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

Part 1 slide for committee – contains redacted information

Technology appraisal committee C [12 September 2023]

Chair: Richard Nicholas

Evidence assessment group: BMJ

Technical team: Catherine Spanswick, Elizabeth Bell, Victoria Kelly, Ross Dent

Company: AbbVie

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ACM1 conclusion: foslevodopa-foscarbidopa is not recommended

- Because of 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

Approach for 2nd committee meeting (ACM2)

Part 1 slides will cover:

- **Technology and treatment pathway recap**
- **ACM1 conclusions and stakeholder comments**
- **Key issues at ACM2**
- **Results summary and base case assumptions**

Confidential results presented in Part 2

Please refer to ACM1 slides for:

- Background on Parkinson's
- Decision problem
- Clinical evidence (trial evidence and indirect treatment comparisons)
- Other considerations (equality; company assessment of uncertainty; severity)

Technology and treatment pathway recap

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RECAP

Foslevodopa-foscarbidopa (Produodopa, AbbVie)

Technology details

Marketing authorisation	• 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
Mechanism of action	• A prodrug combination of levodopa and carbidopa • Levodopa is metabolised to dopamine once it has reached the brain, improving nerve conduction and reducing the physical symptoms associated with Parkinson's • Carbidopa prevents metabolism of levodopa until it has crossed the blood-brain barrier
Administration and dosing	• By continuous subcutaneous infusion via a pump (24 hours a day) • Dose adjusted to reach clinical response: maximal functional 'ON' time and minimal number and duration of OFF episodes and ON episodes with troublesome dyskinesia • Maximum recommended daily dose is 6000 mg (25 ml fos-fos per day, equivalent to approximately 4260 mg of levodopa per day) • People with Parkinson's or carers can independently administer an extra dose to manage acute OFF symptoms experienced during continuous infusion
List price	• **Fos-fos ~£31,000 per year**: £592.90 per week or £84.70 per 10 ml vial (per day [max. recommended 25 ml per day]) • Confidential simple patient access scheme (PAS) discount

Abbreviations: max. maximum; MHRA, Medicines and Healthcare products Regulatory Agency; ml, millilitre

Treatment pathway for advanced Parkinson's that is levodopa-responsive with severe motor fluctuations and hyperkinesia or dyskinesia

RECAP

ACM1 conclusion

- Company's narrower population reflects greatest area of unmet need, but committee would prefer fos-fos to be evaluated for all people within its marketing authorisation

ACM1 conclusion

- People for whom apomorphine or DBS is suitable may also be a relevant to include

Foslevodopa-foscarbidopa (fos-fos)

Technology being appraised

LCIG (levodopa-carbidopa intestinal gel, continuously delivered into small intestine via pump)*

Suitability criteria:
- Apomorphine or DBS unsuitable
- ≥50% OFF periods

BMT (amantadine and levodopa plus adjunct therapies†)

Used when LCIG, apomorphine or DBS are unsuitable

Comparators in company model

*LCIG has NHS Commissioning Policy

Apomorphine (+/- BMT)

DBS

Suitable for some people with advanced Parkinson's but not included as comparators in company modelling

Not included as comparators

Broader population preferred by clinicians at ACM1, but positioning of fos-fos unchanged at ACM2 and narrower than fos-fos marketing authorisation

Abbreviations: BMT, best medical therapy; DBS, deep brain stimulation; fos-fos, foslevodopa-foscarbidopa; LCIG, levodopa-carbidopa intestinal gel

ACM1 conclusions and stakeholder comments

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Summary of stakeholder comments on draft guidance

Consider fos-fos may offer benefits over existing treatments for Parkinson's

Association of British Neurologists (also endorsed by Royal College of Physicians):

- Those unsuitable for apomorphine or DBS are frailer with possibly worse outcomes than study populations
- Agree that fos-fos should be evaluated across its marketing authorisation – could potentially be used over LCIG or DBS as is much easier to start/stop and therefore more reversible, and not requiring surgery
- Agree with EAG's conclusion of equal efficacy for fos-fos and LCIG

