Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2507

levodopa 20mg/mL + carbidopa monohydrate 5mg/mL + entacapone 20mg/mL intestinal gel (Lecigon®)

Britannia Pharmaceuticals Ltd

10 January 2023 *(Issued 08 November 2024)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process

levodopa 20mg/mL + carbidopa monohydrate 5mg/mL + entacapone 20mg/mL intestinal gel (Lecigon®) is not recommended for use within NHSScotland.

Indication under review: treatment of advanced Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available oral combinations of Parkinson medicinal products have not given satisfactory results.

In a phase I pharmacokinetic study, in patients with advanced levodopa-responsive Parkinson's disease, dose-adjusted levodopa exposure was significantly higher with Lecigon® treatment, when compared with levodopa / carbidopa monohydrate intestinal gel.

The submitting company did not present a sufficiently robust clinical or economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

Indication

Treatment of advanced Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available oral combinations of Parkinson medicinal products have not given satisfactory results.[1]

Dosing Information

Lecigon® is administered as a continuous intestinal infusion directly into the duodenum or upper jejunum via percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Alternatively, a radiological gastrojejunostomy may be considered if PEG is not suitable for any reason. Dose adjustments and any surgery to establish the administration tube should be conducted in association with a neurological clinic.

The total daily dose is delivered through a portable Crono LECIG (CE 0476) pump and comprises three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses. Treatment is usually limited to the patient's awake period but can be administered up to 24 hours per day, if medically justified. The dose should be titrated to achieve the optimal clinical response in the individual patient. The total morning dose is usually equivalent to 100mg to 200mg levodopa and should not exceed 300mg levodopa. The maintenance dose is usually 15mg to 100mg levodopa per hour. The maximum recommended daily dose is 2,000mg levodopa. Extra bolus doses, usually less than 3mL, can be given if the patient becomes hypokinetic and can be adjusted individually. An increase in the maintenance dose should be considered if the need for extra doses exceeds five per day.

Lecigon® is initially given as monotherapy. If required, other anti-Parkinsonian medicinal products can be taken concurrently. If treatment with other anti-Parkinsonian medicinal products is discontinued or changed, it may be necessary to adjust the doses of Lecigon®.

Please see the summary of product characteristics (SPC) for further information.[1]

Product availability date

01 October 2024
Lecigon® meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Parkinson's disease (PD) symptoms are related to the lack of dopamine in the corpus striatum. While dopamine does not cross the blood-brain barrier, its metabolic precursor, levodopa, does. However, since only a small proportion of a given levodopa dose reaches the central nervous system, it is usually administered with carbidopa to inhibit extracerebral levodopa decarboxylation and increase levodopa availability. Entacapone is a catechol-O-methyltransferase (COMT) inhibitor which reduces clearance of levodopa from the blood, allowing more levodopa to reach the brain. Lecigon® is a combination of levodopa, carbidopa and entacapone (ratio 4:1:4) intestinal gel for

administration directly into the duodenum or upper jejunum. Lecigon® is available in cartridges for administration using a portable pump (Crono LECIG). Continuous infusion of the intestinal gel aims to reduce motor fluctuations and 'off' time for patients with advanced PD as a result of less variable levodopa plasma concentrations.[1, 2]

The submitting company has requested that SMC considers Lecigon® when positioned for use in the treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results in patients who are not eligible for deep brain stimulation (DBS).

