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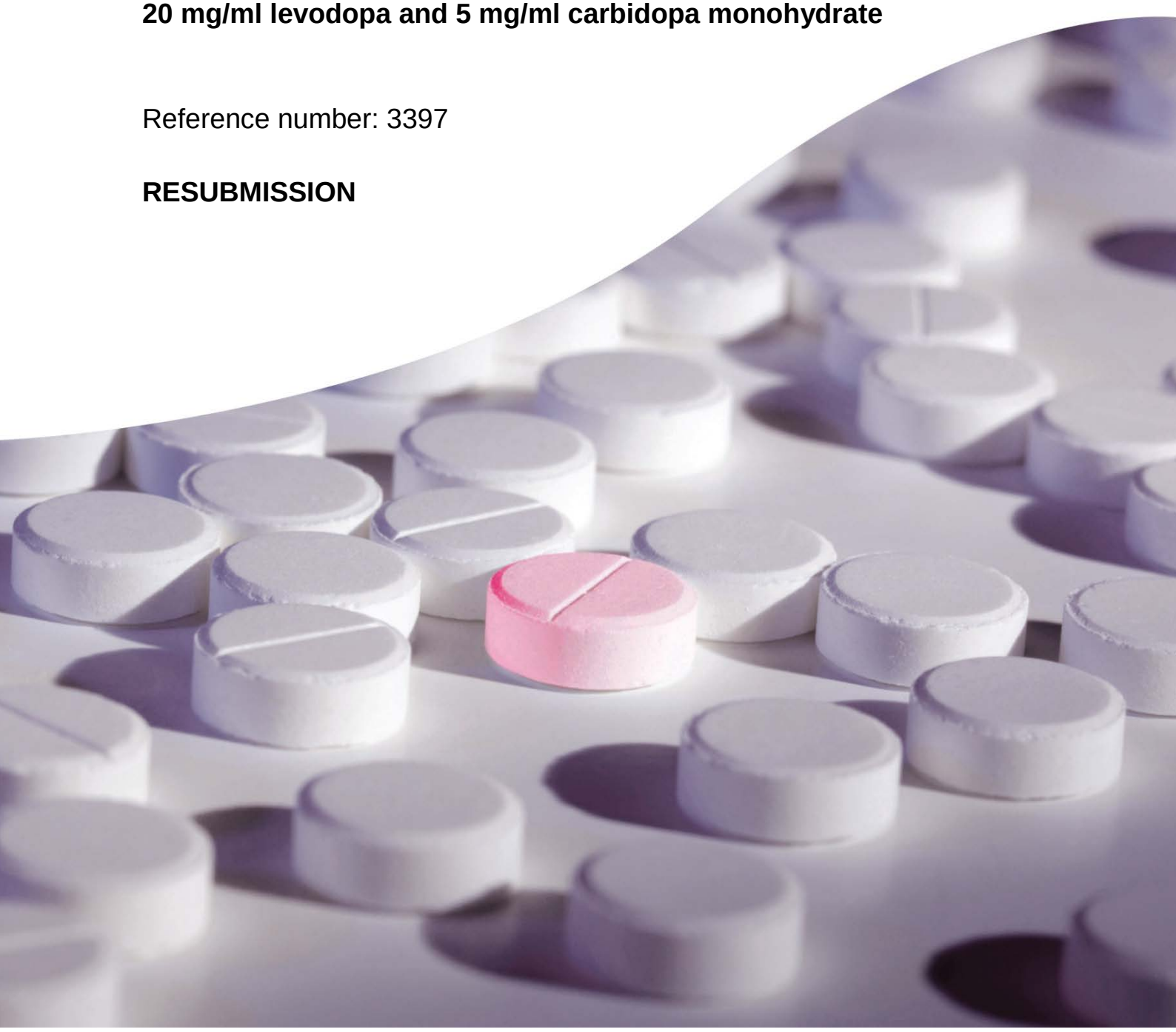
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Levodopa-carbidopa intestinal gel (Duodopa®)
20 mg/ml levodopa and 5 mg/ml carbidopa monohydrate

Reference number: 3397

RESUBMISSION



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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AWMSG Secretariat Assessment Report
Levodopa-carbidopa intestinal gel (Duodopa®) 20 mg/ml levodopa and 5 mg/ml carbidopa monohydrate

This assessment report is based on evidence submitted by AbbVie Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Levodopa-carbidopa intestinal gel (Duodopa®) 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[2].
Dosing	Duodopa® as a continuous intestinal infusion should be administered with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy. Establishment of the transabdominal port and dose adjustments should be carried out in association with a neurological clinic. The total dose/day of Duodopa® is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses administered over approximately 16 hours. Duodopa® should be given initially as monotherapy. If required other medicinal products for Parkinson's disease can be taken concurrently. Refer to the Summary of Product Characteristics for further information regarding dosage[2].
Marketing authorisation date	14 November 2005[2].

2.0 DECISION CONTEXT

2.1 Background

The All Wales Medicines Strategy Group (AWMSG) has previously appraised Duodopa® for the indication under consideration and issued a non-recommendation[3]. An updated submission has been made for Duodopa® which includes additional clinical evidence, a revised cost-effectiveness model and a Wales Patient Access Scheme (WPAS)[1]. The applicant company has highlighted that this resubmission focuses on the use of Duodopa® for the indication under consideration in people who are not eligible for deep brain stimulation[1].

Parkinson's disease is a progressive neurodegenerative condition[4]. Treatments aim to manage the symptoms which include slowness of movement, rigidity and rest tremor. Alongside physical symptoms, people with Parkinson's can also suffer from depression, hallucinations, and dementia[4]. An inability to control these symptoms significantly impacts on a person's quality of life[5].

