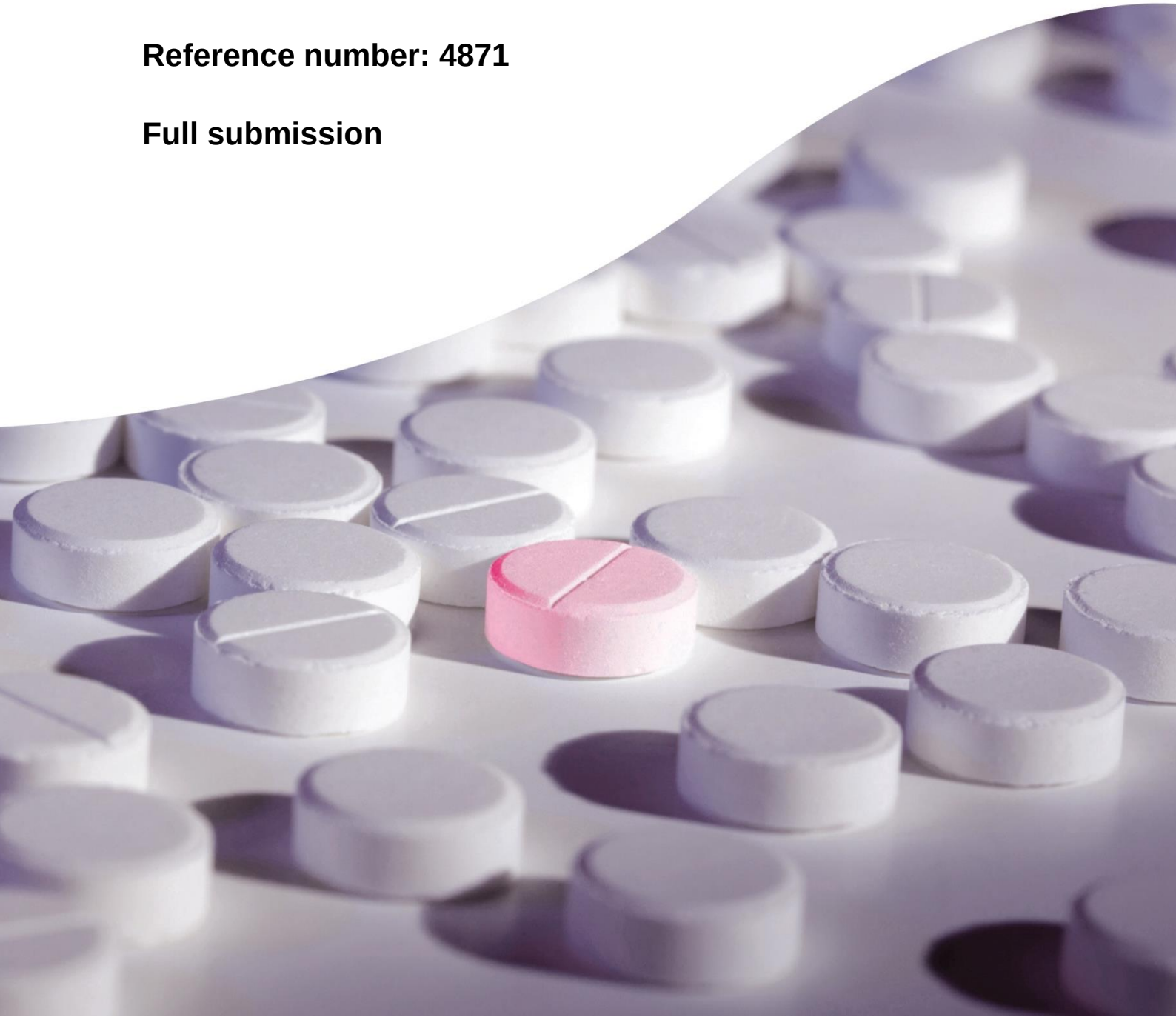
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Levodopa-carbidopa-entacapone (Lecigon®) 20 mg/ml + 5 mg/ml + 20 mg/ml intestinal gel

