National Institute for Health and Care Excellence

Health Technology Evaluation

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Birmingham Women's and Children's Hospital NHSFT	It is certainly appropriate to evaluate this. It is a well-recognised condition with a therapy that has been known about for several years but access to it has been challenging. Having an NHS-wide agreement for its use will mitigate those difficulties by taking it out of the research/compassionate arena. It is a very rare disorder and highly specialised evaluation is the most appropriate route although even with this it may be challenging to complete a full HST evaluation as the clinical trial data is limited due to the extreme rarity of the condition.	Thank you for your comment. Comment noted.
	Genetic Alliance UK	We consider the HST routing to be appropriate.	Thank you for your comment. Comment noted.
	Metabolic Support UK	It is timely and appropriate for this topic to be referred to NICE given that there are currently no specific licensed	Thank you for your comment. Comment noted.

Section	Stakeholder	Comments [sic]	Action
		treatments available in the UK to treat patients living with MoCD type A. The HST route is also considered appropriate.	
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	The remit is appropriate. Similar evaluations have already been performed by FDA and EMA.	Thank you for your comment. Comment noted.
	Sentynl Therapeutics	The company earnestly agrees that NICE should consider this topic for appraisal. The Highly Specialised Technology (HST) evaluation is appropriate for fosdenopterin.	Thank you for your comment. Comment noted.
Wording	Birmingham Women's and Children's Hospital NHSFT	Yes – but I would mention that the marketing authorisation is for MoCD Type A only. In clinical practice unless dealing with a baby with a known family history of MoCD Type A it is not possible quickly to determine whether someone has Type A or Type B disease. It is possible by measuring amino acids and urate to establish a likely diagnosis of MoCD and what ought to happen (this is what happened in compassionate access before) is that all such babies are assessed for treatment as this needs to begin as soon as the condition is suspected. Even a 24h delay in starting treatment could worsen outcomes. Therefore in practice it should be started in all babies suspected to have MoCD but only continued in babies with MoCD Type A [it will not be effective in MoCD Type B anyway].	Thank you for your comment. Comment noted. The evaluation will consider the population in line with the marketing authorisation.

Section	Stakeholder	Comments [sic]	Action
		It may be that the wording of the remit does not need to change to cover this so long as the committee understand this.	
	Genetic Alliance UK	NA	No action required.
	Metabolic Support UK	Yes.	Thank you for your comment. Comment noted.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	The wording should reflect that fosdenopterin treatment is only available as intravenous infusion. Suggest: “To appraise the clinical and cost-effectiveness of intravenous fosdenopterin supplementation within its marketing authorisation for treating MoCD-A”.	Thank you for your comment. Comment noted.
	Sentynl Therapeutics	The wording of the remit is accurate, and the company suggests no further changes.	Thank you for your comment. Comment noted.
Timing issues	Birmingham Women’s and Children’s Hospital NHSFT	I would say this is an urgent evaluation as a baby could be born at any time who might need this treatment and currently it is not clear how this would be sourced. Time is of the essence for this condition.	Thank you for your comment. Comment noted.
	Genetic Alliance UK	Given the lack of alternative treatment options available for affected individuals, we would encourage that this appraisal proceeds without delay.	Thank you for your comment. This evaluation has been scheduled into the work programme.

Section	Stakeholder	Comments [sic]	Action
	Metabolic Support UK	This evaluation is considered very urgent given the current absence of a licensed disease-specific treatment for patients with MoCD type A, their reliance on best supportive care and the poor outcomes associated with the disease.	Thank you for your comment. This evaluation has been scheduled into the work programme.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	It is urgent to provide clarity for newly diagnosed patients where treatment is currently delayed due to uncertainty over funding.	Thank you for your comment.
	Sentynl Therapeutics	The urgency of this evaluation to the NHS is high. The company cannot overstate the significant morbidity and high risk of early mortality associated with molybdenum cofactor deficiency (MoCD) Type A if left untreated, nor the lack of a disease-modifying alternative available to patients suffering with the condition. Fosdenopterin offers a critical intervention that could transform the lives of the extremely small patient population who have been, or will be, diagnosed with MoCD Type A, which is currently an unmet need.	Thank you for your comment. This evaluation has been scheduled into the work programme.
Additional comments on the draft remit	Birmingham Women's and Children's Hospital NHSFT	NA	No action required.
	Genetic Alliance UK	NA	No action required.