Levodopa is the mainstay of treatment, supplemented with other anti-Parkinsonian therapies that include dopamine agonists, catechol-o-methyl transferase (COMT) inhibitors, monoamine oxidase type B (MAOB) inhibitors and other therapies[6]. Levodopa is associated with response fluctuations and dyskinesias; large variations in motor performance occur, with normal function during 'ON' periods and weakness and

restricted mobility during 'OFF' periods[7]. Modified-release preparations of levodopa are able to help with end of dose deterioration and nocturnal immobility, in combination with other adjuvant agents. In advanced disease, subcutaneous injections or continuous infusions of apomorphine may be useful in patients experiencing unpredictable OFF periods and to reduce dyskinesias, but it is also highly emetogenic[7]. Deep brain stimulation, involving the implantation of an electrode directly into a specific nucleus of the brain to allow its direct electrical stimulation, may also be an option for some people with advanced Parkinson's disease[4,8].

Levodopa relieves symptoms of Parkinson's disease following conversion to dopamine in the brain. Carbidopa inhibits extracerebral conversion of levodopa, thus making a higher proportion of levodopa available for transportation to the brain[2].

2.2 Comparators

The comparator included in the company submission is standard of care (SoC), defined by the applicant company as the best available oral treatment with or without apomorphine infusion.

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). NICE guideline [NG71]. Parkinson's disease in adults (2017)[4].
- NHS England. Clinical Commissioning policy: levodopa-carbidopa intestinal gel (LCIG) (2015)[6].

AWMSG has previously issued a non-recommendation for the use of Duodopa® for the indication under consideration[3]. AWMSG stated that the applicant company did not present sufficient clinical and cost effectiveness data to gain approval[3].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company highlights new evidence from two identical randomised controlled pivotal studies which were combined in a single analysis (S187.3.001/002)[9] and a follow on open-label extension study (S187.3.003)[10], as summarised below. Also discussed in this section is a prospective observational study (S187.3.004)[11], which forms the evidence base for the revised cost-effectiveness model and a crossover study (DIREQT)[12], which is the original pivotal study on which the licence was based. The company describes additional case-control and observational studies, and whilst they support the findings of the key studies, they will not be discussed in any detail in this report.

3.1 Studies S187.3.001/002[9] and S187.3.003[10]

S187.3.001/002 was a phase III randomised, placebo-controlled, double-blind 12 week study to assess the safety and efficacy of Duodopa® compared with oral levodopa-carbidopa for the control of Parkinson's disease with motor complications[9]. Patients must have had recognisable ON and OFF periods and experienced a minimum of three hours OFF time each day despite an adequate trial of oral levodopa-carbidopa, dopamine agonist and at least one other anti-Parkinsonian therapy. Concurrent anti-Parkinsonian medicines were allowed, except apomorphine. All patients were surgically fitted with a percutaneous gastrojejunostomy tube under local anaesthetic, prior to being randomised to receive either oral immediate release levodopa-carbidopa plus placebo intestinal gel infusion (n = 34), or Duodopa® and oral placebo (n = 37). Duodopa® or placebo gel were administered as a morning bolus followed by a continuous infusion at a constant rate for the remainder of the patient's waking day, with the infusion being stopped overnight. The dose was titrated for four weeks followed by a maintenance period of eight weeks. The primary outcome was change from baseline to week 12 in the mean number of OFF hours (a 24 hour

home-diary assessment of motor status was completed by patients). The baseline mean in the Duodopa® group was 6.3 hours (standard deviation [SD]: 1.7) and 7.0 (SD: 2.1) in the oral levodopa-carbidopa group. Treatment with Duodopa® achieved a significantly greater reduction in OFF time compared with oral levodopa-carbidopa. In the Duodopa® group, the mean change was −4.04 hours per day (standard error [SE]: 0.65) and in the oral levodopa-carbidopa group, the mean change was −2.14 hours per day (SE: 0.66) (difference of −1.91 hours per day [95% confidence interval (95% CI) −3.05 to −0.76], p = 0.0015). Duodopa® also significantly increased ON time without troublesome dyskinesia. There were significant improvements in some other secondary endpoints including mean Clinical Global Impression-Improvement (CGI-I) score at final assessment. An improvement in quality of life score was observed; EQ-5D of 0.07 (95% CI: −0.01 to 0.15) for Duodopa® versus oral levodopa-carbidopa, however this was not statistically significant (p = 0.067)[9].

Long term safety and efficacy was assessed in a 52–week, open-label extension study (S187.3.003), which enrolled 62 people from the S187.3.001/002 study[10]. Patients who continued on Duodopa® in the extension study maintained their improved OFF time and showed further improvement in ON time without troublesome dyskinesias. Patients who had received placebo gel in the earlier study showed a magnitude of improvement similar to that observed in patients on Duodopa® in the earlier study[10].

3.2 Prospective observational study S187.3.004[11]

S187.3.004 was a large (n = 354) phase III open label, single arm, 54 week study to assess the safety (primary outcome) and efficacy (secondary outcome) of Duodopa® in people with motor fluctuations despite optimised therapy[11]. A significant reduction in OFF time was demonstrated from baseline to week 54 with a mean change of −4.4 (SD: 2.9) hours per day (p < 0.001). There was also a significant improvement in ON time without troublesome dyskinesia of 4.8 (SD: 3.4) hours per day (p < 0.001) and a reduction in ON time with troublesome dyskinesia of −0.4 (SD: 2.8) hours per day (p = 0.023). There were significant improvements in quality of life measures including EQ-5D summary index and EuroQol visual analogue scale; significant improvement (p < 0.001) was observed by week four of long-term treatment and was maintained through the end of the study[11].

