NICE National Institute for Health and Care Excellence

NICE guidance

Foslevodopa–foscarbidopa for treating advanced Parkinson's with motor symptoms

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Foslevodopa–foscarbidopa is recommended as an option for treating advanced levodopa-responsive Parkinson's in adults whose symptoms include severe motor fluctuations and hyperkinesia or dyskinesia, when available medicines are not working well enough, only if:

- they cannot have apomorphine or deep brain stimulation, or these treatments no longer control symptoms, and
- the company provides foslevodopa–foscarbidopa according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with foslevodopa–foscarbidopa that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment for advanced levodopa-responsive Parkinson's includes adding apomorphine, deep brain stimulation or levodopa–carbidopa intestinal gel to standard care (such as oral levodopa–carbidopa). Foslevodopa–foscarbidopa is given as a continuous infusion under the skin (subcutaneous).

The company asked for foslevodopa–foscarbidopa to be considered only for people who cannot have apomorphine or deep brain stimulation, or for when these treatments no longer control symptoms. So foslevodopa–foscarbidopa was only considered as an alternative to standard care and levodopa–carbidopa intestinal gel. This does not include everyone who foslevodopa–foscarbidopa is licensed for.

Evidence from a clinical trial suggests that foslevodopa–foscarbidopa improves motor symptoms compared with standard care. But some people in the trial had previously had apomorphine, so it is uncertain how well foslevodopa–foscarbidopa works for people who cannot have apomorphine. An indirect comparison suggests that

foslevodopa–foscarbidopa works as well as levodopa–carbidopa intestinal gel, but the results are uncertain.

Even when considering this uncertainty, the most likely cost-effectiveness estimates are within the range that NICE usually considers an acceptable use of NHS resources. So, foslevodopa–foscarbidopa is recommended.

2 Information about foslevodopa–foscarbidopa

Marketing authorisation indication

2.1 Foslevodopa–foscarbidopa (Produodopa, AbbVie) is indicated 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for foslevodopa–foscarbidopa.

Price

2.3 The cost of foslevodopa–foscarbidopa is £84.70 for a 10-ml vial for infusion (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes foslevodopa–foscarbidopa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by AbbVie, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Parkinson's is a chronic and progressive disorder of the central nervous system. It is caused by a loss of the cells in the brain that produce dopamine, which helps to control and coordinate body movements. People with Parkinson's typically present with motor symptoms, including slowness or absence of movement, tremors, rigidity and dyskinesia (involuntary, abnormal and excessive movements, also called hyperkinesia). The clinical experts noted that the condition is also associated with non-motor symptoms such as sleep disturbance, brain fog and constipation. They explained that there is no universally agreed definition of advanced Parkinson's. People with advanced Parkinson's may experience complications such as anxiety, depression and dementia. A patient expert described living with the condition as a life sentence lived in a small cell that is getting smaller. They explained that the unpredictability of advanced Parkinson's can mean that planning and doing everyday tasks become increasingly difficult. They also described feeling that they were a burden on their family. Difficulties with concentration and fatigue mean that some people need constant supervision for their safety. They noted that family members and care partners face stress, loss of sleep and financial distress associated with supporting the person with Parkinson's. The committee concluded that advanced Parkinson's severely affects the quality of life of people with the condition and their family and carers.

Motor symptoms

3.2 In advanced Parkinson's the natural level of dopamine in the brain further

decreases and the sensitivity of brain cells to dopamine replacement treatment reduces (see section 3.3). This increases the likelihood of underdosing or overdosing with levodopa, which leads to motor fluctuations. Motor fluctuations include 'on' time when Parkinson's symptoms are well controlled, and 'off' time when these symptoms, including dyskinesias, worsen. A patient expert noted that during 'on' time, they can get up out of bed, move freely and do meaningful activities in the day (for example, working, socialising and sport). The clinical experts added that during 'on' time, dyskinesia can occur with overdosing of medication. A patient expert described that during 'on' time, many people fear having dyskinesia, which can be embarrassing and upsetting. During 'off' time, the patient experts explained that many activities are severely limited or stopped. For example, they need help taking medicine, getting out of bed, at mealtimes and using the toilet. During 'off' time people describe becoming increasingly slow in their movements, more tired and unhappy. The clinical experts noted that the most troublesome symptoms vary widely between people with Parkinson's. For some, an unpleasant feature of 'off' time is freezing, when all movement suddenly stops, which can happen at any moment. The committee concluded that motor symptoms in advanced Parkinson's have wide ranging effects on daily life and are highly variable between people with the condition.

Clinical management

Treatment options

3.3 Oral levodopa is the first-line treatment for people who are experiencing the early stages of Parkinson's and whose motor symptoms affect their quality of life (see section 1.3 of NICE's guideline on Parkinson's disease in adults). Levodopa is taken with a dopa decarboxylase inhibitor, such as carbidopa, which increases the availability of levodopa in the brain. The clinical experts noted that additional treatments are added as part of standard care to manage motor symptoms as Parkinson's progresses (for example, dopamine agonists, monoamine oxidase-B [MAO-B] inhibitors, catechol-O-methyltransferase [COMT] inhibitors or amantadine). They added that, because symptoms are very variable (see section 3.2), management of advanced Parkinson's is highly personalised. They noted that people with advanced Parkinson's will typically be taking 4 different

medicines, with some people taking up to 30 tablets per day for Parkinson's and non-Parkinson's treatments. A patient expert explained that taking many tablets, some of which have specific conditions on how they are taken for optimal absorption, can mean inflexible timing of meals, which can affect family life. The clinical experts noted that strong dopamine agonists, particularly when given orally, can be associated with troubling side effects related to impulse control. The following non-oral treatments may be used in advanced Parkinson's that is not controlled with standard care (also called best medical therapy):

- apomorphine (a dopamine agonist, given by intermittent subcutaneous injection or continuous subcutaneous infusion)
- deep brain stimulation (see the NICE interventional procedures guidance on deep brain stimulation for Parkinson's disease)
- levodopa–carbidopa intestinal gel.