Section	Stakeholder	Comments [sic]	Action
	Metabolic Support UK	NA	No action required.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	NA	No action required.
	Sentynl Therapeutics	NA	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	**Birmingham Women's and Children's Hospital NHSFT**	The background states that palliative care is the only option but doesn't explicitly state that life is shortened – which it invariably is in the severe forms.	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.
	Genetic Alliance UK	The severity of MoCD hasn't been fully captured in the background information. We have been informed by Metabolic Support UK that mortality is high among people	Thank you for your comment. The background section of the scope aims to provide a

Section	Consultee/ Commentator	Comments [sic]	Action
		with MoCD type A. The impact this has on individuals, families, parents and carers is significant and therefore should be included in the draft scope.	brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.
	Metabolic Support UK	The mortality associated with MoCD type A is currently not reflected in the draft scope, thereby omitting the severe and devastating impact MoCD has on patients and their families/carers. We would recommend the following addition: "Mortality is high among MoCD type A patients, with a reported median survival of 2.4 years." (ref: Spiegel et al. Molybdenum cofactor deficiency: a natural history. J Inherit Metab Dis. 2022 May; 45(3): 456–469) Additionally, while brain dysfunction/abnormalities associated with MoCD type A are highlighted, the direct impact this has on the life and abilities of patients is not made clear. We suggest the first sentence sees the addition of: "*[brain dysfunction that worsens over time]*, often resulting in severe developmental delays." We would request that "other features of MoCD type A" is specified. This wording is not helpful to anyone not deeply familiar with the disease and undermines the rarity and severity of MoCD. Consequences of S-sulfocysteine build	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		up that should be considered to substitute this are: feeding difficulties, hypotonia and motor development delays. Finally, the standard management of MoCD type A includes a cysteine-restricted diet to lower sulfite production. This is achieved through a low protein diet, in which whole natural proteins are restricted. This is currently not reflected in the background. Addition of text around dietary management of MoCD type A is needed to ensure the current management of MoCD type A is accurately described.	
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	The background information is incomplete and aspects are not accurate regarding epidemiology and clinical management of individuals affected with MoCD-A.	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.
	Sentynl Therapeutics	The company believes that the word 'brain dysfunction' does not accurately reflect the condition, and that 'sulphite-induced neurodegeneration' would be more appropriate and precise. The true incidence of MoCD Type A is unknown but is estimated to be approximately 1 per 342,000 to 411,000 live births.[1]	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive

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			in its detail. No changes were made to the scope.
Population	**Birmingham Women's and Children's Hospital NHSFT**	No – I think this would be a good place to specify that initially this would be used to treat all patients with MoCD but treatment would only be continued in patients with MoCD Type A who are showing positive signs of benefit.	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.
	Genetic Alliance UK	NA	No action required.
	Metabolic Support UK	Current reports on fosdenopterin's efficacy suggest that the highest therapeutic benefit is obtained when fosdenopterin is initiated within a very short window after manifestation of symptoms. The population under consideration should include a pre-emptive MoCD type A diagnosis in situations where biochemical tests are delayed.	Thank you for your comment. Comment noted.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	Yes	Thank you for your comment. Comment noted.

