NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using foslevodopa–foscarbidopa in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using foslevodopa–foscarbidopa in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 21 June 2023
- Second evaluation committee meeting: 11 July 2023
- Details of the evaluation committee are given in section 4

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1 Recommendations

1.1 Foslevodopa–foscarbidopa is not recommended, within its marketing authorisation, for treating advanced levodopa-responsive Parkinson's disease in adults whose symptoms include severe motor fluctuations and hyperkinesia or dyskinesia, when available treatments are not working well enough.

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 a continuous infusion under the skin (subcutaneous). For this evaluation, the company asked for it to be considered only for people who cannot have apomorphine or deep brain stimulation, or for when these treatments are no longer controlling symptoms. This does not include everyone who foslevodopa–foscarbidopa is licensed for.

Clinical trial evidence suggests that foslevodopa–foscarbidopa improves motor symptoms compared with oral levodopa–carbidopa. 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. The results from indirect comparisons of foslevodopa–foscarbidopa with levodopa–carbidopa intestinal gel and standard care are uncertain and do not include all the relevant data.

Problems with the design of the company's economic model mean that it is not suitable for decision making. These problems include:

- a lack of data to inform the large number of health states, including quality of life and cost data
- uncaptured health effects of advanced Parkinson's
- how stopping treatment is modelled.

This means that it is not possible to determine a reliable cost-effectiveness estimate or if foslevodopa–foscarbidopa is an acceptable use of NHS resources. So, it is not recommended. There is a high unmet need for treatments that control motor symptoms of advanced Parkinson's, and foslevodopa–foscarbidopa has many potential benefits. So, an improved economic model is needed to make it more suitable for decision making.

2 Information about foslevodopa–foscarbidopa

Marketing authorisation indication

2.1 Foslevodopa–foscarbidopa is indicated for '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 per 10-ml vial for infusion (excluding VAT; company submission).

2.4 The company has a commercial arrangement, which would have applied if foslevodopa–foscarbidopa had been recommended.

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 disease (from now, called Parkinson's because this is the term generally preferred by people with the condition), 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 hyperkinesia (excessive movements) or dyskinesia (involuntary movements). 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 planning and doing everyday tasks becomes increasingly difficult. They also described feeling that they were a burden on their family. Brain fog and fatigue means 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

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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 (see section 3.3) reduces. 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 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 over 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. 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 in the NICE guideline on Parkinson's disease in adults). Levodopa is usually taken with dopa decarboxylase inhibitors, such as carbidopa, which increases the availability of levodopa in the brain. 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. A patient expert explained that taking many tablets, some of which have rigid conditions on how they are taken for optimal absorption, can mean inflexible timing of meals, which can affect family life. The following non-oral treatments may be used in advanced Parkinson's that is not controlled on standard care (also called best medical therapy): apomorphine, deep brain stimulation (see the NICE interventional procedures guidance on deep brain stimulation for Parkinson's disease) or levodopa–carbidopa intestinal gel. Clinical experts noted that strong dopamine agonists when given orally can be associated with troubling side effects related to impulse control, so apomorphine (a dopamine agonist) is given by intermittent injection or continuous subcutaneous infusion. They added that deep brain stimulation carries risks associated with surgery and is more effective for people with symptoms such as stiffness and tremor. One of the clinical experts explained that there are strict criteria for using levodopa–carbidopa intestinal gel in NHS clinical practice (see NHS England's clinical commissioning policy on levodopa–carbidopa intestinal gel) and people can have difficulty accessing treatment because it is only available in tertiary centres. They added that having levodopa–carbidopa intestinal gel needs a tube 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

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 3.10). The company noted 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. 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 having foslevodopa–foscarbidopa is more straightforward than having 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. The committee considered that people for whom apomorphine or deep brain stimulation is suitable may be a

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relevant additional population for the company to include. It 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 prefer 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 M15-736 had advanced, levodopa-responsive Parkinson's with motor fluctuations that was inadequately controlled by current treatment, with at least 2 'off' hours per day. The company also provided supporting evidence from non-comparative safety studies of foslevodopa–foscarbidopa, 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, the extent to which the effectiveness of foslevodopa–foscarbidopa differs between the populations in the clinical evidence and the narrower population in the company's population remains uncertain. The committee 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 endpoint 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 on standard care. It suggested that the trial benefit seen in this treatment arm did not reflect the expected treatment effect of standard care outside of a 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 when each dose is taken. Clinical advisers to the company and EAG considered that the trial was well designed and that there was no better approach that

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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 the 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. 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 comparisons

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 3.10). 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 adjust 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 report 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 had 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 concluded that the results of the indirect comparison of foslevodopa–foscarbidopa against levodopa–carbidopa intestinal gel were uncertain.