The clinical experts added that deep brain stimulation carries risks associated with surgery. It is effective for people with significant motor fluctuations with a good levodopa response and for people with levodopa-resistant tremor. One of the clinical experts explained that there are criteria for using levodopa–carbidopa intestinal gel in NHS clinical practice (see NHS England's clinical commissioning policy on levodopa–carbidopa intestinal gel). They also explained that people can have difficulty accessing treatment because it is only available in tertiary centres so is not readily available to most people. They added that before having levodopa–carbidopa intestinal gel, a tube needs to be permanently placed in the small intestine. It is used only if apomorphine and deep brain stimulation are unsuitable, for people with more than 50% 'off' time per day. Foslevodopa–foscarbidopa is a potential alternative non-oral, levodopa-based treatment, which is delivered by continuous subcutaneous infusion. The committee concluded that standard care for advanced Parkinson's needs a highly personalised approach involving multiple medications, but the most relevant comparator is likely to be standard care.

Relevant population and comparators

3.4 The population considered in this evaluation is narrower than NICE's final scope on foslevodopa–foscarbidopa for treating Parkinson's disease with motor symptoms and the marketing authorisation for foslevodopa–foscarbidopa (see section 2.1). This is because the company restricted the decision problem in its company submission to people for whom apomorphine or deep brain stimulation are unsuitable or no longer providing adequate symptom control. As a result, levodopa–carbidopa intestinal gel and standard care are the only treatments included as comparators for foslevodopa–foscarbidopa in the company's model (see section 3.9). The company informed the committee that people whose condition was controlled on apomorphine or deep brain stimulation or for whom the treatments were suitable, were removed from the relevant population to reflect when foslevodopa–foscarbidopa offers best value for money. The EAG noted that the company's narrower population has a high level of unmet need, so narrowing the population might be reasonable. But it added that the company's clinical evidence (see section 3.5) included data from a broader population. The clinical experts suggested that clinicians in the NHS would likely prefer to offer foslevodopa–foscarbidopa to all people within the marketing authorisation. For example, they might prefer to offer foslevodopa–foscarbidopa before offering deep brain stimulation because of the invasiveness of the procedure. They also noted that delivering foslevodopa–foscarbidopa is more straightforward than delivering levodopa–carbidopa intestinal gel, so foslevodopa–foscarbidopa could possibly be provided in a less specialist setting, potentially alongside apomorphine administration services. The experts noted that in the company's narrower population, people have a high unmet need but are likely to be frailer and may also have worse treatment outcomes than the marketing authorisation population. At the first committee meeting, the committee considered that people for whom apomorphine or deep brain stimulation is suitable may be a relevant additional population for the company to include. The company did not change its proposed positioning or provide evidence for this population during consultation, so levodopa–carbidopa intestinal gel and standard care continued to be the only comparators included. The clinical experts considered that many more people with advanced Parkinson's are treated with standard care than with levodopa–carbidopa intestinal gel (around 5%) so standard care was the most relevant comparator. The committee concluded that the company's narrower population does reflect the greatest area of unmet need in advanced Parkinson's

with motor symptoms. But it would have preferred the company to submit evidence that allowed foslevodopa–foscarbidopa to be evaluated for all people within its marketing authorisation.

Clinical evidence

Data sources and generalisability

3.5 The company's key clinical-effectiveness evidence came from a randomised phase 3 trial called M15-736, which compared foslevodopa–foscarbidopa with oral levodopa–carbidopa. People in the trial had advanced, levodopa-responsive Parkinson's with motor fluctuations that was inadequately controlled by their current treatment. They had an average 'off' time of at least 2.5 hours each day (with a minimum of 2 hours each day) recorded over 3 consecutive days. At the first meeting, evidence on oral levodopa–carbidopa from M15-736 was not used for standard care in the company's model. Instead, a naive indirect comparison of foslevodopa–foscarbidopa and published data on natural disease progression was done (see section 3.11). The committee considered that the M15-736 data allowed a direct comparison of foslevodopa–foscarbidopa against standard care. It also considered that the company's naive indirect comparison introduced considerable uncertainty. It added that the company should explore this in its modelling of clinical effectiveness. During consultation on the draft guidance, stakeholders commented that the way standard care is optimised and delivered in the M15-736 trial may not be equivalent to standard care in clinical practice. They also commented that a 12-week study duration may be too short to observe Parkinson's progression. During consultation, the company revised its approach to use the M15-736 trial evidence for standard care in its model. The company also provided supporting evidence for foslevodopa–foscarbidopa from non-comparative safety studies, including M15-741 and M15-737. The committee noted that because people in M15-736 could have previously had apomorphine, the study population was broader than that in the company's submission (see section 3.4). It also noted that people in M15-741 could have had apomorphine or deep brain stimulation. The company said that the subset of people in M15-741 who had prior apomorphine or deep brain stimulation was similar in baseline characteristics to the full populations enrolled in M15-736 and M15-741, so

outcomes for the subset are not expected to be different to the broader populations. The EAG considered that despite this, using a source of clinical evidence for foslevodopa–foscarbidopa that is from a broader population than that considered by the company is a source of uncertainty. The committee concluded that the company's updated approach included a direct comparison of foslevodopa–foscarbidopa with standard care, which reduced some uncertainty. It also concluded that the sources of clinical evidence were from a broader population than those in the company's submission, which is a source of uncertainty.