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	Sentynl Therapeutics	The population is defined correctly.	Thank you for your comment. Comment noted.
Subgroups	**Birmingham Women's and Children's Hospital NHSFT**	In early clinical trials/compassionate access programs it was suggested that the efficacy of the treatment was best if it was started within 5d of birth. I don't see this reflected in the scope and maybe it should be. Fosdenopterin may be more effective in those started before Day 5 and there might need to be a "reassessment" stage for patients started after Day 5 who might still be showing biochemical improvement but not clinical improvement.	Thank you for your comment. Comment noted.
	Genetic Alliance UK	NA	No action required.
	Metabolic Support UK	In recent years, mild/late-onset forms of MoCD type A have been reported. It would be valuable to understand the effectiveness of fosdenopterin in severe/early-onset vs mild/late-onset MoCD type A patients.	Thank you for your comment. Comment noted.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	A minority of individuals with MoCD-A have attenuated disease. There are very limited data on the use of fosdenopterin in this subgroup. In the UK, the incidence of MoCD-A is significantly higher in individuals of South Asian and consanguineous ancestry.	Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		The clinical efficacy of the intervention is dependent on the stage of disease progression at the time of treatment initiation	
	Sentynl Therapeutics	There are no subgroups that should be considered separately. NICE should evaluate fosdenopterin for use in all patients with MoCD Type A.	Thank you for your comment. Comment noted.
Comparators	**Birmingham Women's and Children's Hospital NHSFT**	Yes although established clinical management is not defined – but I see this is one of the questions for the committee. The difficulty with this is that this may be variable across patients depending on what symptoms require treatment and how actively they embrace palliation.	Thank you for your comment. Comment noted.
	Genetic Alliance UK	Existing management of the condition mainly consists of a low protein diet which can be extremely restrictive, may be difficult to adhere to and therefore impacts overall quality of life. This is currently not clear in the draft scope.	Thank you for your comment. Comment noted.
	Metabolic Support UK	The current clinical management of MoCD type A is largely focused on dietary modifications and best supportive care to improve the quality of life and function of patients and minimise complications. No disease-specific treatment for patients with MoCD type A are currently licensed, therefore, there is a very urgent need for a treatment for this patient group.	Thank you for your comment. Comment noted.
	Willink Metabolic Unit, Manchester Centre for	The comparator should reflect that there is a large dichotomy in clinical efficacy, dependent on whether the intervention is started before or after catastrophic brain injury occurred.	Thank you for your comment. Comment noted.

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	Genomic Medicine		
	Sentynl Therapeutics	The noted comparator 'established clinical management without fosdenopterin' is appropriate. Since there is no direct available comparator to fosdenopterin for the treatment of MoCD Type A, the comparator is standard of care (SoC). Current treatments for MoCD Type A only focus on relieving symptoms associated with the disease, or supportive care for the patient. SoC for MoCD Type A consists of antiepileptic drugs (AEDs) to control seizures, and nasogastric feeding.[2]	Thank you for your comment. Comment noted.
Outcomes	**Birmingham Women's and Children's Hospital NHSFT**	Mortality and Survival are the same "Severity of Disease" is difficult to describe – should be captured with the other list of outcomes. The rest are correct but I would mention that outcome comparisons to untreated patients will be limited to natural history studies and not all of these items will have hard data to compare to (eg cognitive function)	Thank you for your comment. The outcomes in the scope have been amended based on consultation comments and feedback heard at the scoping workshop.
	Genetic Alliance UK	NA	No action required.
	Metabolic Support UK	Approximately one in five MoCD type A patients develop ectopia lentis or another ophthalmologic disease during the course of their disease. It would be valuable to understand whether fosdenopterin impacts the development of ophthalmologic disorders in general, and the time to the development of these disorders specifically.	Thank you for your comment. The outcomes in the scope have been amended based on consultation comments

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		MoCD type A patients often present with feeding difficulties. Feeding issues can develop after diagnosis. As feeding issues and associated nutritional issues impact the neurological development of a growing child and can be a source of significant stress and worry for parents/carers, it would be valuable to include the development of feeding issues as an additional outcome measure.	and feedback heard at the scoping workshop.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	Survival and overall mortality refer to the same outcome parameter. Severity of disease summarises many of the individually listed outcome domains and could be omitted. Incidence of disease-related complications should be included	Thank you for your comment. The outcomes in the scope have been amended based on consultation comments and feedback heard at the scoping workshop.
	Sentynl Therapeutics	The company feel that some of these outcomes are duplicative and unclear (for example, development parameters and cognitive function). Additionally, the company would like to highlight that due to the nature and rarity of the disease, no formal health-related quality of life (HRQoL) measurements have been taken for patients with MoCD Type A. The outcome measures proposed by NICE include: • overall survival • cognitive function • gross motor function • adverse effects of treatment	Thank you for your comment. The outcomes in the scope have been amended based on consultation comments and feedback heard at the scoping workshop.

