Cost-effectiveness of levodopa and carbidopa intestinal gel (Duodopa®) for the treatment of advanced levodopa responsive Parkinson's disease.

The NCPE has issued a recommendation regarding the cost-effectiveness of levodopa and carbidopa intestinal gel (Duodopa®). Following assessment of the applicant's submission, the NCPE recommends that levodopa and carbidopa intestinal gel (Duodopa®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (AbbVie) economic dossier on the cost effectiveness of levodopa and carbidopa intestinal gel (Duodopa®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **June 2019**

Summary

In September 2018, AbbVie submitted a health technology assessment dossier. This examined the clinical effectiveness, safety, cost-effectiveness and potential budget impact of levodopa-carbidopa intestinal gel (Duodopa®), for the treatment of advanced levodopa responsive Parkinson's disease with severe motor fluctuations and hyperkinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

Duodopa® is a combination of levodopa and carbidopa in a gel for continuous intestinal infusion. Intestinal infusion of individualised doses of Duodopa® maintains plasma concentrations of levodopa at steady levels within the individual therapeutic window. Duodopa® should be administered with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy; alternatively, a radiological gastro-jejunostomy may be considered. The total daily dose 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. Each Duodopa® cassette is single use only, once opened it must be used immediately and can be used up to 16 hours once it is out of the refrigerator. Each carton of Duodopa® contains seven cassettes. In addition to daytime, if medically justified Duodopa® may be administered during the night. Duodopa® should be given initially as monotherapy. If required, other medicinal products for Parkinson's disease can be taken concurrently.

Duodopa® was previously evaluated by the NCPE for this indication in 2013. At that time, the NCPE did not recommend reimbursement of Duodopa® based on the submitted price.

1. Comparative effectiveness of Duodopa®

The clinical evidence forming the basis of the marketing authorisation for Duodopa® was based on two identically designed Phase III randomised, double-blind studies (S187.3.001/002) (n=71) (Olanow *et al.*, 2013) and an open label phase III study (S187.3.004) (n=354) (Fernandez *et al.*, 2015). The results of the two randomised control trials (S187.3.001/002) were combined and a single analysis was conducted. All of the studies recruited adult patients (≥30 years old), with advanced Parkinson's disease consistent with

UK brain bank criteria and had severe motor fluctuations defined as ≥3 hours daily OFF time at baseline despite optimised treatment with available Parkinson's disease medication.

In S187.3.001/002 patients were admitted to hospital for jejunal placement of percutaneous gastrojejunostomy tube and were randomised equally (1:1) to treatment with immediate release oral levodopa-carbidopa plus placebo intestinal gel infusion, or Duodopa® and oral placebo. Concurrent anti-Parkinson's medications were allowed (apart from apomorphine) if patients were on stable doses at least 4 weeks prior to randomisation, and the dose was not changed during the study. The primary efficacy endpoint was change between baseline and last visit in the mean number of OFF hours collected on the home diary in the three days before each visit, normalised to 16 hour waking day. A key secondary endpoint was change from baseline to last visit in ON-time without troublesome dyskinesia. Health related quality of life data was also collected using the EQ-5D-3L and the Parkinson's Disease Questionnaire summary index which is a Parkinson's disease specific questionnaire. The group treated with Duodopa® achieved a significant reduction in OFF-time in comparison to the group treated with immediate release oral levodopa-carbidopa. From baseline to week 12 there was a mean decrease of 4.04 hours for the Duodopa® group and 2.14 hours for the immediate release oral levodopa-carbidopa group (p=0.0015). This change in OFF-time was associated with a statistically significant increase in ON-time without troublesome dyskinesia (p=0.0059).

S187.3.004 was a 12-month single arm trial in which patients received Duodopa®. Use of other Parkinson's disease medication was permitted in the trial following the initial 28-day titration period at the investigators discretion (excluding apomorphine and controlled release levodopa-carbidopa).The primary efficacy outcome was long term safety of Duodopa®. Secondary endpoints included: OFF-time measured by the Parkinson's disease Diary and ON-time without troublesome dyskinesia. Health related quality of life was measured using EQ-5D-3L and PDQ-39. OFF-time was decreased from baseline to last visit by 4.4±2.9 hours per day (p<0.001) and ON-time without troublesome dyskinesia increased by 4.8±3.4 hours (p<0.001).