Results of key clinical trial

3.6 After 12 weeks of treatment, 'on' time without troublesome dyskinesia (the primary end point of M15-736) was 1.75 hours longer (improved) with foslevodopa–foscarbidopa than with oral levodopa–carbidopa. 'Off' time was 1.79 hours shorter (improved) with foslevodopa–foscarbidopa than with oral levodopa–carbidopa. These improvements are considered clinically significant (using a definition of more than 1 hour) and statistically significant. The company noted that people in the trial who had oral levodopa–carbidopa had an improvement from baseline of approximately 1 hour in 'on' time without troublesome dyskinesia and 1 hour improvement in 'off' time. The company explained that the oral levodopa–carbidopa arm of the trial was intended to represent people whose motor symptoms were not controlled with standard care. It suggested that the trial benefit seen in this treatment arm did not reflect the expected treatment effect of standard care in clinical practice. It considered that this was because of the increased interaction with the healthcare system experienced by people in the trial setting. The EAG agreed that a trial effect (or placebo effect) could be observed but noted that this would be expected in both treatment arms (see section 3.7). The committee noted that foslevodopa–foscarbidopa improved 'on' time without troublesome dyskinesia and 'off' time compared with oral levodopa–carbidopa. It concluded that a treatment benefit for both foslevodopa–foscarbidopa and standard care was observed in the trial.

Uncertainty in treatment effect

3.7 In M15-736, to attempt blinding by treatment arm, people had either foslevodopa–foscarbidopa delivered by a subcutaneous pump and placebo tablets, or levodopa–carbidopa tablets and placebo delivered by a subcutaneous pump. The EAG noted that the trial had a high risk of unblinding, because people could correctly deduce which treatment they were taking. This was because treatment with foslevodopa–foscarbidopa was continuous, so there were fewer symptoms after waking in the morning than with oral treatment, which has a delayed effect from when each dose is taken. Clinical advisers to the company and the EAG considered that the trial was well designed and that there was no better approach that could have avoided potential unblinding. 'On' time without troublesome dyskinesia and 'off' time were recorded by people in the trial in a Parkinson's diary. The EAG noted that this might mean that the effects of foslevodopa–foscarbidopa may be overestimated and the effects of oral levodopa–carbidopa may be underestimated. The company noted that using a diary to record symptoms is the gold standard in Parkinson's trials. It added that people in the trial had to complete each diary entry within 2 days to minimise the likelihood of recall bias. The clinical experts agreed that the use of Parkinson's diaries is a standard approach but acknowledged the limitations of self-reported outcomes. They also noted that they provide valuable direct experience of people living with Parkinson's. The experts agreed with the EAG that by guessing which treatment arm they are on, people might overestimate or underestimate any treatment effect. The committee concluded that the M15-736 trial was well designed but that there was a risk of unblinding. So, there is some uncertainty in the treatment effects, which could lead to the benefits of foslevodopa–foscarbidopa being overestimated.

Indirect treatment comparison

Comparison with levodopa–carbidopa intestinal gel

3.8 Because of the lack of direct evidence comparing foslevodopa–foscarbidopa with levodopa–carbidopa intestinal gel, the company submitted a network meta-analysis involving 3 randomised controlled trials. This included the outcomes of

'on' time without troublesome dyskinesia and 'off' time, but only 'off' time was used in the company's model (see section 3.9). The EAG noted that because the network meta-analysis includes clinical evidence from the M15-736 trial, the results of the analysis are subject to the same uncertainty as the trial results (see section 3.7). It also noted that the company was inconsistent in its use of observed and least squares means data in the network meta-analyses. The EAG preferred to use least squares means data, which adjusts for issues in baseline characteristics that are not matched between studies. This is because a large number of people stopped treatment and there was missing data. The company updated its analysis using all observed means data. It considers the results of the indirect comparison confidential, so they cannot be reported here. The EAG repeated the analysis using least squares means data. But it did not have access to this data for 1 study of levodopa–carbidopa intestinal gel, so advised that the results should be interpreted with caution. The company's and EAG's approaches gave different results, but in both the mean treatment difference for 'off' time was less than 1 hour. The committee noted uncertainty (because of wide credible intervals) in the mean treatment difference presented for the random effects model in both the company's and EAG's analysis. Given the different results of the company's and EAG's analysis and the associated uncertainty, the EAG preferred to assume equal efficacy of foslevodopa–foscarbidopa and levodopa–carbidopa intestinal gel. The committee considered it appropriate to assume no difference in treatment effect in the indirect comparison. The committee concluded that the results of the indirect comparison of foslevodopa–foscarbidopa against levodopa–carbidopa intestinal gel were uncertain.