3.3 Crossover study (DIREQT)[12]

DIREQT was a randomised, controlled, assessor blinded, crossover six week study to assess the efficacy of Duodopa® compared with conventional combination therapies on motor fluctuations and health-related quality of life in people with advanced Parkinson's disease (n = 24) who had experienced motor fluctuations and dyskinesias despite optimised treatment[12]. In this short term study, Duodopa® was administered via a nasoduodenal tube. After the study, the nasoduodenal tube was removed and patients were offered Duodopa® re-instituted by means of a duodenal tube introduced through percutaneous endoscopic gastrostomy (PEG). Long term efficacy was assessed in a six month follow-up extension to DIREQT which looked at the fluctuations in quality of life and motor performance in 12 people who had completed DIREQT. Results for all outcomes demonstrated clinical and statistical superiority of Duodopa® over individually optimised conventional oral anti-Parkinsonian medications (including additional subcutaneous infusion with apomorphine). Patients treated with Duodopa® reported an increase in the proportion of time spent in the ON-state and a concomitant decrease in the proportion of time spent in the OFF-state[12].

3.4 Comparative safety

The SPC for Duodopa® lists a range of special warnings and precautions that are generic to levodopa-carbidopa and so apply to the gel. Many of the adverse effects that occur frequently with the Duodopa® system relate to the device and procedure[2].

In the pivotal studies S187.3.001/002, where Duodopa® was compared to the standard oral formulation of levodopa-carbidopa, ≥ 95% of patients had an adverse effect[9]. The majority of these adverse effects were related to the surgical procedure or the device (89%). Most adverse effects were considered to be mild to moderate in severity[9]. Two patients discontinued from the study because of complications of surgery[9]. In the extension study (S187.3.003), the incidence of infusion-device complications (81%) was stable over time[10].

In the open-label study, S187.3.004 safety was the primary endpoint[11]. For the majority of patients adverse events were mild or moderate and transient[11]. In the post-tube insertion period 298 (92%) of patients experienced adverse events. Severe adverse events were reported in 105 (34.5%) of patients; the most common included complication of device insertion, abdominal pain, and peritonitis and polyneuropathy. Twenty-seven patients withdrew from the study due to adverse events; eight of these patients had procedure-/device-related adverse events.

Limited safety information was provided from the DIREQT study in which the gel was administered via the nasoduodenal rather than transabdominal tube; adverse events did not differ between Duodopa® and conventional treatments.

3.5 AWTTC critique

- Duodopa® is licensed for use in patients with advanced Parkinson's disease who are levodopa-responsive but who are experiencing severe response fluctuations despite optimised treatment with available alternative medications. It is therefore licensed as a last available medical treatment for this rare disease. The company proposes that Duodopa® should be considered for use in people with advanced Parkinson's disease who also are not eligible for deep brain stimulation (i.e. older, less fit patients with advanced Parkinson's disease) and those who have failed or are not eligible for apomorphine infusion - which overall appears in line with clinical practice. Therefore, SoC as a comparator would appear appropriate. However, clinical expert opinion sought by the All Wales Therapeutics and Toxicology Centre (AWTTC) suggests there may be a small number of patients that may be considered for treatment with Duodopa® who may also be eligible for deep brain stimulation. In addition, the company include apomorphine infusion as part of SoC for some patients.
- It is recognised there is currently an unmet need in Wales for those patients with advanced Parkinson's disease. Duodopa® is available for use via health technology appraisal in Scotland for the treatment of advanced Parkinson's disease in those patients deemed unsuitable for deep brain stimulation[13]. Duodopa® is also commissioned for use in NHS England[6]. Eligible patients should have advanced levodopa-responsive Parkinson's disease with severe motor fluctuations with at least 50% OFF periods and be ineligible for apomorphine or have failed, refused to consent to, or be unsuitable for deep brain stimulation[6].
- Despite the availability of Duodopa® elsewhere in the UK, the recently updated NICE guideline for Parkinson's disease states that Duodopa® is not a cost effective use of NHS resources in advanced Parkinson's disease[4] (see section 4.2 for more detail). NICE recommend that the NHS England commissioning policy[6] be reviewed in the light of this guidance. The applicant company highlight that this recommendation was based on health economic analysis undertaken by NICE and was based on all people with advanced Parkinson's disease which is not reflective of clinical practice and the positioning of Duodopa® in the UK (i.e. older, less fit patients with advanced Parkinson's disease)[1].
- There is no universal definition of advanced Parkinson's disease. In this submission, the company define advanced Parkinson's disease as Hoehn and Yahr (HY: see Glossary) stage ≥ 3 (mild to moderate disability with impaired

postural reflexes; physically independent[14]) and OFF periods > 50% whilst awake[1]. This appears in line with clinical practice.