Reference number: 4871

Full submission



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Levodopa-carbidopa-entacapone (Lecigon®) 20 mg/ml + 5 mg/ml + 20 mg/ml intestinal gel

1.0 Key facts

Assessment details	Levodopa-carbidopa-entacapone (Lecigon®) for the 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. The applicant company has submitted evidence for a subpopulation of the licensed indication and request that AWMSG consider levodopa-carbidopa-entacapone (Lecigon®) for the treatment of advanced levodopa-responsive 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 patients not eligible for deep brain stimulation. Lecigon® intestinal gel contains levodopa, carbidopa monohydrate and entacapone and is delivered to the duodenum or upper jejunum through a portable pump in two individually adjusted doses during the day. Some patients may also require an extra bolus dose which is provided on an individual basis.
Current clinical practice	Levodopa-carbidopa intestinal gel (Duodopa®) is available in NHS Wales for patients with advanced Parkinson's disease who are not eligible for deep brain stimulation. Lecigon® is positioned in the same place in the treatment pathway as Duodopa®. The company suggest Lecigon® offers the same clinical benefit as Duodopa® but this is achieved with lower administered levels of levodopa.
Clinical effectiveness	An open-label, single-centre, randomised cross-over study (LSM-003) in 11 patients with advanced levodopa-responsive idiopathic Parkinson's disease showed similar pharmacokinetics using Lecigon® versus Duodopa® despite using a lower administered dose of levodopa. A real-world evidence study compared self-reported symptoms in a further 11 patients who switched from Duodopa® to Lecigon® treatment.
Cost-effectiveness	A cost-minimisation analysis compares Lecigon® with Duodopa® for the indication described above. The company base case, including the Lecigon® Patient Access Scheme, suggests cost savings of [commercial in

	confidence figure removed] over the 15-year model horizon. [commercial in confidence figure removed]. Using cost-minimisation analysis is inappropriate in this instance, given that equivalence is assumed based on similar plasma levels of levodopa in a small, phase 1 study. Also, the company states that the reduced levodopa dose required with Lecigon® has the potential to improve side effects, patient reported outcomes and long-term efficacy which are not considered in the cost-minimisation analysis.
Budget impact	The company estimates that 1 patient is likely to receive treatment with Lecigon® in Wales in Year 1, increasing to 50 patients in Year 5. The company base case suggests cost savings of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 considering the Wales Patient Access Scheme on Lecigon® and no Patient Access Scheme on the comparator. [commercial in confidence figure removed]. The budget impact analysis does not consider treatment discontinuation or any costs other than acquisition costs.
Additional factors to consider	AWTTC considers Lecigon® to be eligible to be appraised as an orphan equivalent medicine.

This assessment report is based on evidence submitted by Britannia Pharmaceuticals Ltd[1] and an evidence search conducted by AWTTC on 5 December 2022.

2.0 Background

2.1 Condition and clinical practice

Parkinson's disease is a progressive neurodegenerative condition leading to motor symptoms such as bradykinesia, rigidity, tremor and postural instability[2,3]. People are commonly diagnosed with advanced Parkinson's disease when their symptoms grow in severity and complexity (involving, for example, dementia, hallucinations, recurrent falls, or dysphagia) and they require assistance to perform basic daily activities[4,5]. Therefore advanced Parkinson's disease can have a significant impact on the quality of life of the person and that of their carers[2,6].