Economic model

Company's modelling approach

3.9 The company used a 2-stage Markov model to estimate the cost effectiveness of foslevodopa–foscarbidopa compared with levodopa–carbidopa intestinal gel and standard care. In the company's original submission, the model included separate health states for each number of hours between 0 and 16 hours of 'off' time during daily waking hours (17 health states) plus a death state. At the first

meeting, the committee noted that the model had a large number of health states. Stakeholders commented on the draft guidance that the clinical significance of differentiating between such a large number of health states was not clear. During consultation, the company reduced the number of health states (see section 3.10). In the first period of the model (cycle 1), people could move between any of the health states so that 'off' hours could improve, stay the same or worsen. The first 3 months of the model cycle were informed by the M15-736 trial results. The trial benefit reported for foslevodopa–foscarbidopa was assumed to be maintained up to 3 years after stopping treatment during the last observation carried forward (LOCF) period. In the second period of the model (cycle 2 onwards), 'off' hours could stay the same or worsen by 1 hour in each cycle. Transitions were based on a publication by Palmer et al. (2002) that describes the natural disease progression of Parkinson's (see section 3.11). Each health state was associated with different quality-of-life and cost estimates, which were combined across model cycles and compared between treatments. The duration of the first and second model cycles was 3 months, and subsequent cycles were 6 months. A half-cycle correction was applied, and the model had a lifetime time horizon (20 years). The base-case modelling perspective was that of people with advanced Parkinson's. Because managing Parkinson's can place substantial demands on family members and care partners (see section 3.1), the company explored a carer disutility (health-related quality-of-life impact) as part of the scenario analysis. In the company's revised approach for modelling standard care (see section 3.5), the trial effect was assumed to be lost after stopping treatment with no LOCF period and people moving to a baseline 'off' state in cycle 2. The company explained that this approach was informed by their clinical experts and evidence from the long-term PROSPECT study, which is investigating the natural history of Parkinson's-related conditions. The EAG noted that the PROSPECT study shows that there is little change from baseline 'off' time at 12 months for people on oral treatment (a small but not statistically significant reduction). So, it preferred to apply the same assumptions to the standard care arm as the foslevodopa–foscarbidopa arm. This was with no return to the baseline 'off' state for standard care and assuming LOCF for up to 36 months. It noted that this approach allowed the observed trial effect (see section 3.6) to be applied equally to both arms. The committee noted that the company and EAG made different assumptions when modelling standard care, and it preferred the EAG's approach. The EAG also noted a minor error in how the company had used the M15-736 trial data in the standard care arm, because no mortality was

applied between cycles 2 and 3. The committee concluded that the company's general approach of using a Markov model was reasonable.

Health states

3.10 At the first meeting, the EAG highlighted that the company modelled 'off' hours only, and considered these may not fully reflect the heterogeneity of Parkinson's. The clinical and patient experts considered that the number of 'off' hours is a key measure for capturing Parkinson's symptoms. The patient experts noted that as well as the duration of 'off' time, other factors may contribute to quality of life during the 'off' state. These include the severity, predictability and time of day of the 'off' state. The EAG also noted concern with the large number of 'off' states. It considered that the company did not have enough data to produce reliable efficacy, utility and cost estimates for each health state. The company suggested that 'off' time was the most appropriate outcome to model the progression and predictability of symptom control, which are important to people with Parkinson's. It added that the company's clinical experts agreed that 1 hour (the difference between each of the 'off' states), is a clinically meaningful change in 'off' time each day. At the first meeting, the EAG noted that most other Parkinson's models incorporated 'off' time and data from the Hoehn and Yahr (H and Y) scale. The EAG suggested that the company could use a similar approach by combining 5 'off' states with 5 health states based on the H and Y scores or from its results for the Movement Disorders Society Modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS). This approach would enable the company to include more than 'off' time in the model and there would be more data from which to derive inputs for the modelled health states. At the second meeting, the clinical experts commented that the H and Y scale may not be a useful additional measure to include, because most benefits of treatment related to the independence of a person with Parkinson's will be captured by their 'off' state. During consultation, the company revised its original model by capping it at 10 'off' hours, with 10 to 16 'off' hours combined into a single 'off' state. This modelling approach was adopted in the company's revised base case. The EAG supported the company's revised approach because there was a lack of data to inform higher 'off' states. As a result, the company's revised approach had fewer health states to be populated by utility values (see section 3.14) and costs (see section 3.15). The company also provided a supportive model, which differed by having 5 grouped

health states corresponding with the categories for time spent in the 'off' state on the MDS-UPDRS scale. The grouped health states were for 0, 1 to 4, 5 to 8, 9 to 12 and 13 to 16 'off' hours. The company considered that the results of the supportive model provided reassurance that its revised model (that was capped at 10 'off' hours) is a reliable basis for decision making. The EAG and the committee preferred the supportive model with grouped health states because, by being combined, these states were informed by more data. The clinical experts added that it was easier to understand clinically what life might be like for people in the different health states when they are grouped. The EAG used the 5 grouped health states model in its preferred base case. The committee concluded that modelling 'off' time was reasonable but 'off' time alone may not capture the range of health effects in advanced Parkinson's that are relevant to the company's decision problem (see section 3.17). The committee also concluded that it preferred the supportive model that had 5 grouped health states, and would use this in decision making.

