SMC2624

fosdenopterin powder for solution for injection (Nulibry®)

Sentynl Therapeutics Inc

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The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A

Key points:

- MoCD Type A is a rare, rapidly progressive, chronic, fatal inherited metabolic condition, characterised by a deficiency in molybdenum cofactor (MoCo). This results in a build-up of sulphite in the brain and leads to irreversible neurotoxicity, with symptoms including seizures, feeding difficulties, missed developmental milestones, psychomotor abnormalities, and neurological impairment.
- Fosdenopterin is a substrate replacement therapy which restores MoCo-dependent enzyme activity and reduces accumulation of neurotoxic compounds. Evidence from an integrated efficacy analysis suggested that fosdenopterin is associated with benefits in outcomes such as overall survival, normalisation of urine S-sulfocysteine **(**SSC) levels, and median time to sustained non-oral feeding.
- The clinical evidence was limited by small sample size, retrospective/observational and prospective/interventional studies that are prone to bias, and differences in baseline characteristics and dosing. There is therefore uncertainty in the magnitude of benefit of fosdenopterin.
- If given early enough, fosdenopterin may offer the potential for patients to participate in normal daily activities. Whilst patients receiving fosdenopterin may not be able to engage with activities to the extent of healthy persons, quality of life may be improved compared to those who do not receive fosdenopterin for MoCD Type A.
- The health economic evaluation indicated that fosdenopterin is associated with a discounted quality-adjusted life year (QALY) gain of 9.96 QALYs compared to standard of care. However, limitations including issues of utility values, outcome data, overall survival extrapolations and model structure increased uncertainty in the economic results. The treatment's cost in relation to its health benefits is high.

Chair,
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Patients with molybdenum cofactor deficiency (MoCD) Type A have mutations in the molybdenum cofactor synthesis 1 (MOCS1) gene, which leads to deficiency in cyclic pyranopterin monophosphate (cPMP). Fosdenopterin is a substrate replacement therapy, providing an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is converted to molybdenum cofactor, which is required for the activation of enzymes such as sulphite oxidase which reduces levels of neurotoxic sulphites. The recommended starting dose of fosdenopterin is 0.40 mg/kg/day administered intravenously once daily for patients less than 1 year of age and who are preterm neonates (gestational age <37 weeks); for patients less than 1 year of age who are term neonates (gestational age ≥37 weeks) it is 0.55 mg/kg/day. The dose is then titrated to the target dose of 0.90 mg/kg/day over a period of 3 months. The recommended dose for patients aged from 1 year to less than 18 years is 0.90 mg/kg once daily. Fosdenopterin is a chronic substrate replacement therapy intended for long-term use. See Summary of Product Characteristics for more details.[1]

1.2. Nature of condition

MoCD Type A is a rare, rapidly progressive, chronic, inherited metabolic condition, characterised by a deficiency in molybdenum cofactor which results in a complete lack of molybdenum-dependent activity. This deficiency leads to a build-up of sulphite in the brain, which causes irreversible neurotoxicity. MoCD Type A will typically present in neonates or early infancy but later onset cases have also been reported. The manifestation of central nervous system (CNS) damage includes seizures, feeding difficulties, missed developmental milestones, psychomotor abnormalities, and neurological impairment. Most patients experience early mortality; expected survival is approximately 36 months. Patients with MoCD Type A are unable to communicate effectively or move without assistance, impacting their ability to participate in normal activities. MoCD Type A has a significant impact on family members/carers in addition to patients, as the burden of care and psychological toll are high.[2 – 6]

There are no other treatments currently licensed for MoCD Type A in Scotland. Patients are treated symptomatically. For example, patients will receive antiepileptic medicines for seizures and may receive supportive care such as placement of a feeding tube if they experience feeding difficulties. Some patients may have seizures that are refractory to treatment, and antiepileptic medicines have no impact on the continued neurologic injury. Clinical experts consulted by SMC considered that fosdenopterin fills an unmet need in this therapeutic area as there are no other treatments available for the treatment of MoCD Type A.[2]