Comparison with standard care

3.9 The committee recalled that the M15-736 trial had a standard care arm of oral levodopa–carbidopa, allowing a direct comparison of foslevodopa–foscarbidopa with standard care. The company suggested that because foslevodopa–foscarbidopa is positioned for people whose symptoms are not controlled by standard care, then it is reasonable to assume standard care gives no clinical benefit, which is equivalent to natural disease progression. The company noted that a 1-hour treatment benefit was observed in the standard care arm of M15-736 (see section 3.6). It considered that this was because of the increased interaction with the healthcare system experienced by people in the trial setting. So, the company did a naive (unadjusted) indirect comparison of foslevodopa–foscarbidopa against standard care. It used the M15-736 trial for foslevodopa–foscarbidopa and, for standard care, used a publication by Palmer et al. (2002) which describe the natural disease progression of

Parkinson's. The EAG highlighted that the company's approach was inconsistent because it used evidence from the standard care arm of M15-736 for adverse events. The company noted that compared with standard care, people having foslevodopa–foscarbidopa or levodopa–carbidopa intestinal gel have greater interaction with the healthcare system. The EAG explained that in the company's modelling, similar interaction with the healthcare system is assumed for foslevodopa–foscarbidopa as for standard care. Also, the company had reduced the number of administration appointments needed for foslevodopa–foscarbidopa in its modelling, making it less like a trial setting. The EAG emphasised that the 1-hour treatment benefit is likely to have occurred in both arms. The benefit reported for foslevodopa–foscarbidopa in M15-736 (see section 3.6) was assumed to be maintained for 3 years during the last observation carried forward (LOCF) period. The EAG added that it is implausible that the small number of additional titration visits for foslevodopa–foscarbidopa compared with standard care included in the model would lead to this sustained benefit. The EAG said that it had concerns about the way in which data from Palmer et al. (2002) was interpreted by the company (see section 3.12). The EAG had asked the company to provide a scenario in which the M15-736 standard care arm was used instead of Palmer et al. (2002) data in the comparison with foslevodopa–foscarbidopa. But this scenario was not provided. As a result, the impact of using M15-736 standard care effectiveness data on the company's cost-effectiveness estimate for foslevodopa–foscarbidopa was unknown. The committee concluded that data from the M15-736 trial would allow a direct comparison of foslevodopa–foscarbidopa against standard care. It added that the company should have explored this approach in its modelling of clinical effectiveness. The committee also concluded that the company's naive indirect comparison introduced considerable uncertainty into the modelled comparison of foslevodopa–foscarbidopa against standard care.

Economic model

Company's modelling approach

3.10 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. 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. The committee noted that the model had a large number of health states (see section 3.11). In the first stage of the model, people could move between any of the 17 health states so that 'off' hours could improve, stay the same or worsen. This model stage was informed by the M15-736 trial (up to 3 months) and an LOCF period (3 to 36 months). Then in the second stage of the model, 'off' hours could stay the same or worsen by 1 hour in each cycle. Each health state was associated with different quality of life and cost estimates, which were combined across model cycles and compared between treatments. The first and second model cycles were 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. But, 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. The committee concluded that the company's general approach of using a Markov model was reasonable but the model had a large number of health states.

Health states

3.11 The EAG highlighted that the company modelled 'off' hours only, and considered these may not fully reflect the heterogeneity of Parkinson's. It also noted its concern with the large number of 'off' states (17 health states; see section 3.10). It considered that the company did not have enough data to produce reliable efficacy, utility and cost estimates for