Natural disease progression

3.11 To model natural disease progression, the company used data from a study by Palmer et al. (2002) to predict how people with Parkinson's move between different health states (the number of 'off' hours each day). For foslevodopa–foscarbidopa and levodopa–carbidopa intestinal gel, natural disease progression was assumed beyond 3 years in the model, and for standard care this was assumed from 6 months (see section 3.9). The committee recalled that the EAG preferred to apply the same assumptions to the standard care arm and to the foslevodopa–foscarbidopa arm (see section 3.9). The EAG agreed with the company that the Palmer et al. (2002) study appears to be the only source of long-term health-state transition data for people with Parkinson's who are taking levodopa. During the committee meeting, the clinical experts agreed that although treatment options and management of Parkinson's symptoms has improved in the 20 years since the Palmer et al. (2002) study was done, the underlying disease progression has not been affected. The EAG noted that the Palmer et al. (2002) study is a limited source with only 2 data points for duration of levodopa treatment: 0 to 4 'off' hours each day and 5 to 12 'off' hours each day. The company and EAG disagreed on the way the 2 data points in the study should be used to model health-state transitions. The company's approach

included using estimated midpoint data to calculate transitions for each health state, while the EAG's approach based transitions on actual midpoint values. The committee concluded that the Palmer et al. (2002) study was a reasonable but limited source of data to inform the modelling of long-term health-state transitions in Parkinson's. Both the company's and EAG's use of the data was associated with some uncertainty, but on balance the committee preferred the EAG's approach.

Effect of stopping treatment

3.12 The patient and clinical experts explained that when people stop treatment for advanced Parkinson's, 'off' time increases within hours. They suggested that it is plausible that some other treatment benefits might continue after treatment is stopped. These relate to the general health and wellbeing effects experienced while on treatment, of having had:

- better sleep
- increased mobility, with falls less likely
- improved functioning
- good fitness.

The clinical experts suggested that while Parkinson's is well controlled a person's ageing may have a trajectory more like that of people without Parkinson's, if there are no other complications or comorbidities. But they highlighted that there is no evidence of levodopa-based treatment having direct neuroprotective effects. In the company's model, people may retain health-related benefits from the improved 'off' time they had while on treatment. After stopping treatment, people are distributed across 'off' states according to the baseline 'off' state distribution until 3 years and natural disease progression is then assumed. This was based on the Palmer et al. (2002) study (see section 3.11). The EAG emphasised that the company modelled treatment effectiveness using daily 'off' hours only. So, the EAG noted that the company should justify how any benefit to the duration of 'off' time (that is, it stays the same or improves) would be retained after stopping

treatment. The EAG also suggested that the company's approach was flawed because it meant that after some months, people discontinuing either foslevodopa–foscarbidopa or levodopa–carbidopa intestinal gel can experience improvements in 'off' time in a way that is clinically implausible. The EAG preferred to assume that, on stopping treatment, people move to the equivalent natural disease 'off' state of people on standard care (which assumes no treatment benefit is retained). The committee concluded that after stopping treatment, people with advanced Parkinson's may retain some benefits related to improvements in general health and wellbeing that were gained while on treatment. But it also concluded that whether any benefit to 'off' time is retained after foslevodopa–foscarbidopa or levodopa–carbidopa intestinal gel is stopped is uncertain. Without further evidence, the committee preferred to assume that no continued treatment benefit is retained.

Evidence on stopping foslevodopa–foscarbidopa

3.13 In the company's model, evidence for people who stopped foslevodopa–foscarbidopa treatment came from the M15-741 study (see section 3.5). The company noted that more people than expected on foslevodopa–foscarbidopa stopped treatment in both pivotal trials (M15-736 and M15-741) because of administration-related adverse events. One of the clinical experts noted that having infections and skin changes contributed to people stopping foslevodopa–foscarbidopa. The company explained that it had taken steps to reduce the likelihood of people in the M15-741 study leaving the study early. For cohort 2 of M15-741 there was an updated protocol, and a new subcutaneous infusion set was introduced for foslevodopa–foscarbidopa administration. Because cohort 2 of M15-741 had the new infusion set, which is the one intended for clinical use, the company considered that this population was an appropriate source of evidence for people stopping foslevodopa–foscarbidopa. The company added that although only a few investigators in the M15-736 trial were familiar with using foslevodopa–foscarbidopa, which it defined as having more than 3 people on treatment, almost three-quarters of investigators were familiar with it in M15-741. The EAG noted that because baseline 'off' time and efficacy evidence in the model was from M15-736, this trial provided the best evidence on stopping

treatment. It noted that a greater proportion of people stopped treatment in the first 3 months in M15-736 compared with in M15-741, and that using M15-741 instead introduces heterogeneity. Stakeholders commented that data from cohort 2 of the M15-741 study was possibly more reflective of the likelihood of stopping treatment if foslevodopa–foscarbidopa was delivered in NHS practice. This is because lessons learned in clinical studies can be implemented in care services. The EAG suggested that the best available data sources for people stopping treatment for each period of the model would be:

- the M15-736 trial from 0 to 3 months
- cohort 2 of the M15-741 study from 3 to 12 months
- the M15-737 study from 12 to 24 months.

It noted that in this scenario, more people on foslevodopa–foscarbidopa were assumed to stop treatment in the first 3 months than in the company's model. The EAG noted that this was a key driver of cost effectiveness. The EAG's preferred assumptions produced incremental cost-effectiveness ratios (ICERs) that suggest foslevodopa–foscarbidopa is not as cost effective as the company's base case suggested, when compared with levodopa–carbidopa intestinal gel and standard care. The committee concluded that the company's modelling of what happens to people after they stop foslevodopa–foscarbidopa was associated with uncertainty. It also concluded that it would consider both approaches.