Oral levodopa is prescribed as a first-line treatment[2], but long-term use is associated with response fluctuations (ON and OFF periods) due to 'wearing off' and dyskinesia, leading to large variations in motor performance and symptom control[2,7]. Levodopa is combined with adjuvants once 'wearing off' starts to occur. Adjuvants include dopamine agonists, catechol-o-methyl transferase (COMT) inhibitors, monoamine oxidase type B (MAOB) inhibitors and other therapies[2]. Treatments that provide continuous stimulation of levodopa are also being considered, in order to provide more consistency in symptom control and treatment-induced side effects[3]. For

example, levodopa can be administered in continuous maintenance doses as an intestinal gel[2].

Deep brain stimulation, involving the implantation of an electrode directly into a specific nucleus of the brain, may also be an option for people with advanced Parkinson's disease, though patients are not always eligible[2,8].

2.2 Medicine

Lecigon® is an intestinal gel containing levodopa, carbidopa and entacapone[9]. Levodopa relieves symptoms of Parkinson's disease after conversion to dopamine in the brain[7]. Carbidopa inhibits extracerebral conversion by reducing decarboxylation of levodopa, thereby making a higher proportion of levodopa available for transportation to the brain[7,9,10]. The COMT pathway becomes the dominant peripheral metaboliser of levodopa once decarboxylation has been reduced by carbidopa[10]. Entacapone is a COMT inhibitor, and its action therefore increases the bioavailability of levodopa in plasma[7,9,11]. Consequently, the additions of adjuvant carbidopa and entacapone both act to prolong the clinical response of levodopa[10].

Lecigon® is administered as three individually adjusted doses: the morning dose; continuous maintenance dose; and extra bolus doses[9]. Lecigon® is delivered to the duodenum or upper jejunum via a portable pump[1,9].

The Medicines and Healthcare products Regulatory Agency granted Lecigon® marketing authorisation in May 2022[10]. It is licensed to treat 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[10]. The company estimate that Lecigon® will be launched in [commercial in confidence text removed]

The company has suggested that AWMSG consider Lecigon® for restricted use within the licensed indication in patients not eligible for deep brain stimulation[1]. This is in line with AWMSG's recommendation for the use of Duodopa®[12].

2.3 Comparator

The comparator included in the company's submission is

- Levodopa-carbidopa (Duodopa®)

2.4 Guidance and related advice

- National Institute for Health and Care Excellence guideline NG71 Parkinson's disease in adults (July 2017)[2].

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of levodopa-carbidopa (Duodopa®) for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results, in patients not eligible for deep brain stimulation[12].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, levodopa-carbidopa-entacapone (Lecigon®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

The company's submission includes a phase I study (LSM-003) in patients with advanced Parkinson's disease, comparing Lecigon® with Duodopa®. It also includes data from a real-world evidence study that assessed patient-reported outcomes. Both are discussed below.

3.1 LSM-003

LSM-003 was a phase 1, open-label, single-centre, randomised crossover study conducted in Sweden, to compare the systemic levodopa exposure over 14 hours after continuous infusion of Lecigon® and Duodopa®[13]. Patients were eligible for inclusion if they had idiopathic Parkinson's disease and were currently stabilised on Duodopa® treatment for 30 days or more. Eleven patients ([commercial in confidence figure removed]) with a mean age of 71 years, were enrolled in the study; on average, patients had been diagnosed with Parkinson's disease for 14 years. Patients were randomised (1:1) to receive one of two treatment sequences: Lecigon® then Duodopa® or Duodopa® then Lecigon®; over two consecutive days. Patients received Lecigon® morning doses corresponding to 80% (n = 5) or 90% (n = 6) of their individual morning dose of Duodopa®, 80% of their Duodopa® maintenance dose, and 80% of extra doses. Duodopa® continued to be dosed at the pre-study optimised rate. Both medicines were administered by duodenal or upper jejunal infusion through permanently inserted gastrojejunostomy tube by means of an ambulatory infusion pump.

The primary outcome compared the systemic exposure of levodopa over a 14-hour period[13]. Secondary objectives compared intra-individual variations of plasma levodopa concentrations at a steady state, the dose-adjusted systemic exposure of carbidopa and 3-ortho methyldopa (3-OMD), motor function according to the treatment response scale, mean percentage of time patients were in an OFF, function ON and dyskinesia state during three separate time intervals, and the safety of Lecigon®[14].