Evidence supporting Lecigon® comes from LSM-003, a single-centre, two day, open-label, randomised, cross-over, phase I pharmacokinetic study that evaluated systemic levodopa exposure following treatment with Lecigon® (levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL + entacapone 20 mg/mL) or Duodopa® (levodopa 20 mg/mL + carbidopa monohydrate 5 mg/mL) intestinal gel.[3] The study recruited 11 adults (aged ≥30 years) with advanced levodopa-responsive PD who were stable on Duodopa® intestinal gel (<125mL per day) for a minimum of 30 days prior to the study. Eligible patients had to satisfy the following criteria: no increased fluctuation in clinical PD symptoms within seven days prior to screening, a body mass index of 17kg/m^2 to 31kg/m^2, and no exposure to entacapone within seven days of study drug administration. Concomitant anti-PD medicines, such as dopamine agonists and monoamine oxidase B inhibitors, were allowed if the doses had been stable for more than 30 days before the study. Patients were randomised equally to receive one of two treatment sequences over two consecutive days: Lecigon® followed by Duodopa® (n=6) or Duodopa® followed by Lecigon® (n=5). Both treatments were administered via the same gastrojejunostomy tube and consisted of three individually adjusted and pre-defined doses within a 14-hour period: a morning dose, a continuous 14-hour infusion (maintenance dose), and extra bolus doses (if required). The Lecigon® doses (morning, maintenance, and bolus) corresponded to 80% of the pre-study Duodopa® doses, except in six patients who received morning doses corresponding to 90% of the pre-study Duodopa® doses. All maintenance Duodopa® doses corresponded to 100% of the pre-study individually optimised doses of Duodopa®. All patients completed the 14-hour infusion on day 1 and crossed over to receive the alternative study treatment on day 2. Oral levodopa / carbidopa immediate release tablets, as PD rescue, were permitted from infusion stopping up to 3 hours before the second infusion.[3, 4]

The primary outcome was systemic exposure of levodopa, measured by the dose-adjusted Area Under the Curve (AUC) between hours 0 to 14 (AUC_{0-14}/dose) for levodopa. Other secondary outcomes evaluated safety by monitoring of adverse events and the pharmacokinetics of levodopa, carbidopa, and 3-O-methlydopa (3-OMD). Statistical comparisons were conducted for the AUC_{0-14} and AUC_{0-14}/dose for levodopa, carbidopa, and 3-OMD (only AUC_{0-14}); using the paired, 2-tailed student t-test on the logarithmic values, with back-transformation to nominal values of point estimates and the 95% confidence interval (CI). Treatment response scale (TRS) scores were additional exploratory outcomes that assessed patient motor function; the statistical comparison of the ordinal mean TRS scores was done with Wilcoxon's signed rank test.[3, 4]

The dose-adjusted AUC (AUC_{0-14}/dose) for levodopa was higher with Lecigon® compared with Duodopa®, with a ratio of 1.34 (95% CI: 1.19 to 1.45); this was statistically significant. Systemic exposure to levodopa was similar for both formulations; AUC ratio 1.10 (95% CI: 0.95 to 1.17).[3, 4]

The TRS is a 7-point scale ranging from -3 (severe parkinsonism) to 0 ("on" state with no dyskinesia) to +3 ("on" state with severe choreatic dyskinesia). Trained study nurses assessed patient motor function according to the TRS at the same times as the pharmacokinetic blood sampling. Mean TRS scores did not differ significantly between Lecigon® and Duodopa® treatments.[3, 4]

The submitting company also provided observational data from a study of 24 patients with idiopathic PD undertaken at a hospital in Sweden. The study aimed to investigate patient-reported effectiveness, tolerability and usability of Lecigon® over the first year of treatment. Outcomes were patient-reported using questionnaires to determine experience of any change in symptoms, the user-friendliness of the drug delivery system, activities of daily living, health-related quality of life and, for patients switched from Duodopa® to Lecigon®, a comparison of these two therapies. The median daily dose of levodopa reduced from 1,210mg (range: 435mg to 2,400mg) prior to Lecigon® to 1,040mg (range: 370mg to 2,000mg) on commencing Lecigon® and to 1,080mg (range: 510mg to 1,822mg) at the end of the study. The dosing regimens were used to inform the scenario analysis of the economic analysis. For patients switching directly from Duodopa® (n=12), a median of 100% of the Duodopa® morning dose was used at initiation, while the continuous infusion rate was 76% of the Duodopa® dose. Two patients were switched from apomorphine infusion therapy and three patients switched to Lecigon® infusion from levodopa/carbidopa micro tablets. Other dopaminergic PD medications received by patients prior to and during Lecigon® included oral sustained release levodopa (n=19), dopamine agonist (n=9) and amantadine (n=2). More than half of the evaluable patients (n=21) reported an improvement in their ability to perform daily activities (57%) and in their self-rated quality of life (62%) with Lecigon® treatment. A high proportion of patients (70%) who had previously not used any form of levodopa infusion (n=10) perceived that their symptoms had improved. In patients who had previously used the Duodopa® pump, 45% (5/11) reported no change in PD symptoms, 36% (4/11) were minimally to very much improved and 18% (2/11) were minimally to very much worse. Most patients reported that the pump was user-friendly which included the majority of patients who had experience with the Duodopa® pump and all agreed that the size and weight had improved.[5]