Utility values

3.14 For the utility assumptions in the model, the company used a linear mixed model to derive a utility estimate for each 'off' health state. This was based on a combined dataset of the foslevodopa–foscarbidopa arms in 4 studies (including M15-736) informing the utility values. The EAG noted that the baseline utility values from the 2 main studies (M15-736 and M15-741) informing the model utility values, differed for the same 'off' health states. The company explained that the combined dataset increased the sample sizes, including those in longer 'off' time health states, which improved the precision of the utility estimates. The EAG preferred to use only M15-736 data to inform the utility values, because this trial

provided the efficacy evidence in the model, including baseline 'off' states. At the first meeting, the EAG noted that the company's approach was a consequence of having a model with a large number of health states and insufficient data to populate these (see section 3.10). It suggested that changes in 'off' time should be aggregated to give larger sample sizes for the utility estimates. It noted that even with the company's combined dataset, the utility estimates for 10 'off' hours and above were based on very few people and so may be very uncertain. The committee recalled that the company's revised and supportive models (see section 3.10) had fewer health states to be populated than its original model, which reduced some uncertainty. At the second meeting, 1 of the clinical experts noted that people in M15-741 could have their foslevodopa–foscarbidopa dose adjusted throughout this open label study. They commented that this could have provided more optimised Parkinson's management than in M15-736 in which continued dosage adjustment was not permitted. The expert suggested that this may be a reason for preferring to use the pooled utility data including M15-741. The EAG noted that it is unclear why age, sex, baseline 'off' hours and treatment duration were not tested as variables in the regressions used by the company to estimate utilities, because some of these characteristics may correlate with quality of life. One of the clinical experts suggested that a person's sex is unlikely to affect quality of life in advanced Parkinson's, but age might. The EAG noted that the company's utility values did not decrease smoothly with increasing 'off' time, which provided clear evidence of external factors influencing quality of life across the 4 trials. A clinical expert suggested that quality of life is likely to be affected by how predictable patterns of 'off' hours are. The committee concluded that both the company's and EAG's utility assumptions were associated with some uncertainty. It also concluded that it would consider both approaches.

Costs

3.15 For the cost assumptions in the model, the company used a regression model fitted to resource-use costs collected in a real-world study (the Adelphi study). The committee noted that this study included people with early, intermediate and advanced stage Parkinson's. The company commented that people with all stages of Parkinson's were included to increase the sample size. The EAG suggested that only resource-use costs for people with advanced Parkinson's should have been used. It added that although this was a smaller group it was

still a reasonable sample size. Stakeholders noted that terms such as intermediate and advanced Parkinson's needed to be clearly defined. They suggested that in the Adelphi study, people with intermediate Parkinson's were most similar to trial populations, and those with advanced Parkinson's were more likely to be in a nursing home. The committee recalled that advanced Parkinson's is not universally defined (see section 3.1). The EAG highlighted that alongside the potential issues of the population that was used to estimate the costs, the company's regressions for health-state costs appeared flawed. The EAG said that this led to costs for each health state being overestimated compared with the observed data available. It noted that this overestimate was largely driven by healthcare professional costs, and the lower 'off' time health states because these had many more people to inform them. It added that for health states with more than 6 'off' hours each day, costs from the regression model were based on very few people, leading to high uncertainty. The committee noted that the company's costing assumptions were affected by its modelling approach, with a large number of health states and insufficient data to populate these (see section 3.10). It also noted that the company's revised and supportive models had fewer health states to be populated than its original model, which reduced some uncertainty. Because the company's regression model did not fit well, the EAG preferred to use direct data from the Adelphi study. At the second meeting, the EAG provided an updated and more complete analysis using observed values from the Adelphi study to inform health-state costs. It noted that using this analysis, the observed cost data was reasonably similar to the company's regression model costs, particularly in the grouped health-state model preferred by the EAG. The committee noted that there was a large difference in costs between the company's and the EAG's updated analysis for the grouped 'off' state of 5 to 8 hours, with the EAG's approach showing little change from 1 to 4 'off' hours. Clinical experts considered that in advanced Parkinson's, the biggest impact of the condition would be seen moving from 1 to 4 'off' hours to 5 to 8 'off' hours each day. They noted that having 5 to 8 'off' hours would impact most of a person's day. The committee noted that the company's modelled costs now appeared more linear across the grouped health-state model and that costs for 5 to 8 hours 'off' appeared more reasonable than in the EAG's updated analysis. The committee concluded that it preferred the company's resource-use cost assumptions and it would consider these in its decision making.