Systemic exposure to levodopa, determined using the area under the plasma concentration-time curve between 0 and 14 hours, did not differ significantly between Lecigon® and Duodopa® treatments (ratio of Lecigon® to Duodopa® = 1.10; 95% confidence intervals [CI]: 0.95 to 1.17; P = 0.27)[13]. This suggests that comparable levels of levodopa were available to cross the blood-brain barrier in patients receiving Lecigon® despite receiving a levodopa dose 10–20% lower than that given with Duodopa® treatment. The mean treatment response scale scores did not differ significantly between Lecigon® and Duodopa® (P = 0.84).

3.2 Real-world evidence study

An observational study carried out in 24 patients with Parkinson's disease[15] analysed patient-reported symptoms, tolerability and usability of Lecigon®. The median

treatment duration in the study was 305 days. 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®. Eleven patients in the study had switched from Duodopa® to Lecigon®[15]. In this subgroup a reduced dose of Lecigon® versus the prior dose of Duodopa® was used[15]. Within the subgroup of eleven, five reported no change in symptoms, four reported improvement and two reported worsening[15]. Additional information, requested by AWTTC and provided by company in February 2023, is that [commercial in confidence figure removed] of these eleven patients reported an improvement in their quality of life; [commercial in confidence figure removed] reported no change, and [commercial in confidence figure removed] reported worsening.
Real-world use of Lecigon® has also been reported in three other studies in small cohorts of patients for periods less than one year[16,17].

3.3 Safety information

The expected safety profile for Lecigon® is based on available data from clinical studies and post-marketing experience of Duodopa® and oral levodopa-carbidopa-entacapone[9].The LSM-003 study showed Lecigon® to have a similar safety profile to Duodopa®, with both treatments reporting a total of 9 adverse events (AEs) related to the study drug, pump or procedure. No serious AEs or unexpected AEs were reported by patients receiving Lecigon® or Duodopa®. The most commonly reported AEs during the study were headaches and injection site haematomas which each occurred [commercial in confidence figure removed] in the Lecigon® arm and once in the Duodopa® arm. All AEs reported during the study were mild in nature and there were no discontinuations from the study due to AEs.

The LSM-003 study found nausea and dizziness as adverse reactions associated with both Lecigon® and Duodopa®. Additionally, headaches were found to be associated with Lecigon® whilst diarrhoea was found to be associated with Duodopa®[9]. A meta-analysis of the use of entacapone as an adjuvant in levodopa-carbidopa treatment found a slight increase in adverse events when using entacapone compared with placebo, but overall it was effective in disease management[18]. Oral entacapone has been in use for several years and is known to be associated with gastrointestinal side effects such as diarrhoea[9,10,19].

3.4 Ongoing studies

ELEGANCE is a two-year real-world evidence study to assess the safety and efficacy of Lecigon® in 300 people with advanced Parkinson's disease[1,20]. The study will be multicentre and take place in locations across Europe including the UK. Estimated completion date is July 2025.

3.5 AWTTC critique

- The applicant company has submitted evidence for a subpopulation of the licensed indication for Lecigon® and has requested that AWMSG consider this medicine in patients not eligible for deep brain stimulation. This positions Lecigon® at the same point in the treatment of advanced Parkinson's disease as Duodopa®.
- The studies, in a small population, suggest that Lecigon® has similar efficacy and bioavailability of levodopa to Duodopa®, achieved with a lower administered levodopa dose.
- The company suggests that, by the addition of entacapone, Lecigon® may have clinical benefits when compared to Duodopa® including a reduction of the

side effects of levodopa (e.g. dyskinesia). However, there is limited evidence for this and the clinical significance of this is uncertain. It is acknowledged that continuous infusion of intestinal gel aims to reduce motor fluctuations and 'off' time for patients with advanced Parkinson's disease as a result of less variable levodopa plasma concentrations.