2. Impact of new technology

Comparative efficacy

Evidence to support the use of fosdenopterin in patients with MoCD Type A comes from an "integrated efficacy analysis", which combined data from five clinical studies. This included a total of 15 patients with MoCD Type A who received treatment with recombinant cPMP (rcPMP) (which has identical active moieties to fosdenopterin, n=4) or fosdenopterin (studies MCD-501, MCD-201 and MCD-202, n=11) and 37 untreated patients with MoCD Type A (studies MCD-502 and MCD-503). The studies were a mixture of observational (MCD-501, MCD-502, MCD-503) and interventional, single-arm studies (MCD-201, MCD-202). The dosing schedules of fosdenopterin/rcPMP varied between studies; patients in MCD-501 received rcPMP in line with named-patient treatment plans, patients in MCD-201 initially received fosdenopterin doses that matched their current rcPMP dose, doses were then escalated after two months on a monthly basis up to a maximum dose of 1.2 mg/kg; patients in MCD-202 received daily intravenous (IV) infusions of fosdenopterin starting at either 0.7 mg/kg (term neonates, infants, and children) or 0.525 mg/kg (preterm neonates), doses were then escalated to a maximum of 1.3 mg/kg.[2]

Efficacy outcomes evaluated in the integrated efficacy analysis included (but are not limited to) overall survival, change from baseline in urine SSC levels, change from baseline in feeding patterns, changes in growth parameters, changes in unassisted sitting, change from baseline in seizure frequency. The integrated efficacy analysis was primarily assessed in the full analysis set (FAS), defined as all treated and untreated patients with MoCD Type A. The integrated efficacy analysis is descriptive in nature; the analysis was not powered to detect statistical differences between treated and untreated patients.[2]

Treatment of patients with MoCD Type A with rcPMP/fosdenopterin led to improvements in overall survival and other outcomes compared with that observed in the untreated patient population. See Table 2.1 for details.

Table 2.1. Selected efficacy outcomes from the integrated efficacy analysis (FAS population).[2]

	rcPMP/fosdenopterin-treated patients (n=15)	Untreated patients (n=37)
Overall survival (data-cut 31 October 2021)		
Number of deaths	2	24
Median OS	NE	50.7 months
Hazard ratio (95% CI)	5.5 (1.44 to 21.04)	
KM survival probability at 1 year	93%	75%
Urine S-sulfocysteine (SSC) levels (data-cut 31 October 2021)		
Baseline urinary SSC level (µmol/mmol)	166.3	136.3

Last visit urinary SSC level (µmol/mmol)	8.6	156.6
Mean change from baseline (µmol/mmol)	-157.7	24.8
Feeding patterns (data-cut 31 October 2020)		
	n=14	n=33
Number of patients feeding orally	8 (57%)	10 (30%)
Odds ratio (95% CI)	7.8 (1.38 to 43.84)	
Median time to non-oral feeding	75.0 months	10.5 months
Growth parameters (data-cut 31 October 2020)		
	n=14	n=37
Baseline mean weight Z-score	-0.18	-0.28
Last visit mean weight Z-score	-0.33	-0.70
	n=12	n=33
Baseline mean height Z-score	-0.96	-0.44
	n=13	n=33
Last visit mean height Z-score	-0.88	-1.05
Unassisted sitting (data-cut 31 October 2020)		
	n=7	n=27
Able to sit independently for 30 seconds at 12 months	3 (43%)	3 (11%)
Seizure status at last assessment		
	n=14	n=37
Not present	2 (14%)	3 (8.1%)
Resolved	3 (21%)	1 (2.7%)
Controlled	2 (14%)	20 (54%)
Present	7 (50%)	13 (35%)
Odds ratio (95% CI)*	1.216 (0.337 to 4.387)	
Gross Motor Function Classification System Results at last assessment (PFAS population; data-cut October 2020)		
	n=9	n=11
Level 1	4 (44%)	1 (9.1%)
Level 2	0	0
Level 3	1 (11%)	0
Level 4	0	1 (9.1%)
Level 5	4 (44%)	9 (82%)

*The Odds Ratio represents the odds of the treated patients to have seizure status as either Not Present or Resolved versus Controlled or Present, compared to the untreated patients.