- The original submission considered by AWMSG provided limited short-term efficacy and safety data due to the small number of patients taking part (in the DIREQT study n = 24). As part of this updated submission, the applicant company included new clinical evidence from two randomised controlled studies, a follow on extension study, as well as a number of supportive studies and reviews. Overall, the findings were consistent with those of the studies presented in the original submission, reducing OFF time and increasing ON time without motor fluctuations whilst improving quality of life.
- However, there are still limitations in the evidence provided including a number of open-label designs and the inclusion and exclusion criteria for the pivotal studies - which may lead to uncertainties as to the transferability of the results to the eligible population as described by the applicant company. For example, concurrent use of apomorphine was not allowed and it is not clear whether patients were eligible for deep brain stimulation[9-12].
- Duodopa is administered as a continuous infusion using a portable pump via a permanent PEG tube. It is given via a single use cassette and generally one cassette contains a single day's treatment[6]. Due to the nature of the intervention, patients need continued support for fashioning and managing the PEG. Device and procedure related complications can occur frequently with the PEG tube, and include abdominal pain, complications of device insertion, excessive granulation tissue, incision site erythema, postoperative wound infection, post procedural discharge, procedural pain and procedural site reaction[2]. Therefore, correct selection of suitable patients is essential and, despite the likely small number of patients eligible, there will be likely service implications for administration and maintenance of treatment.
- The SPC states that a temporary nasoduodenal/nasojejunal tube should be considered to determine if the patient responds favourably to this method of treatment before a permanent PEG tube is placed[2]. In cases where the physician considers this assessment is not necessary, the nasojejunal test phase may be waived and treatment initiated directly with placement of the PEG tube[2]. However, clinical expert opinion sought by AWTTC indicates this test phase is still considered routine practice in Wales.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis comparing Duodopa® with SoC in patients who have largely exhausted other treatment options. SoC consisted of conventional oral/topical medication with subcutaneous apomorphine infusion used in a proportion of patients (assumed to be 20%). The patients considered in the economic evaluation are a sub-set of the licensed population, restricting to those with advanced Parkinson's disease who are considered not eligible for deep brain stimulation.

The economic model has a Markov structure consisting of 25 health states representing a combination of HY stage (1–5, higher stage signifying greater severity) and the proportion of the waking day spent in the OFF state (OFF 0–4, with higher score signifying greater OFF time). Patients enter the model aged 64 years, the model cycle length was six months and the time horizon was lifetime (20 years). Patients start in state HY3/OFF3 or higher state and can transition to better or worse states in the first model cycle, but only to the same or worse health state in subsequent cycles. As patients progress quality of life decreases and costs increase.

The clinical data for Duodopa® baseline health state distribution and transition probabilities over the first two cycles are derived from a 52 week single arm study (study S187.3.004)[11]. The transition probabilities from cycle 3 onwards are derived from published natural history studies on Parkinson's disease progression[15,16]. SoC transition probabilities are based on the natural history data from cycle 1[15,16]. It is, however, assumed that Duodopa® patients experience a 0.5 relative risk (50% lower risk) of progression to OFF states than SoC over the remainder of the model time horizon, to reflect evidence supportive of the long term efficacy of Duodopa®[17-19].

Duodopa® discontinuation rates are based on data from the S187.3.004 study[11] for the initial titration phase and from a Duodopa® retrospective chart review in the UK for the rest of the first six month cycle (17.1% overall discontinuation in cycle 1), which is also the source for long term discontinuation rates (2.5% per cycle beyond six months)[20]. Study 10119, a retrospective UK analysis, was used for discontinuation rates for 12 months onwards, and for months 6–12 together with the S187.4.004 study. Regression analysis on pooled EQ-5D data from several Duodopa® studies and Parkinson's disease observational study (the Adelphi Real World Parkinson's Disease Specific Programme[1,21]) was performed to determine utility estimates for each health state. Disutilities for caregivers of advanced Parkinson's disease patients by HY stage are also estimated based on an analysis of EQ-5D data from the Adelphi study[1,21].

Costs included in the model comprise Duodopa® and SoC drug acquisition costs, Duodopa® drug administration costs, and monitoring costs. Drug costs are based on the British National Formulary[22]. SoC consists of a wide range of conventional Parkinson's disease medications, with proportions of patients receiving each medicine based on the Adelphi observational data. Health state costs covers hospitalisations, nurse and doctor consultations, tests, and professional care giving (nursing home, home care) and was estimated based on regression analysis using data from a UK subset of the Adelphi observational study[1]. Treatment specific resource use covering Duodopa® cassette costs and administration (tube insertion and removal, with in-hospital titration assumed in 50% of patients, and monitoring), follow-up visits, and Duodopa® adverse event management is estimated. The resource use estimates are based on the expert opinion of a clinician with experience of Duodopa® treatment and management in Wales. Resource use costs for the health states and Duodopa® administration are estimated using NHS tariff costs 2016–2017. Ninety percent of patients are assumed to require one Duodopa® cassette per day, with 10% requiring two, based on clinical expert opinion. The costs of Duodopa® adverse events consists of the removal of the percutaneous endoscopic gastronomy tube with or without surgery, and are derived from study S187.3.004 and its extension study for up to 3.5 years[11]. No adverse event's costs are assumed for the SoC comparator.

Deterministic sensitivity analyses are undertaken to assess the impact of uncertainty in parameters relating to efficacy, resource use/costs, adverse event rates, discontinuation rates, and the discount rate. Probabilistic sensitivity analysis based on Monte Carlo sampling are performed to explore the impact of joint parameter uncertainty. A scenario analysis is conducted including caregiver disutilities.

4.1.2 Results

The base case results are presented in Table 1. The incremental cost effectiveness ratio (ICER) of [commercial in confidence figure removed] per quality-adjusted life year (QALY) gained is based on an incremental cost of [commercial in confidence figure removed] and incremental QALY gain of [commercial in confidence figure removed] over the 20 year model time horizon. The key cost drivers are the incremental drug costs for Duodopa®, but with significant cost offsets associated with reduced health state costs for Duodopa®. Disaggregated QALYs have not been presented; however, the company suggest that QALY differences in the model are driven exclusively by the reduced OFF time associated with Duodopa®.

Table 1. Results of the base case analysis (WPAS applied to Duodopa®)

	Duodopa®	Standard of Care	Difference
Total costs	¶¶	£367,653	¶¶
Total life-years	10.87	10.80	0.06
Total QALYs	¶¶	3.304	¶¶
ICER (£/QALY gained)	¶¶		

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year.
¶¶ Commercial in confidence figure removed.