Sleep

3.16 At the first meeting, the committee noted that the benefits of foslevodopa–foscarbidopa for improved sleep could potentially be explored in modelling. During consultation, the company updated the model to include a sleep benefit in the foslevodopa–foscarbidopa arm by adding an improvement in utilities and a cost saving. The company used M15-736 trial data for the Parkinson's Disease Sleep Scale-2 (PDSS-2) in which a score of 18 or more indicates sleep disturbance. Weighted average utility values associated with avoiding sleep disturbance were calculated for foslevodopa–foscarbidopa and standard care. Also, weighted average costs associated with excessive sleepiness were calculated for the 2 arms. The treatment differences for the utilities and costs were applied as a utility benefit and a cost saving to the foslevodopa–foscarbidopa arm of the model. The company noted that there was no equivalent data for levodopa–carbidopa intestinal gel, which is only administered during waking hours and stopped before sleep. So, this was assumed to have the same sleep-related utility and costs as standard care. The EAG noted that in the company's approach to adding a sleep benefit for foslevodopa–foscarbidopa, the costs of excessive sleepiness appeared implausibly high. It also noted that the costs were not specific to sleep and may double-count some of the cost savings from a reduction in 'off' time. The EAG agreed that people would likely have improved quality of life associated with better sleep on foslevodopa–foscarbidopa. But, it did not consider that the company's approach to modelling this was appropriate. The EAG provided an exploratory analysis based on a company scenario, which added PDSS-2 data to the utility regression for the 'off' hours each day. The patient experts explained that even without an increased sleep duration, being more 'on' at night means you do not have to wake up to turn over in bed and when you get out of bed you are less likely to have a fall so are more independent. Care partners added that their own sleep was less disturbed and they were more able to leave the person with Parkinson's alone for some of the time. The clinical experts noted that managing sleep disturbance in Parkinson's is complicated by balancing the side effects of other medicines that cause drowsiness and issues such as rapid eye movement (REM) sleep disorder. The committee noted that the benefits of good sleep in Parkinson's extend into early waking hours. It also noted that neither the company's sleep benefit assumption for foslevodopa–foscarbidopa nor the EAG's exploratory analysis were satisfactory. The committee concluded that

foslevodopa–foscarbidopa is likely to be associated with health-related quality-of-life benefits related to sleep. It concluded that direct cost savings related to these benefits are less clear. It also concluded that health benefits related to sleep were not adequately captured in the modelling.

Cost-effectiveness estimates

Acceptable ICER

3.17 NICE's manual on health technology evaluation notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of confidential commercial arrangements for foslevodopa–foscarbidopa and levodopa–carbidopa intestinal gel, the ICERs are confidential and cannot be reported here. The committee noted a number of uncertainties, specifically:

- that sources of clinical evidence were from a broader population than those in the company's submission (see section 3.5)
- that because of the risk of unblinding in the trial (see section 3.7) the results of the indirect treatment comparison (see section 3.8) were subject to the same uncertainty as the trial results for foslevodopa–foscarbidopa, which likely meant that the cost-effectiveness estimates compared with levodopa–carbidopa intestinal gel were overestimates
- how longer-term data on advanced Parkinson's treated with standard care was modelled (see section 3.11)
- the effect of stopping treatment with foslevodopa–foscarbidopa or levodopa–carbidopa intestinal gel early, and whether any benefit to 'off' time was retained after stopping (see section 3.12)
- the best source of evidence on stopping foslevodopa–foscarbidopa (see section 3.13)

- the utility values used in the modelling, in particular the best source of evidence for this (see section 3.14)
- the resource-use cost assumptions used in the modelling (see section 3.15)
- how a sleep benefit for foslevodopa–foscarbidopa was modelled (see section 3.16)
- potential uncaptured benefits of foslevodopa–foscarbidopa, including non-health factors (see section 3.22).

When considering an acceptable ICER, the committee agreed that this would be at the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Comparison with levodopa–carbidopa intestinal gel

3.18 In the company's revised and EAG's preferred base cases, foslevodopa–foscarbidopa was less expensive and slightly less effective than levodopa–carbidopa intestinal gel. The committee noted that the ICER estimates were in the southwest quadrant of the cost-effectiveness plane. Higher ICERs in the southwest quadrant show that more cost is saved per QALY lost, so they could be considered as evidence of cost effectiveness if the estimates were reliable. The committee concluded that the ICER for foslevodopa–foscarbidopa compared with levodopa–carbidopa intestinal gel was within the range that NICE usually considers an acceptable use of NHS resources. But, the committee recalled that the more important comparator for foslevodopa–foscarbidopa in the company's restricted population was standard care because only around 5% of people have levodopa–carbidopa intestinal gel (see section 3.4).

Comparison with standard care

3.19 In the company's revised base case, foslevodopa–foscarbidopa was less expensive and more effective than standard care (it dominated). But in the EAG's preferred base case, the ICER was substantially higher than £30,000 per QALY

gained (foslevodopa–foscarbidopa was not cost effective). The exact ICERs cannot be reported here because of confidential commercial discounts. The committee noted that while it preferred the modelling approach and most of the assumptions in the EAG base case, it preferred the resource-use cost assumptions in the company's revised base case (see section 3.15). The committee considered the incremental QALY gains that were shown for foslevodopa–foscarbidopa compared with standard care in the company's revised and EAG's preferred base cases. It recalled that for the utility assumptions in the model it would consider both the company's and EAG's approaches (see section 3.14). The committee noted that the small incremental QALYs in the EAG's base case (0.05), which excluded any sleep benefits on health-related quality of life, did not appear to capture the potential quality-of-life benefits that had been described by people with Parkinson's and clinicians for foslevodopa–foscarbidopa. The committee considered that the incremental QALYs of 0.30 in the company's revised base case were more credible, and used this in its preferred base case. The committee explored a scenario based on its preferences that also included the company's assumed cost savings associated with a sleep benefit (see section 3.16). This resulted in ICERs towards the lower end of the £20,000 to £30,000 per QALY gained range. It recalled that the direct cost savings related to sleep benefits were less clear than the health-related quality-of-life effects. But it also noted that the economic modelling of foslevodopa–foscarbidopa was associated with potential uncaptured benefits, including innovative aspects and healthcare system benefits (see section 3.22). Overall, the committee concluded that foslevodopa–foscarbidopa is a cost-effective option when compared with standard care.