Abbreviations: CI = confidence interval; KM = Kaplan Meier; NE = non-estimable; OS = overall survival; PFAS = prospective full analysis set (all patients who were followed prospectively in studies MCD-502, -201, and -202) rcPMP = recombinant cyclic pyranopterin monophosphate.

Comparative safety

At the time of data-cut 31 October 2021, across the 15 patients with MoCD Type A who had been treated with fosdenopterin or rcPMP, the median total time on treatment was 5.4 years (6.3 years for 11 patients who received fosdenopterin). In MCD-501, MCD-201, and MCD-202 studies respectively, any treatment-emergent adverse event (TEAE) was reported by 90% (9/10), 100% (8/8), and 100% (3/3) of patients that received fosdenopterin/rcPMP; data for severe TEAE were not available, 62%, and 67%; no TEAE in any studies led to dose modification or treatment discontinuation; 20%, 0%, and 0% of TEAE led to death.[2]

The most commonly reported adverse events (both overall and serious) were related to central line complications, and respiratory tract and viral infections that are also frequently observed in otherwise healthy children. Complications associated with the device occurred in 7 out of 10 patients, including device dislocation and catheter site infection (3 patients each), and catheter site extravasation, catheter site pain, central venous catheterisation, catheter site discharge, device leakage, device occlusion, bacteraemia, sepsis, and vascular device infection (2 patients each). Infections included viral infections (0% in study MCD-501, 62% [5/8] in study MCD-201, 33% [1/3] in study MCD-202), pneumonia (30% [3/10] in study MCD-501, 38% [3/8] in study MCD-201, 33% [1/3] in study MCD-202) and influenza (0% in study MCD-501, 50% [4/8] in study MCD-201, 0% in study MCD-202). Skin and subcutaneous tissue disorders were reported in five out of 10 patients in study MCD-501, seven out of 8 patients in study MCD-201, and one out of 2 patients in study MCD-202.[2]

Since fosdenopterin is identical to endogenous cPMP, the regulatory bodies expect the safety profile to be mild, which is in line with observations from clinical studies. Photosensitivity is a potential risk and is mentioned in the SPC. It has not been possible to fully characterise the safety profile of fosdenopterin at present; further safety data are awaited.[1, 2]

No comparative safety data are available. Refer to the SPC for details.[1]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- Fosdenopterin is the first medicine licensed for the treatment of MoCD Type A. It is a substrate replacement therapy which restores MoCo-dependent enzyme activity and has a well understood mechanism of action.[2]
- There is an overall survival benefit associated with treatment with fosdenopterin. Median overall survival has not been reached in the fosdenopterin treatment group, compared with 50.7 months in the natural history cohort. The survival probability of 1 year of age is

93% in treated patients and 75% in the control group. This can be considered clinically relevant, although more mature overall survival data are awaited.[2]

- Treatment with fosdenopterin/rcPMP led to normalisation of urine SSC levels, which is associated with neurotoxicity. However, regulatory bodies noted that fosdenopterin does not reverse neuronal injury once present.[2]
- There is an improvement in median time to sustained non-oral feeding; 75.0 months for treated patients and 10.5 months for untreated patients.[2]
- Growth parameters (height, weight and head circumference) appeared favourable in patients who received fosdenopterin/rcPMP, although variance was high.[2]
- Five of the ten prospectively followed patients had improvements in motor and cognitive assessments using the Bayley scales of infant development. This contrasted with patients in the natural history control group, who scored low on these assessments.[2]
- By 12 months of age, three of seven treated patients (43%) were able to sit unassisted for 30 seconds which was higher than in untreated patients (3/27 [11%]). Most of the treated patients were able to sit unassisted at any time (7/10 [70%]) compared with 11% (3/27) of untreated patients.[2]
- Regulatory bodies considered the safety profile of fosdenopterin to be mild, although further data are awaited to fully characterise the profile.[2]
- Clinical experts consulted by SMC considered that fosdenopterin is a therapeutic advancement and should be considered for all patients with MoCD Type A. They noted that there may be benefits in patients with a prenatal diagnosis of MoCD Type A and benefits may be limited in those who are at an advanced stage of disease.