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		• body weight and nutritional • parameters (including growth and development) neurological development parameters • frequency of seizures • mortality • severity of disease • health-related quality of life (for patients and carers). The suggested outcome measures to be considered include: • Overall survival and mortality • MoCD associated Biomarkers • Feeding patterns • Growth parameters, including height, weight and head circumference • Developmental Assessments • Adverse effects of treatment • Impact on seizures • Adverse effects of treatment.	
Equality	**Birmingham Women's and Children's Hospital NHSFT**	I can't think of any equality of access issues here.	Thank you for your comment. Comment noted.

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	Genetic Alliance UK	NA	No action required
	Metabolic Support UK	MoCD type A is a genetic condition with a reported higher prevalence in communities where consanguineous marriage is more prevalent. Special consideration must be given to communities where consanguineous marriage is/was common. We understand that fosdenopterin requires storage in a medical grade freezer. Given that regular household freezers do not meet these requirements, families will need to acquire a medical grade freezer. This may be particularly challenging for lower/middle income families and may introduce inequal access to fosdenopterin, especially in light of the current cost of living crisis.	Thank you for your comment. The Technology Appraisal Committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No changes to the scope required.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	This policy will over-proportionately impact on individuals with South Asian ancestry	Thank you for your comment. The Technology Appraisal Committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No
	Sentynl Therapeutics	The company have identified no issues in the draft remit or scope pertaining to equality.	Thank you for your comment. Comment noted.

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Other considerations	**Birmingham Women's and Children's Hospital NHSFT**	The economic analysis needs to include the administration costs of fosdenopterin. This is a daily IV infusion and therefore realistically this is going to require homecare nurses administering the infusion or the parents being trained to do this themselves. These costs must be factored into the analysis so that when approved this is not a stumbling block. Will a homecare provider be stipulated in any agreement? If homecare is being provided then initial hospital admission may be shorter. If homecare is not to be funded, then initial hospitalisation will be much longer until the caregivers are suitably trained in administering the therapy. The cost of permanent IV access are also	Thank you for your comment. Comment noted.
	Genetic Alliance UK	NA	No action required.
	Metabolic Support UK	The physical, psychological and financial benefits of this treatment to carers/families should be considered in the appraisal.	Thank you for your comment. Comment noted.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	The technology needs to be embedded in an adequate testing and education strategy to enable early diagnosis and treatment and improve the clinical efficacy of the intervention.	Thank you for your comment. Relevant costs associated with diagnostic tests, will be considered by the Technology Appraisal Committee.