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these. It added that this compounded problems with deriving the utility values (see section 3.16) and costs (see section 3.17) used in the modelling. 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 17 'off' states, is a clinically meaningful change in 'off' time per day. The company and EAG both did model validation exercises that compared the company's model with a published model by Chaudhuri et al. (2022) of levodopa–carbidopa intestinal gel cost effectiveness. The Chaudhuri model combined 'off' time with the Hoehn and Yahr (H and Y) scale as a measure of Parkinson's symptom progression. The company noted that its validation exercise, which explored how 'off' hours changed over time, supported the company's approach. The EAG explained that its validation exercise compared health-state utility and cost inputs from the 2 models. This exercise showed significant variation in health-related quality of life and costs, separately from any variation in 'off' time. The company suggested that H and Y scores included in the Chaudhuri model does not capture quality of life. It added that as a clinical measure of Parkinson's progression, the H and Y scale is not a relevant measure of a person's experience of their condition. The EAG noted that an increase in H and Y score reduces the quality-of-life benefit gained from reduced 'off' hours, implying that the company's model may overestimate this benefit for later time periods. 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 timing (for example, early morning) of the 'off' state. The EAG reported that its model validation exercise showed that a large number of 'off' states in the analysis did not appear to produce valid results. This was particularly in the longer 'off' states, because of a lack of data. The EAG noted that most other Parkinson's models incorporated 'off' time and data from H and Y. 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 scale. It suggested that data could be derived from its results for the Movement Disorders Society Modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS), or could use MDS-UPDRS data directly instead of H and Y scores. 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. The committee concluded that modelling 'off' time alone did not capture the range of health effects in advanced Parkinson's that are relevant to the company's decision problem. Also, the company had insufficient data to inform the large number of 'off' states in its model.

Interpretation of Palmer et al. (2002) study data

3.12 In addition to its use in the indirect treatment comparison of foslevodopa–foscarbidopa against standard care (see section 3.9), the company used data from the Palmer et al. (2002) study to model how people with Parkinson's move between different health states ('off' hours) for all treatments: foslevodopa–foscarbidopa, levodopa–carbidopa intestinal gel and standard care, beyond 3 years. 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, 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 per day and 5 to 12 'off' hours per day. The company and EAG disagreed on the way in which the 2 data points should be used to model health-state transitions. 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 justification for it approach.

Effect of stopping treatment

3.13 Patient and clinical experts explained that when people stop treatment for advanced Parkinson's, 'off' time worsens 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 of having had better sleep, increased mobility, improved functioning and good fitness while on treatment. Clinical experts suggested that while Parkinson's is being well controlled, a person's ageing may have a trajectory more like that of people without Parkinson's. 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, after which natural disease progression (based on the Palmer et al. [2002] study; see section 3.12) is assumed. The EAG emphasised that the company modelled treatment effectiveness using daily 'off' hours only. So, it should justify how any benefit to 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 most recent natural disease 'off' state of people on standard care (assuming 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

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levodopa–carbidopa intestinal gel is stopped is uncertain. Without further evidence, the committee preferred to assume no continued treatment benefit is retained.

Evidence on stopping foslevodopa–foscarbidopa

3.14 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 a large number of people on foslevodopa–foscarbidopa stopped treatment in both pivotal trials (M15-736 and M15-741) because of administration-related adverse events. A clinical expert 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 made foslevodopa–foscarbidopa less cost effective than levodopa–carbidopa intestinal gel and standard care, compared with the company base case. 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.

Troublesome dyskinesia

3.15 Dyskinesia in advanced Parkinson's (see section 3.2) is a symptom that could be recorded in the Parkinson's diary in the trial as troublesome or non-troublesome. The company included dyskinesia in its modelling as an adverse event, but not as a symptom (troublesome dyskinesia) when recorded in the Parkinson's diary. It noted that in the M15-736 trial, troublesome dyskinesia was rare in both treatment arms and lasted less than 1 hour. The company assumed the same low rate of adverse event dyskinesia for foslevodopa–foscarbidopa as for levodopa–carbidopa intestinal gel, which it considered conservative for levodopa–carbidopa intestinal gel. The EAG suggested that troublesome dyskinesia is a source of unaccounted burden for people in the company's model because of the discrepancy between symptoms recorded in the Parkinson's diaries and adverse events reported. The EAG added that although short-term trial data was available, longer-term modelling of troublesome dyskinesia was difficult because of a lack of data. It agreed with the company that management of dyskinesia in clinical practice has improved significantly. Stakeholders commented that dyskinesia can

cause worry and stigma but that a minority of people with Parkinson's experience dyskinesia. They also explained that people with Parkinson's would prefer to have 'on' time with dyskinesia than to have 'off' time. The committee concluded that not including troublesome dyskinesia in the model was reasonable.