- AWTTC-sought clinical expert opinion suggests that Lecigon® may be useful as an option for patients who are suitable for continuous dopaminergic infusions and that the addition of entacapone can improve the availability of levodopa for patients who, in practice, may already be experiencing some wearing-off. Clinical experts also highlighted that oral entacapone is used in addition to Duodopa® with the aim of improving the availability of levodopa and helping to ensure that patients can remain on one cartridge per day, as the addition of another cartridge to the regimen can increase cost of treatment significantly and is less convenient for the patient.
- Clinical experts highlighted that some patients are not tolerant of oral entacapone due to gastrointestinal side effects. Use of oral entacapone in clinical practice is well established but the evidence submitted in support of the safety profile of Lecigon® is limited.
- Both studies submitted were conducted in small numbers of patients and a larger, longer-term comparative study is needed to confirm that the reduction in levodopa dose using Lecigon® is sufficient to produce clinically meaningful benefits compared to Duodopa®.
- LSM-003 study[13] reports on the systemic exposure to levodopa in patients treated with Lecigon® compared to Duodopa® over a 14-hour period, and does not present longer-term data on outcomes and adverse events.
- Patient views obtained by AWTTC via Parkinson's UK suggest that quality of life for people with treatment-resistant advanced Parkinson's can be extremely poor and that treatments like deep brain stimulation and continuous dopaminergic infusions such as Duodopa® and Lecigon® can be life-changing, enabling people to socialise, have hobbies and even return to work. They can also reduce the risk of falls and reduce the amount of medication, health and social care support needed. People with advanced Parkinson's typically have very significant care requirements and can live with these needs for many years.
- Patients wear the pump for around 16 to 17 hours per day and AWTTC sought clinical expert opinion suggest that patients at this advanced stage of Parkinson's are often frail and the weight and comfort of the pump is a consideration.

4.0 Cost-effectiveness

4.1 Context

The company's submission[1] includes a cost-minimisation analysis (CMA) comparing Lecigon® with Duodopa® for the treatment of patients with advanced Parkinson's disease. A simple decision analytic model is used to estimate the difference in treatment costs. The model adopts a 15-year time horizon and an NHS Wales/Personal and Social Services perspective with a discount rate of 3.5% applied. The model assumes that Lecigon® will directly replace Duodopa®. Patients enter the model at the age of 71 years based on the median age in the pivotal studies[13,15] and are treated with either Lecigon® or Duodopa®.

The only cost considered in the model is the treatment acquisition cost. The base case assumes the use of one cartridge per day and maintenance dosing to last for 15 hours based on the average dose and duration in the pivotal LSM-003 study[13]. Disease-related costs, cost of concomitant medications as well as treatment administration, procedure-related costs and monitoring are assumed similar and are not considered in the model. Furthermore, adverse events are assumed to be identical and are also not included. The acquisition cost for Duodopa® is sourced from the British National Formulary (BNF)[21] with the acquisition cost of Lecigon® provided by the company. The submission incorporates a simple Wales Patient Access Scheme (WPAS) discount of [commercial in confidence figure removed] for Lecigon®. The company conducted a simple sensitivity analysis to test the impact of varying the Patient Access Scheme (PAS) of the comparator treatment on the base case results. They also provided scenario analyses to investigate the effect of different dosing assumptions on the results.

4.2 Results

The results of the base case analysis and scenario/sensitivity analyses are detailed in Table 1. When compared with Duodopa®, Lecigon® is less costly in the base case, with suggested savings of [commercial in confidence figure removed] over the 15-year model horizon. [commercial in confidence figure removed]. The results of the CMA indicate that Lecigon® is cost-saving compared with Duodopa® only if the comparator PAS is below 15%. Since the analysis only considers treatment acquisition cost, any cost differences can only be attributed to differences in cost of treatment.