Table 2 summarises the deterministic sensitivity analysis provided by the company in order to address uncertainty around the key input parameters. The scenario analysis including caregiver disutility reduced the ICER to [commercial in confidence figure removed] per QALY gained. The results of the deterministic sensitivity analyses indicate that the ICER shows sensitivity to changing assumptions regarding the percentage of patients receiving one Duodopa® cassette per day, the proportion of patients assumed to receive apomorphine as part of the comparator, the long term discontinuation rate, costs of the HY/OFF time health states, the assumption for the long term relative OFF time efficacy of Duodopa®. In probabilistic sensitivity analysis (PSA) the probability of Duodopa® being considered cost-effective at willingness to pay thresholds of £20,000 and £30,000 with WPAS are [commercial in confidence figure removed], respectively.

Table 2. Results of scenario analyses (with WPAS)

Scenarios/sensitivity analysis	ICER	Plausibility
Including caregiver disutilities.	¶¶	A useful analysis which has plausibility as a scenario analysis.
Assuming 70% of patients use 1 Duodopa® cassette per day, 30% use 2 cassettes per day.	¶¶	Clinical expert opinion, sought by AWTTC, suggests that 80–90% of patients would use only one cassette per day.
Assuming 80% of patients use 1 Duodopa® cassette per day, 20% use 2 cassettes per day*.	¶¶*	
Assuming 100% use 1 Duodopa®cassette per day.	¶¶	
SoC assuming 10% use of apomorphine alongside conventional Parkinson's disease medicines*.	¶¶*	A potentially plausible assumption based on clinical expert feedback.
SoC assuming 0% use of apomorphine alongside conventional Parkinson's disease medicines*.	¶¶*	Maybe a pessimistic assumption for use of apomorphine, in clinical practice but would be in line with company position for use of Duodopa® in patients who have failed apomorphine or are not eligible.
Long term relative OFF time efficacy of Duodopa® is 100% greater than SoC.	¶¶	This lacks plausibility due to pessimistic assumptions regarding SoC efficacy, and uncertainty over lifetime efficacy of Duodopa®.
Long term relative OFF time efficacy of Duodopa® is the same as SoC.	¶¶	This could be considered plausible due to uncertainty over the relative effectiveness of Duodopa® versus SoC, and the absolute efficacy of SoC with a proportion of patients receiving apomorphine.
Long term relative OFF time efficacy of Duodopa® has a RR of 0.75*.	¶¶*	
Combined scenario: 10% use of apomorphine, and long term relative OFF time efficacy of Duodopa® is the same as SoC*.	¶¶*	Combined scenario so is potentially pessimistic, but upper estimate re plausibility.
Time horizon of 10 years*.	¶¶*	Not necessarily more plausible than the base case, but indicates impact of uncertainty over long term efficacy on the ICER.
Decreasing Duodopa® long term (beyond 12 months) discontinuation rate by 30%.	¶¶	Lacks plausibility suggesting limitations in the modelling of discontinuation; i.e. infers that non-discontinuation of Duodopa® after 12 (or even after 6 months) will worsen the ICER, hence greatest cost-effectiveness could be achieved by discontinuing treatment from 6 or 12 months. See section 4.1.3 for more detail.
Increasing Duodopa® long term (beyond 12 months) discontinuation rate by 30%.	¶¶	Lacks plausibility suggesting limitations in the modelling of discontinuation; i.e. infers that discontinuation of Duodopa® after 12 (or even after 6 months) will improve the ICER, hence greatest cost-effectiveness could be achieved by discontinuing treatment from 6 or 12 months – applying the increased discontinuation rate to the 6–12 month period reduces the ICER to [commercial in confidence figure removed]. See section 4.1.3 for more detail.
30% increased health state cost.	¶¶	Not necessarily more plausible than the base case, but shows the impact of uncertainty in the robustness of the health state costs analysis on the ICER.
30% reduced health state cost.	¶¶	

AWTTC: All Wales Therapeutics and Toxicology Centre; ICER: incremental cost-effectiveness ratio; RR: risk reduction; SoC: standard of care.

* Additional analyses that were performed by the All Wales Therapeutics and Toxicology Centre.
¶¶ Commercial in confidence figure removed.

4.1.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The economic analysis uses a model which despite a large number of health states can be considered to be an appropriate structure and time horizon for the condition which is chronic and progressive.
- As Duodopa® is positioned by the company to be used as a later line therapy in patients not eligible for deep brain stimulation (i.e. older, less fit patients with advanced Parkinson's disease), the SoC comparator is appropriate, although based on clinical expert feedback there is some uncertainty over the use of apomorphine infusion alongside conventional oral/topical medications in these patients, and whether there are patients in practice considered eligible for Duodopa® who would also be eligible for deep brain stimulation (the company claim the eligible patient populations differ).

Limitations:

- The base case ICER with WPAS is [commercial in confidence figure removed] gained but could be higher under certain other potentially plausible scenarios, as indicated in Table 2. There is uncertainty over the assumed 0.5 relative long term OFF time reduction over the 20 year duration of the model. This is an arbitrary estimate based on an assumption that the short term benefits of Duodopa® in reducing patient OFF time are durable. Removing this benefit increases the ICER with WPAS to [commercial in confidence figure removed]. Further, the treatment benefit derived from year 1 for Duodopa® is assumed to be maintained over the model time horizon, which may be optimistic. Hence, overall the incremental benefits of Duodopa® may be overestimated in the base case.
- The proportion of patients assumed to be receiving more than one Duodopa® cassette per day, which in the base case is set at 10%, is based on clinical opinion. If this proportion is increased to 20% or 30% the ICER increases to [commercial in confidence figure removed] with WPAS (analysis performed by AWTTC using the model) and [commercial in confidence figure removed] with WPAS respectively, but if all patients receive only one cassette, the ICER reduces to [commercial in confidence figure removed]. The company explained that the use of more than one cassette per day may be necessary if symptoms are not controlled with the standard dose. Clinical expert opinion sought by AWTTC suggested that 80–90% of patients would use only one cassette per day. There is also sensitivity in the ICER to the estimates of health state costs and long term discontinuation rates, as indicated in Table 2 above.
- As stated, it is possible that deep brain stimulation could be a relevant comparator for a small number of patients.
- There is also some uncertainty over the use of apomorphine infusion alongside conventional oral/topical medications in the Duodopa® targeted patients. The company claims in the submission that Duodopa® will be used in patients who have failed or are not eligible for apomorphine infusion, but still assume 20% of patients will receive this therapy even though it is assumed to provide no additional benefit. The company have not explored this in the sensitivity analysis presented in the submission but AWTTC analyses using the model indicate if the proportion of patients assumed to receive apomorphine infusion is reduced to 10% the ICER increases to [commercial in confidence figure removed], and to [commercial in confidence figure removed] if no use alongside SoC is assumed.