Parkinson's UK

- Encourage NICE to represent the perspective of care partners of people with Parkinson's in the evidence
- We support the position argued by clinical experts that fos-fos might be a preferred treatment option in Parkinson's, because it is less invasive and easier to use. Comments from people with Parkinson's in our latest submission reiterate this
- Committee's decision to not recommend fos-fos could mean that older people with Parkinson's, especially those over 75 and who are unsuitable for DBS and less likely to have surgery for LCIG will be disadvantaged – **potential equality consideration**

Patient expert: emphasises need for qualitative assessment, for example considering benefits in terms of ability to continue working and improved mental states associated with good control of Parkinson's

Abbreviations: DBS, deep brain stimulation; fos-fos, foslevodopa-foscarbidopa; ICER, incremental cost-effectiveness ratio; LCIG, levodopa-carbidopa intestinal gel

Key issues at ACM2

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Key issues at ACM2

ICER impact*: Large

Key issues following consultation on draft guidance: focus of ACM2 discussion because company or EAG approach has changed

Key issues	**Resolved?** Company approach at ACM2
Limitations with original modelling approach, including high number of OFF states	**Partially**: capped/fewer health states in revised and supportive models
Uncaptured benefits of foslevodopa-foscarbidopa	**No**: Uncertainty. *Sleep benefit in fos-fos arm*
Robustness of utility values used in modelling	**Partially**: fewer health states, *but maintains use of pooled data*
Resource-use cost assumptions used in modelling	**Partially**: fewer health states, *but maintains regression approach*
Use of M15-736 trial data to model BMT OFF time and assumptions	**Partially**: M15-736 trial data now included, *but assumptions applied are questioned*

**Further explanation of impacts of EAGs preferred assumptions on fos-fos cost-effectiveness results presented later in Part 1 and in Part 2*

Abbreviations: ACM2, 2nd appraisal committee meeting BMT, best medical therapy

Other key issues at ACM2

*ICER impact: Large  Unknown  Quadrant change 

Other key issues following consultation on draft guidance: not the focus of ACM2 discussion because no change to company's approach or now resolved

Key issues	**Resolved?** Company approach at ACM2
Generalisability of M15-736 trial population to population of interest and reliability and magnitude of treatment effect	**No:** Uncertainty. *No change at ACM2* [See slides 14-15 in ACM1 Part 1 deck]
LCIG comparison: company maintains improved efficacy seen with fos-fos, EAG assumes equal efficacy	**No:** Uncertainty. *No change at ACM2* [See slides 17-18 in ACM1 Part 1 deck]
Modelling long term natural disease progression (Palmer): company maintains extrapolation approach, EAG maintains this approach is inappropriate	**No:** Uncertainty. *No change at ACM2* [See slides 20-21 in ACM1 Part 1 deck]
Uncertain benefit after stopping treatment: company maintains people are redistributed to baseline, EAG maintains people should revert to BMT outcomes	**No:** Uncertainty. *No change at ACM2* [See slides 29-30 in ACM1 Part 1 deck]
Discontinuation data: use of M15-736 trial data for first cycle (3 months)	**Yes.** M15-736 data now included

**Further explanation of impacts of EAGs preferred assumptions on fos-fos cost-effectiveness results presented later in Part 1 and in Part 2*

Abbreviations: ACM1 or 2, 1st or 2nd appraisal committee meeting; LCIG, levodopa-carbidopa intestinal gel

Key issue: Limitations with company's original modelling approach including high number of OFF states

Company adjusts original model and provides additional supportive model

ACM1 conclusion

- Company's model has many health states and little quality of life and cost data to inform them

Stakeholder comments – ABN

- Clinical significance of differentiating between such a large number of health states is not clear

Company's consultation comments:

- Original model more representative of daily fluctuations in OFF time in Parkinson's and hourly changes are clinically meaningful, so is retained for cost-effectiveness evaluation