Utility values

3.16 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 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 baseline 'off' states and efficacy evidence in the model. It 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 3.11). The EAG suggested that changes in 'off' time should be aggregated to give larger sample sizes for the utility estimates (for example, 0% to 25%, 26% to 50%, 51% to 75%, and 76% to 100% of the day spent in 'off' time). It noted that even with the company's combined dataset, the utility estimates for 'off' time health states 10 and beyond were based on very few people and so may be very uncertain. It suggested that more utility data could be obtained by incorporating MDS-UPDRS scores into the modelling. The EAG also noted that it is unclear why age, gender, 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. A clinical expert suggested that gender 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 the company's utility assumptions were associated with high uncertainty. It also concluded that this was partly a result of the company's model structure including the large number of health states.

Costs

3.17 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 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 real-world 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 used to estimate the costs, the company's regressions for health-state costs appeared flawed, leading to costs being overestimated. It noted that this was largely driven by healthcare professional costs, and the lower 'off' time health states which had more data to inform them. It added that for health states with more than 6 'off' hours per 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

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these (see section 3.11). Because the company's regression model did not fit well, the EAG preferred to use direct data from the real-world study. It asked the company to provide cost data for the advanced Parkinson's subset, but the company did not provide it. So, the EAG's exploratory analysis using direct cost data was based on people with all stages of Parkinson's. The EAG noted that using direct cost data substantially reduced resource-use costs. This had a large impact on the incremental cost-effectiveness ratio (ICER), which changed the cost-effectiveness result for the comparison of foslevodopa–foscarbidopa against standard care. It cautioned that if this exploratory analysis was based on the advanced Parkinson's subset only, higher costs would be expected. But the costs are unlikely to be as high as those assumed by the company. The committee concluded that the company's resource-use cost assumptions appeared flawed and were associated with high uncertainty. It also concluded that this was a result of the company's model structure including the large number of health states. But it noted the limitations of the EAG's approach and considered that the costs may be somewhere between the company's and the EAG's estimates.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.18 The company submitted ICERs for foslevodopa–foscarbidopa compared with levodopa–carbidopa intestinal gel and standard care, incorporating a patient access scheme discount. The ICERs cannot be presented because they include confidential discounted prices for foslevodopa–foscarbidopa, levodopa–carbidopa intestinal gel and pramipexole, which is a component of standard care. The EAG could not provide a preferred base case because of:

- uncertainty in the clinical evidence, including that standard care evidence from M15–736 was not used (see section 3.9)

- concerns with the modelling approach including the large number of health states (see sections 3.10 and 3.11)
- uncertainty associated with the assumptions for utilities (see section 3.16) and costs (see section 3.17).

In the company's base case, foslevodopa–foscarbidopa was less costly and less effective than levodopa–carbidopa intestinal gel. Applying the EAG's scenarios and preferred assumptions to the company's base case suggested that foslevodopa–foscarbidopa continued to be less costly and less effective (with an ICER above £30,000 per quality-adjusted life year [QALY] lost) 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 noted that there was a large difference between the deterministic and probabilistic ICERs in the comparison of foslevodopa–foscarbidopa against levodopa–carbidopa intestinal gel. The EAG noted that this was mainly because of the non-linear impact on the ICER of varying the levodopa–carbidopa intestinal gel's relative risk in the network meta-analysis informing the model. The committee recalled that few people have levodopa–carbidopa intestinal gel (see section 3.3) and the most likely comparator for foslevodopa–foscarbidopa in the company's restricted population was standard care.

In the company's base case, foslevodopa–foscarbidopa was less costly and more effective than standard care (it dominated). But applying the EAG's scenarios and preferred assumptions to the company's base case suggested that foslevodopa–foscarbidopa was not cost effective. It became substantially more costly than standard care compared with the company's base case, and the ICER was substantially higher than £30,000 per QALY gained.

The EAG noted that of the scenarios it explored, those with the biggest impact on the cost-effectiveness estimates for foslevodopa–foscarbidopa were:

- assuming equal efficacy of foslevodopa–foscarbidopa against levodopa–carbidopa intestinal gel in the indirect treatment comparison (see section 3.8)
- using a combination of evidence from M15-736, cohort 2 of M15-741 and M15-737 for data on people stopping treatment with foslevodopa–foscarbidopa (see section 3.14)
- using direct data to inform health-state resource-use costs (see section 3.17).