There are several other uncertainties and issues in the economic analysis that could impact on the robustness of the base case ICER:

- The clinical efficacy of Duodopa® was based on 12 month data from a single arm study and compared to natural history data, rather than from a direct comparative study with SoC, or a formal indirect treatment comparison. The company state this study has been selected for use in the economic model over a recent 12 week randomised controlled trial and 52 week extension study[9,10] on the grounds that the SoC comparator treatment and care has been optimised in the trial, so does not reflects clinical practice or reflect real life disease progression (i.e. would overestimate SoC benefit). However, the use of different sources for relative treatment effect means there is potential bias and inherent uncertainty in the relative effectiveness of Duodopa® versus SoC (conventional medications with or without apomorphine). The company did not provide a scenario analysis using the randomised controlled study (S187.3.001/002)[9] and extension data. The company recognised that there are limitations of the approach used and stated that while an indirect treatment comparison was not possible a match-adjusted indirect comparison may have been a option although is limited by differences in study design.
- The individual patient data for advanced Parkinson's disease patients only (i.e. HY3/OFF3 or higher) from Study S187.3.004 (n = 65) was used to model treatment effect over the first 6 month cycle, but due to small sample size there were no patients in the baseline distribution starting in more severe health states (i.e. HY5 states). In addition, data was only available for all patients (n = 252) with Parkinson's disease from S187.3.004 in order to model cycle 2 transition probabilities to 12 months, hence it was assumed that disease progression is independent of previous progression history and that the whole cohort evidence reflects that of advanced Parkinson's disease patients. However, no evidence is provided to support this assumption so there is uncertainty.
- There is also uncertainty in the absolute efficacy of SoC as the comparator is assumed to infer no treatment benefit over the natural history based estimates. This may be unduly pessimistic, especially given that the comparator includes a proportion of patients who receive apomorphine infusion. It seems unlikely that clinicians would use a relatively costly treatment (compared to conventional therapies) if it was not expected to provide some patient benefit.
- There is some lack of detail in the analysis of health state utilities based on pooled EQ-5D data to fully assess the robustness of the regression performed (e.g. no model fit statistics reported, rationale for only adjusting for HY/OFF time rather than other potential prognostic factors). The company provided a univariate analysis varying health state utilities by ± 10% which resulted in ICERs of [commercial in confidence figure removed] with a 10% increase and [commercial in confidence figure removed] with a 10% decrease. The range of utilities across health states appears potentially plausible and ICERs remain relatively stable when utilities are explored in scenario analysis.
- The analysis of health states costs based on the Adelphi observational dataset also lacks detail on the regression analysis performed to assess robustness, and has limitations in that the costs for more severe HY/OFF health states are based on very limited patient records.
- There is some concern surrounding the discontinuation rate of Duodopa® long term as scenarios run by the company show discontinuation of Duodopa® to benefit the ICER. Increasing the discontinuation rate from 2.5% in the base case, after 12 months of treatment, has a downward effect on the incremental costs due to patients stopping treatment and a small downward effect on the QALY, suggesting that stopping treatment has very little impact on patient outcomes. Based on AWTTC analysis increasing the discontinuation rate to 6% after 12 months of treatment makes Duodopa® dominant. There appears to be limitations in the modelling of discontinuation, in that patients who discontinue Duodopa® move into a non-treatment state and receive SoC at a lower cost but still appear to retain the utility benefits associated with treatment.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified a published study on the cost-utility of Duodopa® compared to SoC in late stage Parkinson's disease patients in the UK[23]. This appears to be the publication of the model used in earlier UK health technology appraisal submissions. The base case result in this analysis was an ICER of £36,024 per QALY gained for Duodopa® compared to SoC. The model had a simpler structure with only 12 HY/OFF states. It does not focus on patients not considered eligible for deep brain stimulation, as per the positioning for the current submission. It was published in 2011 and this model/analysis has now been superseded by the model and analysis performed for the current AWMSG submission.

The Scottish Medicines Consortium's appraisal of Duodopa® in 2016 was based on a cost-utility analysis submitted by the company. This appears to be based on the same model as that submitted to AWTTC. The base case ICER (without PAS) was £58,250/QALY[13].

A further recent economic evaluation of Duodopa® versus Best Medical Treatment (BMT) has been identified that was performed by NICE as part of the recently published clinical guideline for Parkinson's disease in adults[24]. This evaluation used a different Markov model structure than the company model submitted to AWMSG, based on three health states associated with residential status (home care, full time residential care, dead). This structure was stated to have been adopted due to concerns over data availability to populate a model based on HY/OFF time states. The key results of the NICE model were a base case ICER of over £555,201 per QALY gained versus BMT. This differs substantially from the company model estimates, and is driven by higher incremental costs and lower incremental QALYs (of £121,000 and 0.217 QALYs) than in the company submission to AWMSG. In addition to the different model structure, this higher ICER in the NICE model is related to higher costs for Duodopa® (no PAS applied, 20% of patients assumed to receive two cassettes per day). The possible reasons for the lower QALY gains may also be related to the model structure used, a broader advanced Parkinson's disease patient population considered, the handling of discontinuations and the use of the pivotal study data in the model for Duodopa® treatment effect (rather than the single arm study data used in the company model).