Summary of evidence on comparative safety

In LSM-003, 16 adverse events (AEs) were reported in the study. Ten AEs were reported by 55% (6/11) of patients on Lecigon®, and six AEs were reported by 18% (2/11) of patients on Duodopa®. No serious or severe AEs were reported during the study, and no AE led to study discontinuation or change in therapy. No clinically significant changes in vital signs, electrocardiograms, or physical examinations occurred.[3, 4]

The most frequently reported AEs of any grade in patients treated with Lecigon® versus Duodopa® were: diarrhoea (0.0% versus 9.1%), nausea (9.1% versus 9.1%), injection site haematoma (9.1%

versus 9.1%), laceration (9.1% versus 0.0%), dizziness (18% versus 0.0%), headache (27% versus 9.1%), cold sweat (0.0% versus 9.1%). Of these AEs: headache, nausea and dizziness (one event each) were related to Lecigon®; diarrhoea and nausea (one event each) were related to Duodopa®.[3, 4]

Additional safety data were provided from the observational study which had a treatment duration of 305 days though the number of individuals who experienced an adverse event in the RWE study was unclear; this was confirmed by the submitting company. Seven AEs were reported with four of these resulting in treatment discontinuation; hallucination (n=1) and diarrhoea (n=3). Other AEs experienced by three patients included sweating, nausea, freezing and hallucinations. There were a total of five complications associated with the device which did not lead to discontinuation of treatment; one patient experienced a pump breakage while four patients experienced complications relating to intestinal access (stoma infection, dislocation of intestinal tube, tear in PEG tube, leakage and occlusion of the intestinal tube).[5]

Summary of clinical effectiveness issues

PD is a progressive, neurodegenerative movement disorder characterised by the core motor symptoms of: rigidity, postural instability, rest tremor and bradykinesia.[6, 7] It is primarily a condition of older adults, with prevalence rising from 50 years of age.[8] At present, PD is incurable, with the goal of treatment to provide symptom control and improve quality of life. Levodopa, in combination with a dopa-decarboxylase inhibitor, is the mainstay of PD treatment with most patients responding well in the early stages of the disease. However, levodopa treatment is associated with motor complications, including more frequent dyskinesias (abnormal and involuntary movements) and response fluctuations that are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period. 'End-of-dose' deterioration with progressively shorter duration of benefit can also occur. Modified-release preparations may help with 'end-of-dose' deterioration or nocturnal immobility.[6, 9] Patients typically progress to the advanced stages of disease within 10 to 20 years of the early onset of symptoms.[9, 10] The majority of patients with advanced disease experience the following: worsening motor fluctuations, increased dyskinesias, a reduction or failure in the ability to move, difficulty in swallowing, uncontrolled and sometimes painful muscle movements or spasms, as well as increased movements (hyperkinesia).[9, 11-13] For the management of motor complications in advanced PD that cannot be adequately managed with oral treatments, guidelines recommend considering the use of more advanced, but invasive, therapies such as apomorphine (intermittent injections or continuous subcutaneous infusions), deep brain stimulation (DBS), or Duodopa® intestinal gel; these comparators were confirmed by clinical experts contacted by SMC.[14, 15] Duodopa® intestinal gel is accepted for restricted use within NHSScotland (SMC 316/06) for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results for patients not eligible for DBS. Lecigon® meets SMC orphan equivalent criteria.

The submitting company has requested that SMC considers Lecigon® when positioned for use in patients who are not eligible for deep brain stimulation (DBS). The submitting company anticipate that Lecigon® would directly displace Duodopa®.