Other factors

Equality

3.20 Stakeholders commented that if recommended, foslevodopa–foscarbidopa could become more widely available than some other treatments for advanced Parkinson's, in particular levodopa–carbidopa intestinal gel. Clinical experts agreed that because foslevodopa–foscarbidopa could potentially be provided in a less specialist treatment setting than levodopa–carbidopa intestinal gel,

potentially more people could access treatment. They highlighted that people have difficulty accessing treatment with levodopa–carbidopa intestinal gel (see section 3.3) and this can be exacerbated by features of advanced Parkinson's that make it difficult for people to travel to specialist centres. Parkinson's support groups suggested during consultation that older people, particularly those aged over 75, may not be able to have surgery for levodopa–carbidopa intestinal gel or have deep brain stimulation, so they have fewer treatment options. They also noted that people with visual or cognitive impairments may find using the foslevodopa–foscarbidopa subcutaneous pump difficult. A clinical expert commented that pump-based treatments might be less acceptable in some cultural or ethnic groups. The committee noted that if the technology is recommended, a clinician would need to determine if it is suitable for a person with advanced Parkinson's by considering their individual needs. This would include any difficulties they might have using foslevodopa–foscarbidopa. Stakeholders emphasised that although Parkinson's predominantly affects people aged over 65, many working-age people are also living with the condition. They also noted that Parkinson's is a movement-related disorder than can cause physical disability. The committee acknowledged that age, disability, race, and religion or belief are protected characteristics under the Equality Act 2010.

Severity

3.21 NICE's advice about conditions with a high degree of severity did not apply.

Innovation

3.22 The committee considered if foslevodopa–foscarbidopa was innovative, and concluded that not all potential additional benefits were captured by the model, including innovative aspects. People with advanced Parkinson's, their families and clinicians described foslevodopa–foscarbidopa as transformative. Clinical experts explained that it is the unpredictability of motor symptoms that can make day-to-day life very difficult for people with advanced Parkinson's. They added that while the active components of the treatment are not very different to standard levodopa, the same predictability of improved symptoms has not been seen in other levodopa-based treatments. They noted that good dopamine

control has many potential benefits beyond motor symptoms in advanced Parkinson's. These benefits include improved non-motor symptoms, blood pressure and bladder control, and fewer problems with sleep and mood. A patient expert who is taking the treatment emphasised the benefits of having good overnight dopamine control with a continuous infusion. They explained that on waking in the morning they could get out of bed and use the bathroom without help. They explained that this is unlike taking oral treatment, with which dopamine levels can fall overnight, to a level that means people are in an 'off' state when they wake up. This takes time to resolve after taking the first dose of the day, during which time people can be dependent on carers. The clinical experts noted that extra years of well-controlled symptoms enable people with advanced Parkinson's to have improved general health and be mentally and socially active. This also has an impact on the quality of life of family members and carers. They added that people with advanced Parkinson's who have well-controlled symptoms are also less likely to have falls, which reduces the risk of hospital admissions and subsequent infections. A clinical expert recalled that people with advanced Parkinson's may take several different medicines (see section 3.3) and if standard care is not working well, it can take many months to adjust and improve. Having more continuous dopamine control with foslevodopa–foscarbidopa could reduce the need for some other treatments or allow them to be stopped. They added that this has benefits for people with advanced Parkinson's and clinicians in simplifying Parkinson's management. The clinical experts also highlighted benefits related to the mode of administration of foslevodopa–foscarbidopa compared with other treatments. They noted that it is simple to start and is easily reversible if it is not working well. They recalled that foslevodopa–foscarbidopa could possibly be provided in a less specialist healthcare setting than levodopa–carbidopa intestinal gel (see section 3.4), which may be associated with cost savings. They added that another benefit of avoiding referral to a tertiary centre is that people continue to have treatment with their usual doctor who knows them well. The committee concluded that despite the uncertainties around the ICERs for foslevodopa–foscarbidopa, it may have additional benefits that were not captured in the economic modelling, including innovative aspects and healthcare system benefits. The committee included this in their consideration of the range of scenarios that it would consider, particularly around potential sleep benefits (see section 3.19).

Conclusion

Recommendation

3.23 The committee considered that the cost-effectiveness estimates for foslevodopa–foscarbidopa are uncertain. It acknowledged the high unmet need, and the many potential benefits this treatment could bring and that some benefits were not captured in the modelling. The committee concluded that even when considering the uncertainty, the most likely ICERs for foslevodopa–foscarbidopa were within the range that NICE usually considers an acceptable use of NHS resources. So, foslevodopa–foscarbidopa is recommended for treating advanced levodopa-responsive Parkinson's in adults whose symptoms include severe motor fluctuations and hyperkinesia or dyskinesia, when available medicines are not working well enough, only if they cannot have apomorphine or deep brain stimulation, or these treatments no longer control symptoms.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced levodopa-responsive Parkinson's with severe motor fluctuations and hyperkinesia or dyskinesia and available medicines are not working well enough and the doctor responsible for their care thinks that foslevodopa–foscarbidopa is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas
Vice chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Catherine Spanswick
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Accreditation