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company have estimated that there will be 46 patients with advanced Parkinson's disease eligible for Duodopa® in year 1, rising to 53 by year 5 (i.e. 1% of the estimated Parkinson's disease population). This estimate is based on an age standardised prevalence of Parkinson's disease of 142/100,000 derived from a survey of GP practices in Cardiff[25]; an incidence of 15.8/100,000, based on a study in a region of England[26]; and, an excess mortality rate of 6.01% based on a UK study in Parkinson's disease[27]. The proportion of these patients estimated to have advanced Parkinson's disease (defined as HY3/OFF3 time > 50% of waking time or greater) is 10% based on a community based population study of idiopathic Parkinson's disease patients[28]. Of these, 10% have been estimated to be eligible for Duodopa®, with this estimate based on expert opinion from a clinician in Wales[1].

The company assume an uptake rate out of the eligible population of 5% in year 1 rising to 10% by year 5, with the final number of patients estimated to be treated with Duodopa® of 2 in year 1, rising to 5 in years 3–5 (after accounting for discontinuations). Costs of Duodopa® are based on a drug acquisition cost of [commercial in confidence

figure removed] per cassette with WPAS, with the annual cost based on an assumption that 10% of patients receive 2 cassettes per day, and 90% one cassette. The costs of SoC (and supportive medicines for Duodopa®) are based on a mix of conventional Parkinson's disease therapies and a proportion of patients receiving apomorphine infusion, with use based on data from the UK subset of the Adelphi observational Parkinson's disease dataset[1]. Total resource costs included an estimate of additional Duodopa® treatment administration and monitoring costs, covering hospital admission for PEG tube insertion and titration, and repositioning/reinsertion of the PEG tube, with unit costs derived from the NHS tariff 2016–2017.

5.1.2 Results

The estimated net budget impact of Duodopa® in Wales is shown in Table 3. The company estimates that the introduction of Duodopa® would lead to an overall medicine acquisition cost of [commercial in confidence figure removed] in year one, increasing to [commercial in confidence figure removed] in year five. The company performed sensitivity analysis varying the number of patients treated by ± 2 in each year to indicate the impact on the net medicines budget impact. The impact of this was the net acquisition and supportive medicine cost varied between [commercial in confidence figure removed] in year 1, and between [commercial in confidence figure removed] in year 5. The company also perform sensitivity analysis with Duodopa® list price, which increases the medicine acquisition cost to £59,823 in year 1 rising to £146,592 in year 5.

Table 3. Company-reported costs associated with use of Duodopa® for the treatment of advanced Parkinson's disease in patients not eligible for deep brain stimulation (with WPAS)

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Number of eligible patients (Indication covered in this submission)	46	48	50	51	53
Uptake (%)	5%	8%	10%	10%	10%
Treated patients	2	4	5	5	5
Net medicines acquisition costs including supportive medicine costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figure removed.					

The company estimated that net resource implications arising from the introduction of new medicine will lead to a cost of £5,330 in year 1, but £171 in year 2 rising to £285 in year 5. This is a consequence of increased secondary care costs associated with insertion of the PEG tube and six days admission for titration and potential PEG tube repositioning/reinsertion in year 1, and costs of potential PEG tube repositioning/reinsertion alone from year 2 onwards. These resource-type costs are included for potential planning purposes but may be difficult or impossible to realise in practice.

5.1.3 AWTTC critique

The main issues in the budget impact assessment are as follows:

- The estimated number of advanced Parkinson's disease patients in Wales, and the proportion of these who are eligible for Duodopa® is highly uncertain, the former based on a dated community based study and the use of a single clinical expert opinion for Duodopa® eligible numbers. The uptake rate is also an assumption and so is uncertain. However, the number of patients that will be treated with Duodopa® is expected to be small, and the company have performed somewhat rudimentary sensitivity analysis in varying the treated

number by the same ± 2 patients in each year (which actually leaves a lower estimate of no patients treated in year 1).

- It is not clear if the net number of patients eligible for Duodopa® is consistent with the positioning of the use of Duodopa® in advanced Parkinson's disease patients who are not eligible for deep brain stimulation.
- The SoC cost is dependent on use of apomorphine infusion in Welsh clinical practice, and maybe overestimated. An estimate of 20% of patients receiving apomorphine could be too high for the eligible patient population. Reducing the use of apomorphine in the budget impact model would increase the net cost of Duodopa®.
- Duodopa® cost and net budget impact is dependent on number of cassettes used per day, which was based on expert opinion only[1]. If a greater proportion of patients were assumed to receive 2 cassettes per day the net budget impact will increase.
- The estimate of additional resource costs due to Duodopa® administration is much higher in year 1 than years 2–5, which is based on an assumption of no new patients after year 1, which does not seem realistic.

5.2 Comparative unit costs

Annual acquisition costs of Duodopa® are described in Table 4. The SoC comparator in the economic evaluation consisted of conventional oral/topical Parkinson's disease medications. Due to the large number of medications this consisted of, these are not included in Table 4 below. However, apomorphine continuous subcutaneous infusion was assumed to be used in a proportion of patients as part of SoC; the annual acquisition costs of apomorphine continuous subcutaneous infusion are provided in Table 4.