In LSM-003, the dose-adjusted $AUC_{0\text{-}14h}$ for levodopa were similar with Lecigon® compared with Duodopa®, despite giving a reduced levodopa dose with Lecigon®.[3, 4] The submitting company advised that the total daily dose of Lecigon® should be reduced by approximately 20% to 35% compared with previous doses of levodopa and carbidopa from Duodopa®, with larger reductions expected in high-dose patients; the SPC provides further advice.[1] Additionally, the observational study showed that most patients reported an improvement in their ability to perform daily activities and in their self-rated quality of life with Lecigon®.[5]

The efficacy and safety of levodopa, carbidopa and entacapone have been established and oral combinations of all three of these medicines are available.[16, 17] However, there were several limitations with the evidence presented for this new combination intestinal gel. No data were submitted from clinical efficacy or safety studies for Lecigon®. The evidence-base is limited to one phase I pharmacokinetic study and the supportive observational study. LSM-003 was a single-centre, two-period, open-label, randomised, cross-over, phase I pharmacokinetic study. Whilst it may have provided useful information on bioavailability, it was not primarily designed to compare the Lecigon® and Duodopa® treatments with regard to clinical response; TRS was assessed as an exploratory outcome only. The study also had very limited patient numbers (n=11) and a very short observation period (17 hours repeated over two consecutive days); therefore it is unclear if these results translate into meaningful clinical outcomes.[3, 4]

The observational study also had several limitations including its observational design. Firstly, there was incomplete reporting of the selection criteria and primary outcome. The study focused on patient-reported outcomes, which whilst complementaryto the pharmacokinetic outcomes in LSM-003, limits the assessment of generalisability and real-life implementation issues. Data were extracted from medical records as opposed to a study pro-forma that may result in missing data. There was an assumed duration of infusion of 15 hours when the administration times were not documented; this assumption was used to inform the dosing scenarios in the economic evaluation and may not be valid considering it is reported that three patients received night-time dosing. In terms of generalisability, although some of the baseline characteristics of the patients (such as the median age of 71.5 years) align with the anticipated population who would use Lecigon® in Scottish clinical practice, the study population differs to the marketing authorisation of Lecigon® (an idiopathic PD population was used, not a population with advanced PD) and to the submitting company's proposed positioning (three patients had previously undergone DBS). The small number of patients from one centre only may limit the external validity of the findings.[5]

Due to the lack of clinical study safety data, the longer-term safety of Lecigon® is unknown. The addition of entacapone could result in an increased risk of adverse events and drug-drug interactions. Given the limited number of patients evaluated in both studies, no safety conclusions can be drawn from these results. [3-5]

The submitting company explained that levodopa-induced side effects, such as dyskinesia and polyneuropathy, are relatively common with Duodopa® and may be due to high levodopa exposure; the rationale for the addition of entacapone to Duodopa® is to reduce levodopa exposure which could potentially reduce the risk of these side effects. While this is plausible, it is only theoretical and non-conclusive based on these data and the dearth of published literature. While the pharmacokinetic outcomes from LSM-003 were promising, the submitting company's claims of potential benefits resulting from reduced exposure to metabolites (for example 3-OMD) and degradation products (for example hydrazine) of levodopa-carbidopa require confirmation and should be interpreted with caution.[4]

The submitting company highlighted that the Lecigon® pump with a full cartridge is less than half the weight of the Duodopa® pump with a full cassette (227g versus 550g) and is smaller (152 x 55mm versus 197 x 100mm). Lecigon® cartridges and Duodopa® cassettes have the same storage requirements (within a refrigerator at 2°C to 8°C) and shelf-life (15 to 16 weeks unopened; 24 hours once opened).[1, 3, 18] The submitting company provided evidence from a retrospective study that most study participants found that the Duodopa® pump was large, heavy and bulky, however despite these issues 96% would still strongly recommend it to others.[19] It is unclear what impact the different product characteristics of Lecigon® versus Duodopa® will have on clinical and quality of life outcomes for patients in practice. This is supported by the findings of the observational study that showed that switching from Duodopa® to the Lecigon® pump may improve user-friendliness but may result in little to no improvement in PD symptoms.[5]