Table 1. Results of the base case analysis and scenario/sensitivity analyses

Scenario	Lecigon® costs†	Duodopa® costs†	Difference	Plausibility
Base case (0% PAS for Duodopa®)				
Lecigon® versus Duodopa®	¶¶	£336,264	¶¶	
Sensitivity analysis: Changing comparator PAS				
5% PAS	¶¶	£319,451	¶¶	The most plausible scenario is the row corresponding to the actual value of the Duodopa® PAS.
10% PAS	¶¶	£302,638	¶¶	
15% PAS	¶¶	£285,825	¶¶	
20% PAS	¶¶	£269,011	¶¶	
25% PAS	¶¶	£252,198	¶¶	
30% PAS	¶¶	£235,385	¶¶	
40% PAS	¶¶	£201,759	¶¶	
50% PAS	¶¶	£168,132	¶¶	
60% PAS	¶¶	£134,506	¶¶	
70% PAS	¶¶	£100,879	¶¶	
80% PAS	¶¶	£67,253	¶¶	
90% PAS	¶¶	£33,626	¶¶	
Scenario analysis: Changing average daily dose				
Average daily dose from real world study[15]	¶¶	£336,264	¶¶	While dosing was slightly different to the base case, all scenarios were ultimately based on one cartridge per day.
Average daily dose[15] of sub-population who switched from Duodopa®, to Lecigon® in real world study (n=11)	¶¶	£336,264	¶¶	
Including night-time dosing based on real world study[15]	¶¶	£336,264	¶¶	This scenario is plausible as night-time dosing was required for some patients in a small observational study[15].
Oral entacapone used in some patients in combination with Duodopa®	¶¶	£340,733	¶¶	This scenario is plausible as clinical experts suggest the use of entacapone in combination with Duodopa®.

Scenario	Lecigon® costs†	Duodopa® costs†	Difference	Plausibility
Scenario analysis: Changing average daily dose				
Oral entacapone used in all patients in combination with Duodopa®	¶¶	£344,605	¶¶	This scenario is plausible as clinical experts suggest the use of entacapone in combination with Duodopa®.
Oral opicapone once daily used in all patients in combination with Duodopa®	¶¶	£349,933	¶¶	This scenario is considered plausible by clinical experts, however the AWMSG recommendation for opicapone is restricted within the licensed indication for use after failure of entacapone, or in patients who cannot tolerate entacapone.

†Only acquisition costs included, no other costs were considered in the model.
¶¶ commercial in confidence figure removed

PAS: Patient Access Scheme

The results of the sensitivity and scenario analysis show that cost savings are most sensitive to the PAS for Duodopa®.

4.3 AWTTC critique

The reliability of the CMA depends on the extent to which Lecigon® is considered to be therapeutically equivalent to Duodopa®. The company justified using a CMA, as opposed to a cost-utility analysis, on the basis that the supporting study, LSM-003[13], reported comparable plasma concentration of levodopa over 14 hours when using a reduced administered dose of Lecigon® compared to Duodopa®. These comparable plasma concentrations were found to translate to comparable TRS scores. This led to the assumption that a lower dose would result in similar clinical outcomes.

In the absence of well-designed equivalence trials and/or evidence of close comparability of other effects (impact on health-related quality of life, adverse events, patient preference, adherence and survival), AWTTC considers a CMA to be an inappropriate approach in this instance.

The submission is characterised by both strengths and limitations:

Strengths:

- The model reflects the correct patient population and adopts an appropriate perspective and time horizon.
- The comparator is appropriate and relevant.