Table 4: Examples of medicine acquisition costs

Regimens	Example doses	Approximate costs per patient
Duodopa®	40 mg to 120 mg per hour for 16 hours by continuous intestinal infusion *	£28,105 per year
Apomorphine continuous subcutaneous infusion	0.015 to 0.06 mg/kg/hour by continuous subcutaneous infusion over 12 hours †§	£2,772 to £5,336 per year

See relevant Summaries of Product Characteristics for full licensed indications and dosing details.
Costs are based on BNF list prices as of 7th July 2017[22].
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.

* Usual maintenance dose is presented, dose expressed in terms of Duodopa® and does not account for morning bolus dose.
† Dose based on suggested hourly infusion rate over12 waking hours: does not account for initial dose or additional intermittent bolus doses.
§ Dose based on 70 kg body-weight.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company anticipates that levodopa-carbidopa intestinal gel (Duodopa®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted two studies that are currently in press:

- Krueger et al. The effect of levodopa-carbidopa intestinal gel on activities of daily living and quality of life: results from the MONOTREAT study in patients with advanced Parkinson's disease. Parkinsonism & Related Disorders.
- Standaert et al. Baseline characteristics associated with therapeutic response to levodopa-carbidopa intestinal gel treatment for advanced Parkinson's disease. Movement Disorders Clinical Practice.

6.3 AWMSG review

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

6.4 Evidence search

Date of evidence search: 13 and 15 June 2017
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that Duodopa®, for the indication under consideration, meets the AWMSG criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted European Medicines Agency (EMA) designated orphan status and is used to treat conditions affecting not more than 1 in 50,000 in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[29].

The company have estimated that up to 53 patients will be eligible by year 5 for Duodopa®. However, although not entirely clear from the budget impact assessment this presumably is based on a subset of the licensed advanced Parkinson's disease patient population who are not eligible for deep brain stimulation. Hence, the full population of the licensed indication could be associated with higher patient numbers, hence it is uncertain that Duodopa® will meet the criteria to be considered as an ultra-orphan medicine (i.e. less than 60 patients)[29]. In addition, there is high uncertainty associated with the proportion of advanced Parkinson's disease patients who would be considered eligible for Duodopa® as it is based on a single expert clinical opinion. If higher than the 10% estimated then it is likely that Duodopa® would not meet ultra-orphan criteria. It is likely that Duodopa® would meet orphan medicine criteria; it previously had EMA designated orphan status which expired in November 2015 as a matter of course, but the company have stated in response to an AWTTC question on this that there have been no epidemiological changes in the condition or in the number of people suitable for treatment with Duodopa® since this.

The criteria for assessing clinical effectiveness and cost-effectiveness of orphan and ultra-orphan medicines are the same as those applied to other medicines, but recognising that the evidence base may be weaker. If the medicine is considered to meet the criteria for an orphan/ultra-orphan medicine, the New Medicines Group (NMG) and AWMSG may consider additional criteria for appraising these medicines (see Table 5) if the cost per QALY is above the normal thresholds applied.

Table 5. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases: considerations for NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	The patient population are those with advanced Parkinson's disease who are experiencing severe motor and non-motor symptoms. Parkinson's disease is a progressive disease and many studies have shown that quality of life deteriorates and is very poor in patients with advanced Parkinson's disease.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	Duodopa® is intended to be used in advanced Parkinson's disease patients who have exhausted other treatment options, and are not eligible for deep brain stimulation, and have failed or not eligible for apomorphine infusion. Hence, there appears to be no other effective licensed treatment options remaining, although it could be considered inconsistent with a proportion of patients in the economic model assumed to receive apomorphine infusion.
Whether the medicine can reverse, rather than stabilise the condition.	Parkinson's disease is a progressive disease and the medicine is not intended to reverse or stabilise the condition over the long term.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	Duodopa® is not intended to bridge to a definitive therapy.
The innovative nature of the medicine.	The company consider that Duodopa® is innovative as it is an effective treatment due to a novel mode of administration (continuous intraduodenal infusion), which allows patients to have better symptom control and so experience quality of life gain. It does offer a new option for a small proportion of advanced Parkinson's disease patients. However, it is associated with service delivery implications, and the availability of only one cartridge size could be considered a limitation in terms of Duodopa® being considered innovative.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	There is added value to the patient from reducing OFF time by better symptom management offered by the use of Duodopa® over SoC in advanced Parkinson's disease patients. Improvements in daily living, ability to perform daily activities, and QoL is expected to be improved. However, these aspects are likely to have been largely captured by the EQ-5D utility assessment performed by the company as part of the economic analysis.
Added value to the patient's family (e.g. impact on a carer or family life).	Caregivers experience a significant burden from their role with advanced Parkinson's disease patients, so there is a benefit if Duodopa® can reduce this burden on caregivers, which evidence has shown may have to give up work, experience higher rates of depression and lower QoL due to the caring role. The company have usefully captured the QoL/QALY decrement associated with caregiver burden, which has improved the cost-effectiveness of Duodopa® (improved ICER – see Table 2).
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; QoL: quality of life; SoC: standard of care.	

GLOSSARY

Hoehn and Yahr Scale[1,14]

The Hoehn and Yahr Scale describes how the motor symptoms of Parkinson's disease progress. It includes stages from 1 through to 5 plus intermediate stages 1.5 and 2.5. Stages indicate the relative level of disability:

- Stage 1: Unilateral symptoms only.
- Stage 1.5: Unilateral and axial involvement.
- Stage 2: Bilateral symptoms. No impairment of balance.
- Stage 2.5: Mild bilateral disease with recovery on pull test.
- Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
- Stage 4: Severe disability, but still able to walk or stand unassisted.
- Stage 5: Needing a wheelchair or bedridden unless assisted.

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