The introduction of Lecigon® would offer an alternative to Duodopa® for patients with advanced PD who have severe motor fluctuations and hyperkinesia or dyskinesia when available oral combinations of Parkinson medicinal products have not given satisfactory results. From the evidence provided, when compared with Duodopa®, Lecigon® treatment resulted in a higher dose-adjusted Area Under the Curve (AUC) between hours 0 to 14 (AUC_{0-14}/dose) for levodopa. However, with the limitations of the studies, including the small patient numbers and lack of formal assessment of clinical outcomes, there is large uncertainty over whether these results will translate into clinical benefits in practice. Clinical experts highlighted that the intestinal gel delivery system is invasive and requires inpatient stay for surgery to fit the duodenal tube. It requires careful selection of patients alongside ongoing monitoring to confirm maintenance of benefit. They also noted that the intestinal gel may reduce the burden on family members who have often given up work to become full-time carers.

Patient and clinician engagement PACE

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **levodopa/carbidopa/entacapone (Lecigon®),** as an **orphan equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced Parkinson's disease is a progressive and debilitating condition that can adversely affect a person's cognition, physical and mental health, and has many recognised symptoms that can negatively influence their movement and activity.
- Mental health symptoms are a major aspect of many people's experience of PD. In addition to the neuropsychiatric symptoms arising as the condition progresses, the unexpected nature of the condition can place a significant toll on an individual's mental health; unexpected aspects include: the shock of the initial diagnosis, the individual variations in treatment responses and side effects, and the length and difficulty in stabilising the disease.
- There can be vast differences in how individuals with PD respond to treatments. Since every patient with PD responds differently to each medicine, it is important that there are more potential treatment options for patients with advanced PD.
- Similarly to Duodopa®, Lecigon® delivers the drug directly to the part of the bowel where it needs to be absorbed. It also provides a more continuous delivery of medicine, which may result in sustained efficacy and could translate into several wellbeing benefits for those with PD such as improved independence and a reduced dependence on carers.
- The Lecigon® pump and cassette are lighter in weight (easier to carry) and smaller in size (more discreet) which could be advantageous for some patients.
- There is an established PD service for the assessment and initiation of a similar product (Duodopa®); this has been used successfully for patients with advanced PD which reduces some uncertainties of introducing Lecigon® in NHS Scotland.
- Concerns have been raised by PACE participants about the ongoing follow-up and support for these patients. Localised company support based within Scotland would allow appropriate expert monitoring and titration of the medication for the duration of treatment – reducing the burden on the local PD services. A potential additional benefit would be the possibility of developing a home titration option for suitable patients - to reduce the burden on NHS bed days for titrations.

Additional Patient and Carer Involvement

We received a patient group submission from Parkinson's UK Scotland, which is a registered charity. Parkinson's UK Scotland has received 0.11% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from Parkinson's UK Scotland participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) comparing Lecigon® to Duodopa® within the submitting company's proposed positioning as described above. The time horizon used in the analysis was 8 years.

The clinical data used to underpin the assumption of comparable efficacy and safety between treatments were based on analyses of the Phase I, open-label, single-centre, randomised, cross-over LSM-003 study.[3] The company concluded that, on the basis of the results of this study, Lecigon® is likely to be of similar efficacy to Duodopa® and have a comparable safety profile.

Medicine acquisition costs were the only costs explicitly included in the analysis. No costs were included for percutaneous endoscopic gastro-jejunal insertion, monitoring requirements, administration or subsequent treatment of 'drop-outs' on the basis that these are expected to be similar across treatments. The cost of proprietary pump devices for Lecigon® and Duodopa® were excluded from the analysis given that these are provided by each company free of charge. The dosages of Lecigon® and Duodopa® used in the analysis were set equal to the mean-average daily doses observed in the LSM-003 study. This translated to use of one cartridge of Lecigon® or Duodopa® per day. The company considered the implications of using mean-average dosing data from either the overall population or a subgroup of patients who switched from Duodopa® to Lecigon® in a RWE study described above.[5] Analysis of these data suggested that the assumption of one cartridge per day was reasonable; however, concerns were raised around whether the mean-average dose in these populations appropriately reflects the number of cartridges per day required by all patients.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is also in place for Duodopa® and was accounted for in the results for decision-making used by the SMC by using estimates of the comparator PAS price.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS and the confidentiality of the list price, SMC is unable to publish any economic results.