In addition to these pivotal trials supporting product registration the applicant presented a number of additional clinical studies to provide further evidence of the long term safety and efficacy of Duodopa®, including two open label extension studies of S187.3.001/002 and S187.3.004. S187.3.003 (Slevin *et al* 2015) was a 52 week open label extension study in which the participants from S187.3.001/002 continued on Duodopa® while those who had received immediate release oral levodopa-carbidopa during the previous trial were switched to Duodopa® treatment. The continuing Duodopa® patients maintained their improved OFF-time obtained during the previous study although further improvement from baseline in the extension phase was not statistically significant (p=0.377). The participants who were switched from immediate release oral levodopa-carbidopa to Duodopa® showed significant decrease in OFF-time of 2.34 hours per day starting at week 4 which persisted to the final visit.

S187.3.005 (Fernandez *et al* 2018) is an ongoing phase III study for all participants who completed S187.3.001/002, S187.3.003 and S187.3.004. Efficacy was measured in the US subset of the trial (n=81), patients experienced a significant decrease of nearly 4 hours in OFF-time from prior to initial Duodopa® infusion to study endpoint (p<0.001), with no significant change from study baseline to end point. The review group's main concern with the clinical evidence provided for the comparative effectiveness of Duodopa® was that, apart from S187.3.001/002, the rest of the studies were open label and mostly single arm. Therefore bias is a risk in these studies.

2. Safety of Duodopa®

The safety of Duodopa® was compared to standard oral levodopa-carbidopa in a total of 71 advanced Parkinson's disease patients who participated in S187.3.001/002. Additional safety information was collected in the open label 12 month study (S187.3.004) (n=354) and in open label extension studies (S187.3.003 & S187.3.005).

In S187.3.001/002 adverse events occurred in 95% of patients in the Duodopa® group and 100% of patients in the immediate release oral levodopa-carbidopa group. Serious adverse events occurred in 14% of patients in Duodopa® group and 21% of patients in oral levodopa-carbidopa group. Most adverse events were related to the surgical procedure or the device,

were mild to moderate in severity, occurred mostly in the first weeks and were resolved in all cases. The most common device complications included: pump malfunctions, tube dislocations, percutaneous gastrojejunostomy insertion complications, stoma leakage and insertion complications. Other adverse events reported included abdominal pain, nausea, procedural pain, constipation, incision site erythema and orthostatic hypotension. Four patients reported symptoms of poly-neuropathy; one in the Duodopa® group and three in the oral levodopa-carbidopa group. Similar results were observed in the extension study (S187.3.003) with 95% of patients reporting an adverse event and 23% of patients reporting a serious adverse event. The most frequently reported AEs were incision site erythema, fall, decreased vitamin B6 and post-operative wound infection.

In S187.3.004 the most common adverse events were; device insertion, abdominal pain and procedural pain. Serious adverse events were reported in 32.4% patients, the most common included; device insertion, abdominal pain, peritonitis and polyneuropathy. The open label extension study (S187.3.005) provides additional long term safety of Duodopa®. An adverse event was reported in 94% of the safety population and 53% reported a serious adverse event during the course of the study. The adverse events lead to discontinuation of treatment in 9% of patients. Complications of device insertion was one of the most common adverse events (2%) resulting in treatment discontinuation.

3. Cost effectiveness of Duodopa®

Methods

A state transition Markov model was used to evaluate the cost effectiveness of Duodopa®. The comparator was standard of care, which was assumed to include conventional Parkinson's disease medication, with or without continuous subcutaneous infusion apomorphine and subcutaneous apomorphine. The casemix for standard of care was 91.8% conventional or Parkinson's disease medication, and 8.2% subcutaneous apomorphine infusion, and was based on medication utilization observed in the Adelphi Real World Parkinson's Disease Specific Programmes 2012. The perspective of the cost-effectiveness evaluation was that of the HSE in Ireland. An annual discount rate of 5% was applied to costs and outcomes.

The health states are defined by the Hoehn and Yahr disease stage categories and the amount of OFF-time experienced (expressed as percentage of the waking day spent in OFF). The Hoehn and Yahr scale describes how the motor symptoms of Parkinson's disease progress. It includes five stages with stage 1 representing the least impairment (unilateral movement only), and stage 5 representing the most impairment (wheelchair bound or bedridden). Time spent in OFF (as a percentage of a 16 hour waking day) is categorised as OFF 0: 0%, OFF I: 1 -25%, OFF II: 26-50%, OFF III: 51-75%, and OFF IV: 76-100%. Theoretically, a patient could occupy any Hoehn and Yahr state, while occupying any OFF time state. Therefore, the combination of Hoehn and Yahr and OFF categories comprises 25 PD health states; death is incorporated into the model as a separate state, giving a total of 26 health states.