Key uncertainties:

- The integrated efficacy analysis had a small sample size which may be expected for an ultra-orphan condition; 15 patients with MoCD Type A have received treatment with fosdenopterin/rcPMP.[2]
- Evidence to support use of fosdenopterin comes from retrospective/observational and prospective, single-arm studies which are prone to bias such as selection bias.[2]
- Data collected from MCD-501, -201, and -202 were compared to a natural history cohort study, known as the integrated efficacy analysis. This analysis was descriptive in nature and not powered to detect statistical differences between treated and untreated patients. This indirect comparison had several limitations and credible intervals were wide suggesting uncertainty in the results. However, given the rarity of the condition and lack of other treatment options, a randomised controlled study is not feasible.[2]
- There were differences in baseline characteristics between the treated group and the untreated natural history cohort. For example, the proportion of patients with seizures at baseline was 71% in treated patients and 92% in the natural history cohort, and the presence of feeding difficulties was 64% and 84% respectively. This may be explained by early initiation of treatment however this cannot be confirmed. It is uncertain if these differences could confound the results, and in addition there may be unknown confounders

biasing the results. The exact magnitude of benefit of fosdenopterin is therefore uncertain.[2]

- The dosing schedules for fosdenopterin/rcPMP differed between studies. The justification for the licensed dosing schedule is limited and it is uncertain whether patients are treated with the optimal dose.[2]
- There are very limited data for fosdenopterin/rcPMP use in patients with late onset MoCD Type A (n=1). However, data in patients with early onset disease (n=14) is expected to be generalisable to the whole patient population given the underlying enzymatic defect and the mechanism of action of fosdenopterin. There are also limited data in adolescents and adult patients.[1, 2]
- The latest data-cut presented was 31 October 2021. No updates to the efficacy data were available. As part of the regulatory bodies' specific obligations, the marketing authorisation holder will provide annual updates on new information on the efficacy and safety of fosdenopterin, which includes data from a non-interventional post authorisation safety study.[2]

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

3. Impact beyond direct health benefits and on specialist services

As the first treatment licensed for MoCD Type A, availability of fosdenopterin could be expected to raise awareness and recognition of the condition. This may improve the diagnosis of MoCD Type A, where timely diagnosis is crucial. Fosdenopterin helps to reduce the build-up of neurotoxic compounds and if given early enough, may offer the potential for patients to participate in normal daily activities such as education. The submitting company recognise that patients may not be able to engage with activities to the extent of healthy persons. However, compared to patients with MoCD Type A who do not receive fosdenopterin, quality of life may be improved.

Caregivers must adjust their lifestyles to provide support for a child with complex medical needs and, in the case of MoCD, prepare for the certainty of premature death. The burden of caring for a child with MoCD begins at birth. Caregivers must manage seizures that continue throughout their child's life and adapt as the child fails to meet developmental milestones and suffers from mobility and cognitive issues. All of these factors are time-consuming and expensive, and in most cases will leave caregivers little time to focus on other aspects of their life such as having a career or looking after their other children. The introduction of fosdenopterin into clinical practice may alleviate caregiver burden, and thus their quality of life would be expected to improve. Although MoCD Type A will still require a high level of management and monitoring, if the timing of treatment initiation is optimised, and patients receive fosdenopterin as soon as they receive a diagnosis of MoCD Type A, sulphite levels should be controlled, thus meaning less neurological damage. In this case, the level of care required may be lower than in untreated controls, because the patient may not exhibit severe clinical signs such as feeding difficulties and severe developmental delay. It is anticipated that the need for full-time caregivers may diminish at the age the patient begins to attend school, however for patients who do initiate treatment later in life it is likely that they will require more extensive caregiving, however to what extent is unknown.