The economic evaluation was subject to the following limitations:

- it is unclear if the assumption of one cartridge of Lecigon® per day reflects the number of cartridges required by all patients receiving this treatment. If a proportion of patients require use of two cartridges per day, this could have an important impact on results. To address this aspect, the submitting company provided additional analyses to account for a proportion of patients receiving Lecigon® who require a second cartridge to be opened. These analyses were performed by calculating the proportional cartridge use of Lecigon® per day for each patient in both the LSM-003 and the observational study. In these analyses, the company assumed that the shelf life of Lecigon® would mean that any unused product in the second cartridge could

be used for the next day's dose rather than treated as wastage. These analyses were helpful in exploring the issues around the base case dosing assumption and impact on the cost-minimisation analysis results.

- the small number of patients in the LSM-003 study makes robust conclusions on comparative efficacy and safety across medicines challenging, creating uncertainty around the appropriateness of using a CMA framework. Given the active ingredient (i.e. levodopa) is the same in both comparators, this may not be a major issue, but this issue was a matter of debate for the committee.

The Committee considered the benefits of Lecigon® in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as Lecigon® is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept Lecigon® for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

In July 2017, the National Institute for Health and Care Excellence (NICE) published clinical guidance for Parkinson's disease in adults (Guideline 71).[14] Levodopa, in combination with a DOPA decarboxylase inhibitor, is recommended first-line treatment for early-stage PD. For people with motor symptoms that do not impact on their quality of life, then a choice of dopamine agonist, levodopa or monoamine oxidase B inhibitor (MAO-B) should be considered. For people with PD who have developed motor symptoms such as dyskinesia or motor fluctuations despite optimal levodopa therapy then adjuvant treatment should be offered with a choice of dopamine agonists, MAO-B inhibitors or COMT inhibitors. This should consider the potential benefits and harms of the different agonists and the recommendation to choose a non-ergot derived dopamine agonist (excluding cases where symptoms are not controlled with a non-ergot-derived dopamine agonist) due to the monitoring requirement of ergot-derived dopamine agonists. For patients whose dyskinesias are not adequately managed, amantadine is recommended. Intermittent apomorphine injection and/or continuous subcutaneous apomorphine infusion is recommended for later-stage PD with DBS only to be considered for people whose symptoms are not well-controlled by best medical therapy. Levodopa-carbidopa intestinal gel is currently available through an NHS England clinical commissioning policy. The guideline also outlines the palliative care referral process, and information and support that can could be provided to people with PD and their family members/carers if palliative care is indicated.

In 2013 the European Federation of Neurological Societies and Movement Disorder Society-European Section (EFNS/MDS-ED) produced a summary of recommendations for the therapeutic management of PD.[15] These recommendations are similar to those made by NICE, though do state that entacapone is not effective in the delay of motor complications. In relation to motor

fluctuations and in the event of 'wearing-off' the following guidance was issued; adjust levodopa dosing; add COMT or MAO-B inhibitor; add dopamine agonists; controlled-release (CR) levodopa; add amantadine or an anticholinergic. For dyskinesias the following guidance was issued; reduce levodopa dose; discontinue /reduce MAO-B or COMT inhibitors; amantadine, DBS of the subthalamic nucleus (STN) or posteroventral pallidum (GPi) stimulation may reduce severe dyskinesia. For severe motor fluctuations, deep brain stimulation of the STN or the GPi is effective against motor fluctuations and dyskinesia in patients under 70 years without major cognitive or psychiatric problems. Intrajejeunal levodopa/carbidopa enteric gel is recommended as a good practice point.

These guidelines predate the availability of Lecigon®.

Additional information: comparators

Levodopa 20mg/mL + carbidopa monohydrate 5mg/mL intestinal gel (Duodopa®).

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
levodopa 20mg/mL + carbidopa monohydrate 5mg/mL + entacapone 20mg/mL intestinal gel (Lecigon®) cartridge (47mL)	1 cartridge per day	£27,667

Costs from the company submission. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 82 patients eligible for treatment with Lecigon® in year 1 rising to 109 patients in year 5. The estimated uptake rate was 20% (16 patients) in year 1 and 75% (82 patients) in year 5. No discontinuation rate was applied.