During the initial 12-month period (the first two cycles) of the model, the applicant assumed that patients receiving Duodopa® may experience improvement due to their treatment. After the third cycle, transitions are unidirectional: patients can move to a worse (higher) Hoehn and Yahr stage during a Markov cycle and/or any adjacent worse (higher) OFF category, but they cannot experience improvement. For all model cycles, the applicant assumed that patients receiving standard of care can only transition to worse Hoehn and Yahr stages, OFF states or remain in the current health state. Patients receiving standard of care do not experience improvement at any point in the model, and instead follow natural disease progression. The review group does not consider that it is plausible to assume that there can be no improvement on any treatment other than Duodopa®, as improvement in both OFF time and Hoehn and Yahr stage were observed in the randomised controlled trial S187.3.001/002 for the standard of care arm. The review group believe that this evidence is contradictory to the natural disease progression assumption in the model. Therefore the review group assumed a risk ratio for both progression and improvement for Duodopa® versus standard of care, based on data from the randomised controlled trial S187.3.001/002.

The applicant assumed a long-term discontinuation rate of 5.1% per 6 month cycle which was obtained from S187.3.005. This was much higher than the rate of 1.4% used in the 2013 submission. The review group believed that 5.1% was too high as patients who died in

S187.3.005 study were counted as discontinued. When the deaths are omitted the discontinuation figure is 3.5% per 6 month cycle. The review group believe that this is still quite high compared to other studies and amended the figure to 2.5%, based on Kalabina *et al*, 2018, a cost effectiveness study highlighted by the applicant, which assumed a discontinuation rate of 2.5% per 6 month cycle.

In 2013 the applicant assumed that patients could continue on Duodopa® even if they were in the worst health state (Hoehn and Yahr 5-OFF IV). However, in this submission the applicant assumed that patients would discontinue treatment in the cycle immediately after reaching Hoehn and Yahr 5-OFF IV. The review group obtained expert opinion from a number of clinicians regarding this assumption. Given the strong consensus among experts, the NCPE preferred base case concurs with the 2013 Duodopa® submission where patients discontinued Duodopa® in the Hoehn and Yahr 5-OFF IV state, at the same rate as from other states in the model.

Results

The applicant conducted an incremental analysis of the costs and benefits of Duodopa® versus standard of care. In the original applicant base case the ICER was €35,077/QALY (Incremental Costs: €35,212, Incremental QALYs: 1.00).

Following changes from the review group (of which the main changes were implementing a risk ratio for both progression and improvement for Duodopa® versus standard of care, decreasing the discontinuation rate, and assuming that patients in Hoehn and Yahr 5-OFF IV will continue on Duodopa®), the NCPE preferred base case ICER is €124,765/QALY (Incremental Costs: €125,781, Incremental QALYs: 1.01).

Using the NCPE preferred base case the results from the probabilistic sensitivity analysis gave an ICER of €114,252/QALY (Incremental Costs: €118,313, Incremental QALYs: 1.04). At a willingness-to-pay threshold of €20,000/QALY, the probability of being cost-effective is 1%, while at a willingness-to-pay threshold of €45,000/QALY, the probability of being cost-effective is 4%. Applying a deterministic sensitivity analysis to the NCPE preferred base case, the most impactful parameters were the long-term risk ratio of OFF-time progression for

Duodopa® relative to standard of care (lower bound €61,888/QALY, upper bound €200,086/QALY), and the relative improvement of Duodopa® relative to standard of care for OFF stage (lower bound €83,065/QALY, upper bound €161,544/QALY), and for Hoehn and Yahr stage (lower bound €107,127/QALY, upper bound €181,956/QALY).

4. Budget impact of Duodopa®

The price to wholesaler of Duodopa® (for 7 cassettes) is €722.23. The average cost per patient per year (including 23% VAT) is € 47,988.11.

The applicant estimates that 227 patients will be on treatment by year 5. The cumulative 5-year gross budget impact is estimated to be approximately €44.1million.

5. Patient Submission

No patient submissions were received during the course of this appraisal.

6. Conclusion

Following assessment of the applicant's submission, the NCPE recommends that levodopa and carbidopa intestinal gel (Duodopa®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.