Fosdenopterin is administered intravenously once daily, requiring central venous access. Treatment should be coordinated and managed by a metabolic disease centre of excellence.

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Metabolic Support UK, which is a registered charity.
- Metabolic Support UK has received 47.5% pharmaceutical company funding in the past two years, with none from the submitting company.
- MoCD Type A is an ultra-rare, autosomal recessive inherited metabolic disorder characterised by progressive, life-limiting symptoms, leading to severe brain damage and a significantly reduced life expectancy, with most affected children dying before age three. Home care involves regular administration of numerous medications to manage seizures, high muscle tone, dystonia, reflux, and bowel movements. This profoundly impacts parents' lives, especially their sleep due to administration frequency. Babies are usually fed through a nasogastric tube, with some requiring a more permanent gastrostomy tube to manage symptoms like vomiting and dehydration. The burden on parents is immense, leading to anxiety, social isolation, and often job loss due to the intensive care requirements.
- Families report satisfaction with the rapid diagnosis but disappointment with the lack of disease-modifying treatments. Currently treatments focus only on symptom management. The care of children with MoCD Type A involves coordination with numerous healthcare professionals, adding to the family's stress due to travel and appointment burdens.
- Fosdenopterin, the only disease-modifying treatment available, has shown positive impacts when administered early, before extensive brain damage occurs. However, fosdenopterin cannot reverse existing brain damage and has challenges, such as severe vomiting and there are logistical complexities around its storage.

5. Value for money

5.1. Economic case

The submitting company provided an economic case, summarised in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	100 years.
Population	The submitting company requested SMC consider fosdenopterin for the treatment of all patients with MoCD Type A in Scotland.
Comparators	Standard of care. This included anticonvulsants to control seizures, and nasogastric feeding. Standard of care costs were also included in the fosdenopterin arm.
Model description	A two-state survival model was used with health states of alive and dead. All patients entered the model in the alive state, and either remained alive or transitioned to the dead state.
Clinical data	Overall survival patient-level data from the prospective studies MCD-201 and MCD-202, as well as the retrospective, observational study MCD-501 were pooled and informed overall survival in the fosdenopterin arm. Due to chemical equivalence, efficacy and safety, data from rcPMP in study MCD-501 were used to determine the safety and efficacy of fosdenopterin. Overall survival data for standard of care were from the natural history study, MCD-502 (full analysis set). Adverse events occurring in at least 10% patients in the pooled fosdenopterin treated population in MCD-201, MCD-202 and MCD-501 were included in the fosdenopterin arm. No adverse event data were available for the standard of care arm. As such, the proportions were assumed equivalent in both arms apart from those relating specifically to the administration of fosdenopterin. The data cut for all analyses included patient outcomes up to July 2019.
Extrapolation	Overall survival data were extrapolated in the economic model in both arms using a jointly fitted log-logistic distribution. Parametric survival predictions were also combined with Scottish life tables to reflect the increased all-cause risk of death over time.
Quality of life	Utility values in the model were defined for each age (in years) and were dependent on treatment arm, except the baseline utility value at 0 years old of 0.656 which was equal in both arms. The standard of care arm used utility values mapped from caregiver-reported Paediatric Quality of Life Inventory (PedsQL) values reported in a Dravet syndrome quality of life study, applying a mapping algorithm by Kahn et al., 2014 to generate EQ-5D utility values.[8, 9] Dravet syndrome was selected as a proxy condition for MoCD due to the similarities in disease characteristics and greater availability of quality-of-life data in Dravet syndrome. The utility values obtained from the mapping were applied from the ages of 0 to 18 years and ranged from 0.656 to 0.552. Post-18 years of age, the utility values then declined proportionally to those of the UK general population. The fosdenopterin arm utility values used UK general population utility values for ages of 1 year and above.[10] The utility value at 1 year of age was 0.965, with utility values for subsequent ages declining over time.
Costs and resource use	Costs included in the model were medicine acquisition, adverse events, disease management, laboratory tests, specialist visits and terminal care.