*Other data were also assessed but remain confidential.**

References

1. Lecigon Summary of Product Characteristics (SPC). Available at: https://mhraproducts4853.blob.core.windows.net/docs/947ff01a8fb8b3e129010fae797286ee9079136a [Last accessed: 25/05/22].
2. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report (PAR). Lecigon 20mg/ml + 5mg/ml + 20mg/ml intestinal gel. PL 53856/0001. Available at: https://mhraproducts4853.blob.core.windows.net/docs/c185704f891ba495196f5ff181df176d3d53b37b [Accessed 26.09.2022].
3. Senek M, Nielsen E, Nyholm D. Levodopa-entacapone-carbidopa intestinal gel in Parkinson's disease: A randomised crossover study. Mov Disord. 2017; 32: 283-286.
4. Swedish Medical Products Agency. Public Assessment Report. Lecigon® (entacapone, carbidopa (monohydrate), levodopa). SE/H/1986/01/E/01. Available at: https://docetp.mpa.se/LMF/Lecigon%20intestinal%20gel%20ENG%20PAR_09001bee813fbfeb.pdf . [Accessed on: 26.09.2022].
5. Öthman M, Widman E, Nygren I, Nyholm D. Initial Experience of the Levodopa–Entacapone–Carbidopa Intestinal Gel in Clinical Practice. Journal of Personalised Medicine. 2021;11(4):254.
6. Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(8):795-808.
7. Kouli A, Torsney KM, Kuan W-L. Parkinson's disease: etiology, neuropathology, and pathogenesis. Exon Publications. 2018:3-26.
8. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Movement disorders. 2014;29(13):1583-90.
9. Antonini A, Jenner P. Apomorphine infusion in advanced Parkinson disease. Nature Reviews Neurology. 2018;14(12):693-4.
10. Parkinson's UK. The Incidence and Prevalence of Parkinson's in the UK. Results from the Clinical Practice Research Datalink Reference Report. Available at: https://www.parkinsons.org.uk/sites/default/files/2018-01/Prevalence%20%20Incidence%20Report%20Latest_Public_2.pdf [Last accessed: 29.06.21].
11. Lokk J, Delbari A. Clinical aspects of palliative care in advanced Parkinson's disease. BMC palliative care. 2012;11(1):1-8.
12. Fasano A, Fung VSC, Lopiano L, Elibol B, Smolentseva IG, Seppi K*, et al.* Characterizing advanced Parkinson's disease: OBSERVE-PD observational study results of 2615 patients. BMC neurology. 2019;19(1):50.
13. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. Journal of neurochemistry. 2016;139:318-24.
14. National Institute for Health and Care Excellence (NICE). Management of Parkinson's Disease in adults. NICE Guidelines [NG71]. Published: 19 July 2017. Last updated: May 2022. Available at: https://www.nice.org.uk/guidance/ng71/resources/parkinsons-disease-in-adults-pdf-1837629189061. [Last accessed: 26.09.2022].
15. Ferreira J J, Katzenschlager R, Bloem B R, Bonuccelli U, Burn D, Deuschl G, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. European journal of neurology. 2013; 20: 5-15. 2013.
16. Orion Pharma (UK) Limited. Stalevo 150 mg/37.5 mg/200 mg Film-coated Tablets. Summary of product characteristics. Electronic Medicines Compendium **www.medicines.org.uk/emc/** Last updated [12 May 2021].
17. Accord-UK Ltd. Sastravi 100mg/25mg/200mg Film-coated Tablets. Summary of product characteristics. Electronic Medicines Compendium **www.medicines.org.uk/emc/** Last updated [13 April 2021].

18. AbbVie Ltd. Duodopa intestingal gel. Summary of product characteristics. Electronic Medicines Compendium. www.medicines.org.uk/emc/. Last updated [11 Jan 2021].
19. Scott B, Nyholm D. Patient-perceived retrospective outcome of duodenal levodopa infusion in advanced Parkinson's Disease. Eur Neurol J. 2010; 2: 3-10. 2010.

This assessment is based on data submitted by the applicant company up to and including 01 October 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.