The committee considered that the company's and the EAG's estimates were subject to substantial uncertainties, including:

- that sources of clinical evidence were from a broader population than those in the company's submission (see section 3.5), which had an unclear impact on the cost-effectiveness results
- that the reliability and magnitude of any treatment effect (see section 3.7) likely meant that the foslevodopa–foscarbidopa cost-effectiveness estimates compared with both comparators presented to the committee were overestimates, particularly for the comparison with standard care
- that the results of the indirect treatment comparisons (see sections 3.8 and 3.9) were subject to the same uncertainty as the trial results for foslevodopa–foscarbidopa (see section 3.7), which had an unclear impact on the cost-effectiveness results
- that the naive indirect comparison of foslevodopa–foscarbidopa against standard care did not incorporate trial evidence for standard care (see section 3.9), which had an unknown impact on the cost-effectiveness results because the company did not explore using standard care evidence from the trial

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- that the model had a large number of health states and the company has insufficient data to inform these; this was a key problem that led to other uncertainties (see section 3.11) and had an unclear impact on the cost-effectiveness results
- how longer-term data on advanced Parkinson's treated with standard care was modelled (see section 3.12), which had an unclear impact on the cost-effectiveness results
- 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 3.13), which had an unclear impact on the cost-effectiveness results
- the best source of evidence on stopping foslevodopa–foscarbidopa (see section 3.14), which had a large impact on the cost-effectiveness results of foslevodopa–foscarbidopa compared with levodopa–carbidopa intestinal gel
- the utility values used in the modelling (see section 3.16), which had an unclear impact on the cost-effectiveness results
- the resource-use cost assumptions used in the modelling (see section 3.17), which had a large impact on the cost-effectiveness results of foslevodopa–foscarbidopa compared with standard care
- potential uncaptured benefits of foslevodopa–foscarbidopa (see section 3.21), which had an unclear impact on the cost-effectiveness results.

Section 6.3 of NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICERs. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee recalled the clinical and modelling uncertainties summarised above and noted that these increased the uncertainty in the cost-effectiveness results. So, the committee

considered that the benefits and costs of treatment with foslevodopa–foscarbidopa were highly uncertain.

Other factors

Equality

3.19 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, 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 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 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 and disability are protected characteristics under the Equality Act 2010. The committee concluded that none of the equality issues raised were relevant to the recommendation. This is because the committee's recommendation does not restrict access to treatment for some people over others.

Severity

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

Innovation

3.21 People with Parkinson's, their families and clinicians described foslevodopa–foscarbidopa as transformative. Clinical experts explained that it is the unpredictability of motor symptoms than 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 has not been seen in other levodopa-based treatments. They noted that good dopamine control has potential benefits beyond motor symptoms in advanced Parkinson's, including reducing 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 oral treatment because 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 committee noted that the benefits of foslevodopa–foscarbidopa on sleep could potentially be explored in modelling. Clinical experts also highlighted benefits related to the mode of administration of foslevodopa–foscarbidopa compared with other treatments. They noted that extra years of well-controlled symptoms enable people with advanced Parkinson's to retain expected levels of health and be mentally and socially active. This also has an impact on the quality of life of family members and carers. Clinical experts 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

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Parkinson's may take several different medicines (see section 3.3), and 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 Parkinson's and clinicians in simplifying Parkinson's management. Clinical experts 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. The committee concluded that foslevodopa–foscarbidopa may have additional benefits that were not captured in the economic modelling, including innovative aspects. But the likely impact of these benefits on the cost-effectiveness results was unclear because of the uncertainties and issues in the modelling described in section 3.18.

Conclusion

Recommendation

3.22 The committee concluded that because of the uncertainty in the clinical evidence and problems with the design of the company's economic model, it was not possible to determine a reliable cost-effectiveness estimate. So, it could not determine if foslevodopa–foscarbidopa is an acceptable use of NHS resources (see 3.18). So, foslevodopa–foscarbidopa is not recommended for treating advanced levodopa-responsive Parkinson's disease in adults whose symptoms include severe motor fluctuations and hyperkinesia or dyskinesia, when available treatments are not working well enough. The committee acknowledged the high unmet need and the many potential benefits this treatment could bring, so it encouraged the company to address as many of the modelling issues as possible in response to the consultation.

4 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
Technical lead

Elizabeth Bell
Technical adviser

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