	Fosdenopterin medicine acquisition costs were calculated according to the licensed dosing schedule in the Summary of Product Characteristics.[1] It was assumed that patients were the 25th percentile for total body weight in a UK general population.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

5.2. Results

The base case results are presented in Table 5.2 below at list price. The majority of incremental costs were from fosdenopterin medicine acquisition. QALYs were gained by patients remaining alive and experiencing a higher quality of life in the fosdenopterin arm.

Table 5.2: Base case results at list price

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Fosdenopterin	33,287,716	15.02	33,153,783	7.64	9.96	3,330,348
SoC	133,934	5.06	-	-	-	-

Abbreviations: ICER = incremental cost-effectiveness ratio; Incr = incremental; LYG, life years gained; QALYs = quality-adjusted life-years; SoC = standard of care.

5.3. Sensitivity analyses

Scenario analysis results are shown in the table below. The base case results were most sensitive to the use of alternative fosdenopterin utility values.

Table 5.3: Scenario analysis results at list price

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case	-	-	33,153,783	9.96	3,330,348
1a	Overall survival extrapolations	Joint log-logistic	Joint gamma	35,783,433	11.30	3,166,877
1b			Joint log-normal	30,248,237	8.42	3,592,924
1c			Joint Weibull	34,820,198	10.87	3,203,842
1d			Independent log-logistic	39,412,175	12.03	3,277,363
2	SoC population	Full analysis set	Early-onset population (N=33).	32,435,551	10.38	3,123,508
3a	Fosdenopterin utility	General population (age 1 onwards)	Reduced utility benefit for fosdenopterin (75% vs. SOC)	33,153,783	8.56	3,874,900

3b			Reduced utility benefit for fosdenopterin (50% vs. SOC)	33,153,783	7.16	4,632,345
4	Caregiver disutility	Excluded	Included	33,153,783	9.40	3,527,841
5	AE disutilities	Excluded	Included	33,153,783	9.93	3,339,953
6	Weight	25th percentile	50th percentile	35,352,180	9.96	3,551,180
7	Low protein diet	Exclude	Include	33,281,755	9.96	3,343,203

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; Incr = incremental; QALYs = quality-adjusted life years; SOC = standard of care.

5.4. Key strengths:

- The submitting company selected an appropriate comparator in the economic study.
- A comprehensive selection of variables was included in the one-way deterministic sensitivity analysis.

5.5. Key uncertainties:

- There were uncertainties in the utility values used. Firstly, as no utility data for MoCD Type A were available, a proxy condition of Dravet syndrome was considered. The use of utility values derived from a proxy condition was subject to uncertainty, although given the data paucity for utility values in MoCD Type A this is challenging to resolve. Secondly, utilities were derived from mapping caregiver-reported PedsQL values in Dravet syndrome to the EQ-5D.[8, 9] The appropriateness of this mapping algorithm was subject to uncertainty, as the algorithm was derived from a cohort reporting a higher quality of life through the PedsQL values compared to those in the Dravet syndrome quality of life study's population. However, given limited mapping alternatives the uncertainty is challenging to resolve. Thirdly, the submitting company highlighted long term face validity issues of the mapped utility values for older ages, with adjustments applied. Standard of care utilities were based on the mapped utilities to 18 years, with proportional decline to those of general population post-18 years. Given this increased standard of care utilities post-18 years compared with the mapped utility values, the adjustment was likely conservative. Finally, it was assumed that general population utilities would apply in the fosdenopterin arm from year 1 onwards based on company expert feedback. However, given the EPAR noted that a developmental delay compared to healthy peers was present for all patients in various degrees under fosdenopterin treatment, there was uncertainty in assuming general population utility values after the age of 1 year. Scenario analyses were conducted that applied 50% and 75% improvements between standard of care utility estimates and

general population utilities, reducing the utility values for fosdenopterin, with the ICER increasing (Scenarios 3a and 3b).