Model	Company's approach at ACM2	EAG's comment and preference
Original	**Revised with health states capped at OFF 10 hours** – conservative approach	Agrees with capping at OFF 10 due to lack of available data
Additional supportive	Has 5 grouped OFF states corresponding with MDS-UPDRS stage	**Prefers this 5-state model** for base case

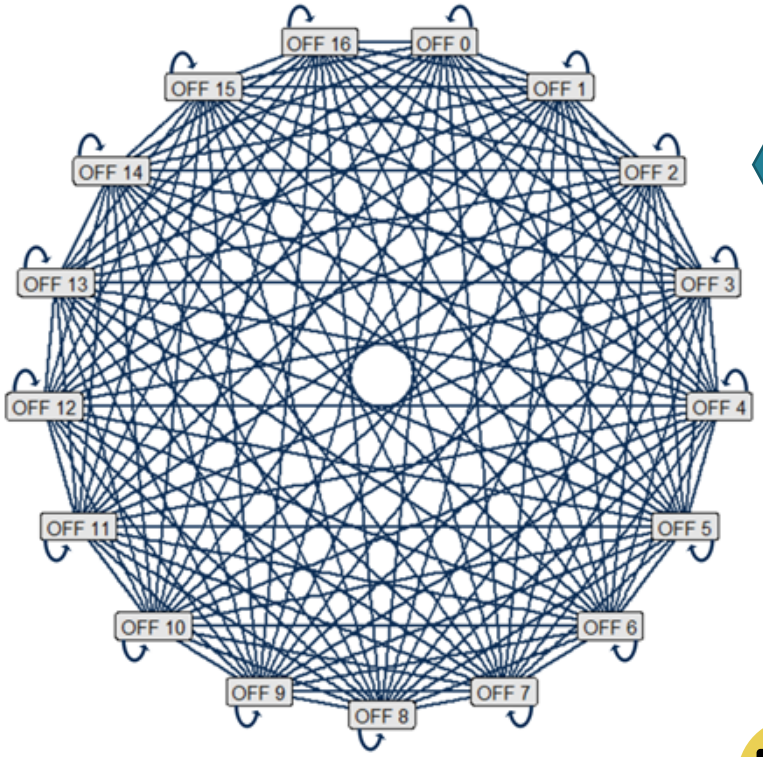
Abbreviations: ABN, Association of British Neurology; ACM2, 2nd appraisal committee meeting; MDS-UPDRS; Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale

Company's revised modelling approach: model structures

Includes 2 Markov health state transition models

Revised original model:

- 17 health states for 0 to 16 hours OFF time
- **Capped at 10 OFF hours:** 11 unique states of 0 to 9 hours OFF time and 10+ hours OFF time



Within trial + LOCF model
transitions possible between all health states within trial period (3 months) and LOCF period (from 3 to 36 months) when trial effect continues with no transition possible

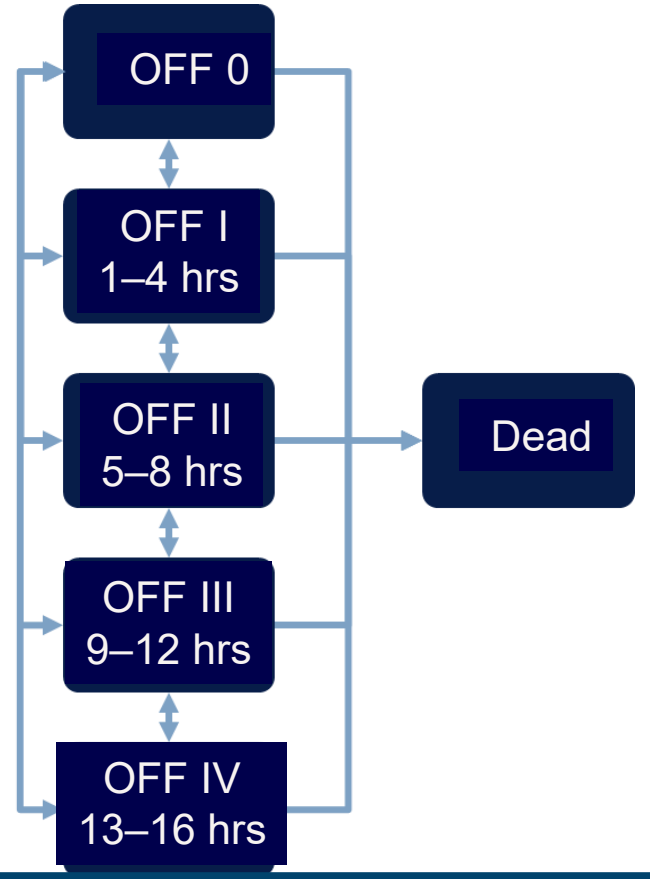
After trial + LOCF period
to end of model time horizon (20 years), OFF state hours can stay the same or worsen

