Cost effectiveness of Duodopa® in the management of advanced Parkinson's patients.

The NCPE has issued a recommendation regarding the cost effectiveness of Duodopa® in the management of advanced Parkinson's patients. The NCPE does not recommend reimbursement of Duodopa® at the current price.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturers (Abbvie) economic dossier on the cost- effectiveness of Duodopa® in the treatment of advanced Parkinson's patients with severe motor fluctuations when combinations of Parkinson's medications are not satisfactory. 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 examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

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 **December 2013**

Abbvie submitted a dossier for levodopa/carbidopa intestinal gel (Duodopa®) on 26th September 2013. Duodopa® is indicated for the treatment of advanced levodopa-responsive Parkinson's disease (PD) with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson's medicinal products have not given satisfactory results. Duodopa® is a gel for continuous intestinal administration and is administered using a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy. It is classed by the EMA as an orphan drug.

1. The economic evaluation compared Duodopa® treatment with standard of care, (SoC) in the management of advanced PD for the licensed indication. SoC was assumed to include conventional oral PD medication (for example levodopa, 2nd generation dopamine agonists, COMT inhibitors) +/- subcutaneous apomorphine infusion and standard follow-up visits.

2. A Markov model was presented with 6 month cycles. Patients were tracked through different health states over time. The health states are those defined by Hoehn and Yahr (H&Y) combined with the amount of OFF-time experienced (percentage of day spent in 'OFF' time OFF 0 0%, OFF I 1-25%, OFF II 26-50%, OFF III 51-75% and OFF IV 76-100%)). The Hoehn &Yahr scale includes five stages with stage 1 representing least impairment and stage 5 representing most impairment. There are 26 health states including death. The time horizon for the model is 20 years.

3. To support the clinical efficacy a number of sources of evidence were presented. One study (Olanow *et al.* 2013 Lancet Neurology) is published as a full paper and is the only double dummy trial. This is a 12 week randomised phase 3 double-dummy trial which evaluated efficacy, safety and tolerability of levodopa/carbidopa gel infusion (Duodopa®) and placebo tablets compared to oral levodopa-carbidopa immediate release tablets (and a placebo gel) in patients with advanced Parkinson's disease (N=71). The primary endpoint was change from baseline to final visit (week 12) in motor off-time (hrs). From baseline to 12 weeks in the full-analysis set, mean off-time decreased by 4·04hrs for 35 patients allocated to the Duodopa® group compared with a decrease of 2·14hrs for 31 patients allocated to immediate-release oral levodopa-carbidopa. The mean on-time without troublesome dyskinesia increased by 4·11hrs in the Duodopa® group and 2·24hrs in the immediate-release

oral group. There was no significant change in 'on' time with troublesome dyskinesias.

4. In a long term study to assess safety of Duodopa® (Fernandez 2010) 87% of patients reported adverse effects and these were classified as serious in 31%; approximately 7% (n=14) discontinued due to AEs. Reasons for discontinuation included dyskinesias and motor symptoms (n=4), gastrointestinal complications (n=6), device complications (n=2), peritoneal abscesses (n=1), hip fracture (n=1) and polyneuropathy (n=1). Four patients died (suicide, septic shock following acute renal failure, cachexia after hip fracture and sudden death following surgery for fractured humerus).

5. Resource use is derived from the Adelphi 2012 UK patient dataset which was assumed to be applicable to Ireland. The model uses the average cost per patient, as found in the Adelphi study for the non-Duodopa® patients but does not use the complete data for the Duodopa® set. Duodopa® is costed separately in the model rather than the average cost as derived from the utilisation from the Adelphi dataset. The variance associated with Duodopa® (dosing) is therefore not captured as it is with the other treatments such as apomorphine.

6. One of the main drivers of the model is the assumption that the long term efficacy for Duodopa® i.e. the initial treatment effect, achieved in the first two model cycles, on the reduction in OFF time, is maintained over the long term. The review group were of the opinion that this may overestimate the benefit of Duodopa® about this as there is currently limited evidence to support this assumption.

7. The incremental cost effectiveness ratio presented by Abbvie for Duodopa® versus SoC was €41,114/QALY (total costs for Duodopa® €537,276 and SoC €465,716 and total QALYs for Duodopa® 4.72 and for SoC 2.98). The review group consider this ICER to be an optimistic estimate of cost effectiveness, primarily driven by the assumption that in the long term Duodopa® patients cannot disimprove in 'OFF' time. When the long term efficacy (beyond 12 months) is assumed to be the same as SoC, the ICER increases to approximately €98,717/QALY.

8. Both one way and probabilistic sensitivity analysis was carried out. The OWSA varied the long term efficacy (demonstrated by reduction in 'OFF' time),

discontinuation rates (in short and long term), health state costs, Duodopa® cassette use, medication costs, device complication rates and discount rates. The number of Duodopa® cassettes used, the health states costs and the long term effect on 'OFF' time had most impact on the model.

9. The probability of cost effectiveness at a threshold of €45,000 calculated by the company is 94%. The review group feel that there is likely to be more uncertainty than this estimate indicates, due to assumptions made around the intervals of uncertainty of some of the parameters.

10. The cost per patient of the initiation phase is €3,281 and the cost of the maintenance phase is €41,397. The ongoing annual cost beyond this is €41,570 per patient. The cumulative budget impact in 2013 is predicted at €2.332m, in 2014 €2.685m, €3.098m, in 2016 €3.453, in 2017 €3.811m and in 2018 €4.168m.

11. Based on the data submitted, the NCPE consider that there is considerable uncertainty in relation to the long term effect of Duodopa® on OFF time and therefore do not recommend reimbursement of Duodopa® at the current price.