- The economic evaluation did not include outcome data from the latest available October 2021 data-cut off in the MCD-201 and MCD-202 studies. The company confirmed that it did not have access to the October 2021 data-cut off patient-level data, and a scenario analysis with efficacy data up to October 2021 was unavailable.
- The clinical data to support comparative efficacy of fosdenopterin were from a small sample size and subject to limitations, which generated uncertainty in the observed and subsequent extrapolation of overall survival data. Although several plausible alternative survival extrapolations were available generating relatively small ICER variation (Scenarios 1a to 1d), the clinical data limitations remain an underpinning uncertainty in estimating long-term extrapolated overall survival.
- There was uncertainty in the two-state model structure. Although the two-state model could capture overall survival and the impact on quality of life, given the model's simplicity, bias may have been present due to the omission of specific health states that characterise MoCD Type A, such as seizures, difficulty feeding, and compromised mobility. The submitting company highlighted that a model with additional health states, covering aspects of seizure frequency and improved mobility, was not possible due to data paucity in quantifying the costs and quality of life impacts and that the impact of fosdenopterin is primarily on patient survival.
- There was inconsistency in the fosdenopterin dosing schedule used in the economic model compared with those used in the clinical efficacy evidence. The dosing schedule used in the economic model was the licensed dosing schedule, but various dosing schedules were used in the clinical studies. Therefore, there was uncertainty in the modelled costs relative to the projected health outcomes due to differences in the dosing schedule used in the economic model compared to the clinical evidence.
- There was uncertainty in the use of Scottish lifetables to reflect the increased all-cause risk of death in the MoCD Type A population. The company noted that as survival data were collected in predominantly paediatric patients, to avoid underestimating mortality it was assumed that patient survival in the trials was due to disease-specific causes with parametric survival predictions combined with Scottish lifetables to reflect the increased all-cause risk of death over time. Whilst this is a conservative approach and avoids underestimating mortality, it also raises an uncertainty as all-cause mortality over time is that of the general population, which may not be generalisable to a MoCD Type A population. Therefore, there may be the potential for upward ICER uncertainty if accounting for all-cause mortality in a MoCD Type A population.
- There was uncertainty in the weights used to estimate medicine acquisition costs. Firstly, it was assumed that patients followed the 25th percentile of general population weights, due to MoCD Type A exhibiting reduced growth. The submitting company highlighted that

patients with MoCD Type A did not achieve 50th percentile weight bands due to difficulty feeding, based on patient-level weight data of MCD-501.[11] However, a scenario considering the 50th percentile weights was available, increasing the ICER (Scenario 6). Secondly, the 25th percentile estimates beyond 5 years old were approximated by reducing average weights from the Royal College of Paediatrics and Child Health UK-WHO growth charts and NHS Digital data by 9%, a figure estimated from the decrement between 50th and 25th percentiles in children aged 5 years .[12, 13] This approximation was subject to uncertainty, as recorded 25th percentile weight data beyond 5 years were not directly available. However, the 9% reduction may be conservative when estimating the 25th percentile weights.

- Adverse event disutilities were omitted in the base case due to the rarity of the condition and the limited safety data. However, these could be applied in the model, generating a small increase in the ICER (Scenario 5).
- No caregiver training, equipment or support costs were included to account for home administration of fosdenopterin. However, the impact of these additional costs on economic results is expected to be minor.

*Other data were also assessed but remain confidential.**

6. Costs to NHS and Personal Social Services

The submitting company estimated there would be 2.1 patients treated with fosdenopterin in year 1, falling to 1.46 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

Consensus guidelines for the diagnosis and management of isolated sulfite oxidase deficiency and molybdenumcofactor deficiencies were published in 2024.[3]

8. Additional information

8.1. Product availability date

26 November 2024

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per 28-days (£)
Fosdenopterin	**The recommended dose for patients aged from 1 to less than 18 years of age is 0.90 mg/kg once daily. For patients aged less than 1 year, see SPC for details.**	**Body weight up to approx. 10.5 kg = £33,754** **Body weight up to approx. 21 kg = £67,509** **Body weight up to approx. 31 kg = £101,263**

Costs from company submission on 03 June 2024. Costs assume target dose of 0.90 mg/kg/day. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

References

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This assessment is based on data submitted by the applicant company up to and including 18 November 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.