Used in company's revised base case

Which modelling approach does the committee prefer?

Additional supportive mode:

- 5 grouped health states for 0 to 16 hours of OFF time, as 0 hours then grouped 4-hourly



EAG's preferred base case
(none preferred at ACM1)

Abbreviations: hrs, hours; LOCF, last observation carried forward

Key issue: Uncaptured benefits of fos-fos

Company maintains OFF time most suitable outcome and now incorporates sleep

ACM1 conclusion

- By modelling OFF hours only, there are uncaptured health effects of advanced Parkinson's, including effects on sleep
- Other models include Hoehn & Yahr (H&Y) scale, a measure of symptom progression
- Fos-fos may have additional benefits not captured in modelling, including innovative aspects

Stakeholder comments – Parkinson's UK

- Testimony: *"My sleep pattern was very erratic, but on [fos-fos] it has started to improve as the meds are being delivered 24 hours, which is a positive key aspect of this drug's delivery"*

Company's consultation comments:

- OFF time is most suitable outcome to model in Parkinson's, supported by clinical experts
- Disagree on including H&Y states – would lead to many health states in model and would not address committee's concerns about uncaptured benefits of fos-fos
- Patient expert emphasised sleep benefits due to continuous 24-hour infusion of fos-fos
- In M15-736 trial, fos-fos significantly improved sleep (PDSS-2 scale) and significantly reduced early morning OFF time (akinesia) compared with vs LD/CD

Abbreviations: EAG, evidence assessment group; H&Y, Hoehn & Yahr; LCIG, levodopa-carbidopa intestinal gel; LD/CD, levodopa/carbidopa; PDSS-2, Parkinson's Disease Sleep Scale-2; TE, technical engagement

Company's approach to incorporating sleep effects in model

Sleep benefit applied to fos-fos as adjustment to health state utilities and costs

In company's revised base case – fos-fos arm only:

- Benefits associated with **avoiding sleep disturbance** have been applied to utilities and costs based on weighted averages, to allow for a broader range of health effects to be considered
- Published utility values based on Parkinson's Disease Sleep Scale-2 (PDSS-2) scores used to derive utility values associated with sleep disturbance
- Yearly cost savings related to 'excessive sleepiness' as reported in Adelphi dataset also applied

Table: M15-736 trial results for sleep outcome at 12 weeks, with utilities and costs

Treatment	PDSS-2 score <18 No sleep disturbance	PDSS-2 score ≥18 Sleep disturbance	Weighted average sleep-related utility	Weighted average costs for sleepiness
Fos-fos	[redacted]	[redacted]	[redacted]	[redacted] per year
BMT	[redacted]	[redacted]	[redacted]	[redacted] per year

Modelled benefits in fos-fos arm: [redacted] utility increment | [redacted] cost saving

- Without equivalent data for LCIG, which is only administered during waking hours and stopped before sleep, assumed to have same sleep-related utility and costs as BMT

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Abbreviations: BMT, best medical therapy; LCIG, levodopa-carbidopa intestinal gel; PDSS-2, Parkinson's Disease Sleep Scale-2

Company's approach to incorporating sleep effects in model – EAG's critique

Uncertainty in sleep benefits - not included in EAG's preferred base case

EAG critique:

- Company's approach suggests a patient with excessive sleepiness will cost >£20,000 a year more than one without, which appears implausibly high
- Source costs (Adelphi study) not specific to sleep disturbance: use in model may double count costs from OFF time
  - Excessive sleepiness / sleep disturbance likely correlated with inadequately controlled Parkinson's in people with higher OFF time
- Company should demonstrate that any QoL or cost benefit is related only to sleep and does not double count any reduction in OFF time with treatment
- EAG acknowledges likely QoL related benefits from improved sleep from fos-fos, but due to uncertainty in **both cost and QoL benefit not included in EAG preferred base case**
  - *EAG scenario analysis:* explores alternative approach (company scenario) of adding PDSS-2 to utility regression for number of OFF hours per day to account for sleep benefit

What is the committee's view on the company's approach to incorporating uncaptured benefits? Is the way a sleep benefit for fos-fos has been added suitable for use in decision making?

Abbreviations: EAG, evidence assessment group; PDSS-2, Parkinson's Disease Sleep Scale-2; QoL, quality of life

Key issue: Robustness of utility values used in modelling

Fewer health states, but EAG disagrees with using pooled trial data

ACM1 conclusion

- Company's utility assumptions associated with high uncertainty. This is partly a result of the model structure including the large number of health states

Company's consultation comments:

- Health state utilities capped at OFF 10 in company's revised base case – reduced uncertainty
- Maintains pooled utility values across 4 fos-fos trials – to maximise patient numbers and produces better-fitting model than EAG's original proposed approach using observed data

EAG critique:

- Although number of health states is reduced, issue with pooling data across multiple trials remains with clear inconsistency in QoL across trials particularly M15-741
- EAG prefers to use only M15-736 trial to inform utilities and uses regression results for this to ensure inputs have clinical validity – **applied in EAG preferred base case**
  - *EAG scenario analysis:* explores use of directly observed M15-736 data for trial utilities (instead of regression) – has large impact with fos-fos dominated by BMT

What is the committee's view on the approach taken by the company? Is the pooled source of utility values suitable for use in decision making?

Abbreviations: EAG, evidence assessment group; QoL, quality of life

Key issue: Resource-use cost assumptions used in modelling (1/2)

Fewer health states, but EAG disagrees with use of regression approach

ACM1 conclusion

- Company's resource-use cost assumptions appeared flawed and are associated with high uncertainty. This is a result of the model structure including the large number of health states
- Noted limitations of EAG approach – costs somewhere between company and EAG estimates

Company's consultation comments:

- Health state costs capped at OFF 10 in company's revised base case – reduced uncertainty
- EAG's preferred use of direct (observed) costs data lacks clinically plausibility and face validity in some health states. Company maintains original regression approach

EAG critique:

- EAG preferred to use real-world data from company's Adelphi study for people of all stages of Parkinson's which reduced resource use costs, although EAG's original approach at ACM1 had limitations
- EAG's updated analysis for ACM2 using observed values to inform all health state cost components, and a more appropriate weighting of professional care costs by numbers – has a large impact on costs (vs EAG's original approach at ACM1) across different health states

Abbreviations: EAG, evidence assessment group

Key issue: Resource-use cost assumptions used in modelling (2/2)

EAG's updated analysis now shows observed data fits expectations

EAG critique *continued*:

- With EAG's updated analysis, observed data appears to fit expectations better than its original approach, particularly when separated out into the 5 health states (EAG preferred model)

Table: Total health state costs using the 5-state grouped model

Health state (grouped)	Company's costs – regression model	EAG's costs – observed data
OFF 0	[redacted]	[redacted]
OFF 1 to 4	[redacted]	[redacted]
OFF 5 to 8	[redacted]	[redacted]
OFF 9 to 12	[redacted]	[redacted]
OFF 13 to 16	[redacted]	[redacted]

- *EAG scenario analysis:* explores use of company's regression model costs (instead of observes costs)

- Note: health state costs are subject to substantial uncertainty due to being driven largely by a very small number of patients' costs for professional care

What is the committee's view on the approach taken by the company? Is the regression approach used to derive cost inputs suitable for use in decision making?