Limitations:

- The company's justification for using a CMA is not convincing, given that the direct comparison of Lecigon® and Duodopa® (LSM-003 trial)[13] showed that the same dose of Lecigon® increased systemic levodopa by 1.34 times. The company therefore suggests that a lower dose of Lecigon® would be required to reach the same levels of levodopa plasma concentration, thus potentially reducing side effects such as dyskinesia. While clinical outcomes for Lecigon® may be similar to those achieved by Duodopa®, the lower dose and lighter pump may have other benefits that are not considered in the CMA. A cost-utility analysis would therefore have provided a more appropriate comparison.
- The model inputs are derived from data from 11 patients in the pharmacokinetic study, LSM-003 trial[13] and from 21 patients in the real world evidence study[15]. The Phase 1 study setting, design and small sample size may cause uncertainty in the median and mean dosing values used in the model. However, this was explored in scenario analyses.
- As highlighted previously (section 3.5), the systemic exposure to levodopa in patients treated with Lecigon® compared to Duodopa® is over a 14-hour period, with longer-term data on outcomes and adverse events (median follow-up 305 days) provided by a small observational study[15]. The extrapolation of clinical effectiveness achieved at a lower dose and comparable safety profiles over a 15-year time horizon will introduce uncertainty[1].
- The model assumes that patients do not require night-time dosing. However, considering that four out of 24 patients in the observational study[15] required treatment during the night (one of which discontinued night-dosing after two weeks), the cost might be underestimated.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by the AWTTC did not identify any studies relevant to the cost-effectiveness of Lecigon® compared to Duodopa® in the treatment of patients with advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia uncontrolled by other Parkinson medicinal products or not eligible for deep brain stimulation.

5.0 Budget impact

5.1 Context and methods

Based on a prevalence of 0.176%[22] applied to the Welsh population[23], the company estimates that there will be 5,578 people with Parkinson's disease in Year 1 in Wales. Of these, 8.8% are assumed to have advanced disease based on a Hoehn and Yahr score ≥4[24], resulting in a prevalence estimate of 491 patients with advanced Parkinson's disease. The incidence is estimated at 44 patients per year based on an incidence of Parkinson's disease of 15.8 in 100,000 people[25], of which 8.8% have advanced disease. This results in a total number of patients with advanced Parkinson's disease of 535 in Year 1, increasing to 711 in Year 5.

Considering an excess mortality rate for patients with advanced disease of 6.01%[26] and that an estimated 10% of these patients are ineligible for deep brain stimulation, this results in an eligible population of 50 patients in Year 1, increasing to 67 patients in Year 5. Of these patients, 10% are assumed to receive treatment in clinical practice in line with the proportion of patients anticipated to receive Duodopa®. This results in 5 patients in Year 1, increasing to 7 patients in Year 5. Discontinuation is not considered. The uptake rate for Lecigon®, based on displacing Duodopa®, is assumed to be 20% in the first year of introduction, rising to 75% in Year 5, which would lead to 1 eligible patient receiving Lecigon® in Year 1 and 5 in Year 5. The annual cost of Lecigon® including a [commercial in confidence figure removed] WPAS is estimated at [commercial in confidence figure removed] per patient, compared to £28,124 for Duodopa® (at list price).

5.2 Results

The budget impact is presented in Table 2. The company estimates that introducing Lecigon® would lead to an overall saving of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of Duodopa®. The company carried out sensitivity analyses, including the WPAS for Lecigon®, changing acquisition cost and uptake rate by 5%. This resulted in a range of [commercial in confidence figure removed] in Year 1, and [commercial in confidence figure removed] in Year 5 when varying acquisition costs and [commercial in confidence figure removed] in Year 1, and [commercial in confidence figure removed] in Year 5 when varying uptake rate. Furthermore, they provided calculations assuming different levels of PAS for Duodopa® which showed that Lecigon® at a WPAS of [commercial in confidence figure removed] is cost-saving compared to Duodopa®. [commercial in confidence figure removed].

