second most common neurodegenerative disorder after Alzheimer's disease and is the fastest growing neurological condition in the world.[21,22] In 2020 it was estimated that there were 121,000 people living in England with PD, and 7,642 in Wales.[22] The prevalence of PD increases with age: the prevalence is 4-5 per 100,000 people aged 30-39 years, compared with 1,696 per 100,000 people aged 80-84 (equivalent to 1.7% of this age group). By 2025, because of a growing and increasingly ageing population the estimated prevalence of PD is expected to increase by 23.2% and the yearly incidence is expected to increase by 23.9%.[23] PD affects men more commonly than women, with males aged 50-89 1.4 times more likely to develop PD than females in the same age category.[22]

In England in 2019-20 there were 192,429 diagnoses of PD (ICD-10 code G20). There were 13,836 finished consultant episodes (FCE) for PD, which resulted in 7,200 admissions and 102,586 FCE bed days.[24] It is estimated that 10% of PD patients have advanced disease.[25,26]

A UK retrospective cohort study using data from 1994–2013 from the UK clinical Practice Research Datalink and Hospital Episode Statistics databases identified that the total costs of PD increased significantly between patients with non-advanced PD and advanced PD (£4422 versus £5491, $p<0.01$).[27] In a further survey providing data on 302 patients with advanced PD reported that annual costs increased significantly among patients with advanced PD from £25,630 in patients spending <25% of waking time in an OFF state to £62,147 for patients spending >75% of waking time in OFF.[28]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for PD, but treatments are available to help relieve the symptoms and maintain the quality of life of the patient.[29] Every person with PD has a different experience of the condition, so PD patients work with a specialist, PD nurse or pharmacist to adapt the type of drug, dosing and timing to find the best treatment regime for the patient. Which medication patients take will depend on the type and severity of their symptoms as well as other factors such as age and lifestyle.[30]

Levodopa is the mainstay of treatment for PD and most patients initially respond well to levodopa therapy.[26,31] Once a patient develops insufficient symptom control or fluctuations in motor control the treatment regime may be adapted through measures such as optimising the dose and timing of levodopa used or the addition of drugs to the treatment regime.[32]It is estimated that around 10% of PD patients will develop advanced disease resulting in physical disabling motor and non-motor complications. Motor complications include wearing off effects and dyskinesia (abnormal involuntary movement) that do not adequately respond to oral medication manipulation. In such cases patients are considered for a number of advanced therapies that include apomorphine subcutaneous infusions, deep brain stimulation (DBS) and levodopa-carbidopa intestinal gel (LCIG) infusion.[26]

CURRENT TREATMENT OPTIONS

LCIG is currently available through an NHS England clinical commissioning policy for patients with advanced levodopa-responsive PD with severe motor fluctuations, including significantly disabling wearing off periods and/or dyskinesia, that have not responded satisfactory to available combinations of PD.[26,33] The NHS England Clinical Commissioning Policy for LCIG recommends it should be restricted to patients unsuitable for deep brain stimulation (DBS).[26]

PLACE OF TECHNOLOGY

If licenced, this medicinal product will offer an additional treatment option for patients with advanced PD.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT02448914, A Single Centre, Two-period, Open Label, Randomised Crossover Study to assess Plasma Levodopa, Carbidopa and Entacapone Concentrations After Continuous Infusion of TRIGEL or Duodopa in Patients With Advanced Parkinson's Disease **Phase I** – Completed **Primary completion date:** July 2015 **Locations:** Sweden
Trial design	Open-label, two-period, randomised, crossover study
Population	N=11; adults aged 30 years and older; advanced levodopa-responsive idiopathic PD currently treated with infusion since minimum 30 days; BMI between 17.0 and 31.0 kg/m^2 (inclusive)

Intervention(s)	TRIGEL, intestinal gel (20mg/mL levodopa, 5mg/mL carbidopa monohydrate, and 20mg/mL entacapone) Administered through duodenal or upper jejunal infusion via the participants permanently inserted infusion pump
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Compare the systemic exposure ($AUC_{0\text{-}14\ h}$) of levodopa after continuous infusion of levodopa, carbidopa monohydrate, entacapone intestinal gel (LECIG) and levodopa, carbidopa monohydrate intestinal gel (LCIG).[2] *See trial record for full list of outcome measures
Results (efficacy)	Systemic exposure for levodopa did not significantly differ between the two treatments, but the dose adjusted levodopa exposure was found to be significantly higher during LECIG administration compared with LCIG. Six patients had a 40% or higher increase in levodopa systemic exposure, whereas 3 patients had the expected 20% increase and 2 patients did not reach the target systemic exposure. An incline in the levodopa LECIG plasma concentration profile during the day was observed. Mean treatment response scores (TRS) did not differ significantly between treatments (P=0.84).[2]
Results (safety)	Six adverse events (AEs) were reported by 2 patients (18%) after LCIG administration, and 10 adverse events were reported by 6 patients (55%) after LEIG administration. Headache was reported by 1 patient after administration of LCIG and 3 patients after LECIG administration. Five unique adverse events in 3 patients were assessed as related to study drug: nausea (1 event after each treatment), diarrhoea (after LCIG administration), and dizziness and headache (both occurring after LECIG administration). All AEs were mild. No serious or severe AEs were reported, and no AEs led to discontinuation or change in therapy. No clinically significant changes in vital signs, electrocardio-grams, or physical examinations occurred.[2]

ESTIMATED COST

The estimated cost of this levodopa, carbidopa and entacapone intestinal gel is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Istradefylline with levodopa for treating motor fluctuations in Parkinson's disease (TA10773). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Foslevodopa-foscarbidopa for treating Parkinson's disease with motor fluctuations (TA10772). Expected November 2022.
- NICE clinical guideline. Parkinson's disease in adults (NG71). July 2017.

- NICE quality standard. Parkinson's disease (QS164). February 2018.
- NICE interventional procedure guidance. Unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease (IPG606). February 2018.
- NICE interventional procedure guidance. Subthalomotomy for Parkinson's disease (IPG65). June 2004.
- NICE interventional procedure guidance. Deep brain stimulation for Parkinson's disease (IPG19). November 2003.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/Sa.
- NHS England. Clinical Commissioning Policy: Levodopa-carbidopa intestinal gel (LCIG). D04/P/E. July 2015.

OTHER GUIDANCE

- Fox, S.H et al. International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease. 2018.[34]
- NICE Clinical Knowledge Summary: Parkinson's Disease. 2018.[35]
- UK Parkinson's Excellence Network. Non-oral treatment integrated pathway in Parkinson's. 2016.[36]

ADDITIONAL INFORMATION

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