Abbreviations: EAG, evidence assessment group

Key issue: Use of M15-736 trial data to model BMT OFF time

Available trial data for BMT incorporated, but assumptions applied are questioned

ACM1 conclusion

- Data from the M15-736 trial would allow a direct comparison of fos-fos against standard care. Not using this data introduced considerable uncertainty

Company's consultation comments:

- Updated base case includes M15-736 trial data for BMT – committee preference
- Assumptions in incorporating data for BMT: return to baseline OFF after trial period (cycle 2) then natural disease progression from cycle 3, no LOCF (from 3 to 36 months) – differs from fos-fos arm

EAG critique:

- Notes minor error in way M15-736 trial data applied – no mortality between cycle 2 and 3
- Given evidence of continued effect of fos-fos long term, and PROSPECT evidence that there is little change in OFF time at 12 months for people on oral treatment, EAG prefers to apply same assumptions for treatment effect (natural disease progression from cycle 2) and LOCF to the BMT arm as applied to the fos-fos arm

Stakeholder comments – ABN

- Oral BMT delivered and optimised in M15-736 study may not be equivalent to standard of care in clinical practice, and 12-week study duration too short to observe disease progression

What is the committee's view on using different assumptions on treatment effect and LOCF for BMT and fos-fos arms?

Abbreviations: ABN, Association of British Neurology; BMT, best medical therapy; EAG, evidence assessment group

Results summary and base case assumptions

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Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential discounts for:

- pramipexole (Commercial Medicines Unit prices)
- fos-fos and LCIG (PAS discount)

Results accounting for all these discounts:

In the pairwise analyses:

- **fos-fos vs BMT:**
  - fos-fos is less costly and more effective (dominates) in company revised base case
  - fos-fos is substantially more costly and slightly more effective (ICER above £500K) in EAG preferred base case
- **fos-fos vs LCIG:**
  - fos-fos is less costly and slightly less effective (cost-effective in south-west quadrant) in company revised base case and EAG preferred base case

In a fully incremental analysis:

- fos-fos is most cost-effective strategy in the company base case
- BMT is most cost-effective strategy in the EAG base case

Abbreviations: BMT, best medical therapy; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; ICER, incremental cost-effective ratio; LCIG, levodopa-carbidopa intestinal gel; PAS, patient access scheme

Assumptions revised at ACM2

Assumptions in company's revised and EAG's preferred base case

BMT assumptions and removal of any sleep benefit have large impacts

Table: Company revised base case assumptions with **cumulatively applied key impact of EAG preferences**

Assumptions	Company revised base case	EAG's preferred base case	Fos-fos cost-effectiveness*
ITC of LCIG and fos-fos	Improvement in efficacy with fos-fos	Equal efficacy assumed	Fos-fos most CE strategy
Model design *Has subsequent impacts*	**17 health states, capped at OFF 10**	**5 grouped health states**	Fos-fos most CE strategy
Effect of stopping treatment	Patients distributed across OFF states by baseline OFF state distribution	Patients revert to most recent natural disease health state	Fos-fos most CE strategy
Use of Palmer data	Created prediction curve	Used 2 known data points	Fos-fos most CE strategy
BMT assumption after M15-736 placebo arm	**Revert to baseline before natural disease progression**	**Natural disease progression**	BMT most CE strategy
Trial effect in BMT arm	**None applied**	**LOCF assumption applied**	BMT most CE strategy
Data to inform costs	Modelled using regression results	**Updated observed data**	BMT most CE strategy
Data to inform utilities	Pooled dataset	M15-736 only	BMT most CE strategy
Sleep benefit of fos-fos	**Utility increment and cost saving**	**Removed: no benefit**	BMT most CE strategy

*Impact of EAG changes to cost effectiveness of fos-fos in a fully incremental analysis with LCIG and BMT

Abbreviations: BMT, best medical therapy; CE, cost-effective; EAG, evidence assessment group; fos-fos, foslevodopa-foscarbidopa; ITC, indirect treatment comparison; LCIG, levodopa-carbidopa intestinal gel

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