Table 2. Company-reported costs associated with use of Lecigon®.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	503	544	586	627	669
Sub-population of eligible patients (indication under consideration)	50	54	59	63	67
Number of eligible patients receiving Duodopa®	5	5	6	6	7
Uptake of new medicine (%)	20%	30%	40%	50%	75%
Number of patients receiving new medicine allowing for discontinuations	1	2	2	3	5
Medicine acquisition costs in a market without new medicine	£141,415	£153,065	£164,714	£176,364	£188,013
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed

The company does not foresee any net resource implications arising from the introduction of Lecigon®.

5.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact. The company has factored excess mortality into the calculations.
- The budget impact considerations are limited to acquisition costs only. Other resource use is not included (e.g. monitoring costs and costs associated with adverse events).
- It is uncertain how the estimates for uptake have been calculated. Any changes in uptake rate will affect the budget impact of Lecigon®. AWTTC-sought clinical expert opinion suggests that the number of patients who would receive Lecigon® is considerably smaller than the estimates in Table 2.

- The analysis does not consider population growth and discontinuations. Considering that four out of 24 patients in the observational study[15] discontinued treatment, this could affect the budget impact.

6.0 Additional factors to consider

6.1 Medicines developed to treat rare diseases

The applicant company suggests that Lecigon® should be considered as an orphan equivalent medicine. The company estimates that 491 people have advanced Parkinson's disease in Wales which equates to 1.5 in 10,000 people. However, the medicine does not have European Medicines Agency (EMA) designated orphan status. AWTTC considers Lecigon® eligible to be appraised as an orphan medicine as the full population of the licensed indication does not exceed the threshold of ≤ 1 in 2,000 people in Wales.

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 3) if they consider Lecigon® is a medicine developed to treat a rare disease.

Table 3. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
Severity of the disease	While Parkinson's disease does not considerably impact life expectancy, the disease has a detrimental impact on patients' mental and physical heath as well as health-related quality of life caused by its four core motor symptoms: rigidity, postural instability, rest tremor and an impaired ability to move the body swiftly on command (bradykinesia)[27]. Patients with advanced disease experience progressively worsening motor fluctuations and involuntary movements (dyskinesias)[28], which affect the ability to move and swallow and cause uncontrolled, painful spasms[29]. Furthermore, non-motor symptoms such as anxiety, depression, and sleep disturbances, autonomic dysfunction and dementia can develop[30]. Eventually, patients become bedridden or wheelchair-bound and become increasingly reliant on carers, with patients in the late stages of disease requiring considerable amounts of care[6]. This introduces a burden to caregivers that increases as the condition progresses affecting their mental and physical health, and social life[6].
Unmet need	Levodopa is the most potent treatment available to treat Parkinson's symptoms and the levodopa dose is directly linked to effective symptom control. With progressive disease, patients require increased levodopa doses to manage their condition, leading to an increased risk of treatment-induced side effects such as neuropathy and dyskinesia[28]. Intestinal gels provide more continuous levodopa exposure than oral treatments. Furthermore, the addition of entacapone may increase the proportion of levodopa that is available to cross the blood-brain barrier[3]. Lecigon® therefore may meet the unmet need for a new treatment option which is able to achieve comparable levodopa

	plasma concentrations at a lower administered dose of levodopa, in order to minimise levodopa-induced adverse events.
Innovative nature of the medicine	Lecigon® adds the additional component entacapone to the existing treatment Duodopa® which may give a comparable therapeutic effect at a lower administered dose of levodopa. This has the potential to reduce the 'wearing off' effect, thereby extending the optimal treatment window.
Societal impact on non-health benefits that may not adequately be captured in the QALY	This criterion is not applicable as the company has submitted a cost-minimisation analysis not a cost-utility analysis.
Does the medicine cure or reverse rather than stabilise the condition?	Lecigon® does not cure or reverse the condition but is a symptomatic treatment only.
Does the medicine bridge a gap to a definitive therapy?	Lecigon® does not bridge a gap to definitive therapy.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; NMG: New Medicines Group	

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