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	Sentynl Therapeutics	The company would like to highlight the following quote from Appendix E: "The results of a study (n=15) treated with fosdenopterin compared with historical data from two studies who did not receive fosdenopterin or any other treatment showed that one year, around 93% of people using fosdenopterin were alive compared to around 75% of those who received no treatment." The incorrect citation was used; Spiegel (2022), not Mechler (2015) and EMA (2022), should have been used. Furthermore, the company does not believe that 'Magnesium supplementation and standardised migraine prophylactics can be used for those with headaches' is applicable to MoCD Type A patients.	Thank you for your comment. Comment noted.
Questions for consultation	Birmingham Women's and Children's Hospital NHSFT	**How many people have MoCD type A in England, and how many would be offered fosdenopterin?** It is very rare – the epidemiological estimates in the background are probably correct. In Birmingham we have seen one new patient with MoCD every 3 years on average (but did have a run a few years ago) – but not all of them were MoCD Type A. **Where do you consider fosdenopterin will fit into the existing care pathway for MoCD type A?** As discussed above – patients with suspected MoCD will be rapidly transferred to a neurometabolic unit capable of initiating this therapy. Therapy would start and genetic	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		testing for MOCD initiated – which would take up to 14 days to return (there may be other ways of this being done but this should come under the R14 pathway for whole genome sequencing as treatment will be impacted by the genetic result) If MOCS1 mutations are found and the baby is improving then treatment would continue – if MOCS1 mutations are not found then the treatment would stop. **Which treatments are considered to be established clinical practice in the NHS for treating MoCD type A?** Disease modifying therapy is not available on the NHS – so the only treatments are symptomatic and this will vary according to the patients' needs. Anticonvulsant treatment, NG feeding, palliative care (which may come with additional medications) are standard. Some families who embrace palliation early may opt for treatment such as subcutaneous infusions early and management only at home. Other families may not embrace palliation so well and may have frequent hospital admissions, sometimes with ICU admissions and invasive/non-invasive ventilation throughout their lifespan. This is going to be very difficult to standardise/measure for all patients. **How effective are the current treatments for the management of MoCD type A?** Disease modifying therapy is not available on the NHS – so the only treatments are symptomatic	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		How should best supportive care be defined? See my comment above – I'm not sure this can be defined as families differ in how actively they embrace palliation. **Are the tests to establish the correct diagnosis of MoCD Type A standard practice in the NHS?** Yes. Uric acid is measurable in all laboratories. All metabolic laboratories that perform amino acid analysis can measure sulphocysteine. Genetic testing for MOCS1 mutations is available on the NHS through R14/R98 genome sequencing. These babies will be acutely ill and in a NICU/PICU so will qualify for rapid WGS under R14 – although if fosdenopterin is approved there could be an argument for establishing a single gene test request code for MOCD if this will be returned more quickly. **Is there any data/evidence available on how long people live with MoCD type A /the impact of MoCD type A on quality of life?** There will be data for untreated patients from the natural history study sponsored by Alexion which was used as the comparator in the clinical trials. **Do you consider that the use of fosdenopterin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The main benefits are in survival and seizure-freedom though this does come with risks (of central venous access and infections for example)	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		What is the impact of living with MoCD type A when treated with standard care or fosdenopterin for patients and carers? **of these benefits.** The impact of both will be significant. Untreated – the impact is of a child with severe neurodisability, requiring constant attention and high levels of caregiver input similar to nursing care. Enteral feeding, suction, oxygen might all be needed. Some patients might even be further technology dependent if commenced on non invasive ventilation. This will be time-limited though as the condition will eventually lead to the patient's early demise On Fosdenopterin – the caregiver will have to administer a daily IV infusion including the preparation and aseptic technique associated with this. There will be restrictions on where the family can travel to and who can look after the child. Central line care is essential as infections are common and if infections occur then hospital admissions for treatment are necessary. But the benefit would be that the child might develop normally.	Thank you for your comment. Comment noted.
	Genetic Alliance UK	**NA**	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Metabolic Support UK	**Question: How many people have MoCD type A in England, and how many would be offered fosdenopterin?** We believe that the reported prevalence for MoCD type A in the European Union is accurate and can be extrapolated to England. This would imply there are approximately 28 patients in England. Every newly diagnosed patient would be expected to receive fosdenopterin upon diagnosis. The low prevalence underscores that the HST is the correct route for fosdenopterin **Question: Where do you consider fosdenopterin will fit into the existing care pathway for MoCD type A?** MoCD type A is a rapidly progressing disorder. There is currently no licensed disease-specific treatment for patients with MoCD type A. As a result, toxic levels of sulfite and s-sulfocysteine build up in the body and brain of a child. Fosdenopterin is the first MoCD type A-specific treatment. To prevent the rapid accumulation of toxic levels and thus rapidly progressive nature of MoCD and thus to achieve optimal outcomes for families, we consider that	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		fosdenopterin should be initiated as early as possible following diagnosis. **Question: What is the impact of living with MoCD type A when treated with standard care or fosdenopterin for patients and carers?** A diagnosis of MoCD type A requires many parents/carers to leave work and become full time carers to provide the care their child needs. This has a negative psychosocial impact on the parent/carer, who have shared this impacts their social life, mental health and energy levels. They are often faced with little respite, relying on hospices for short term breaks and respite from care. Additionally, medical care appointments for patients with MoCD type A often substantially impact the lives of both the patient and parent/carer, requiring long-distance travel to reach metabolic treatment centres, which is associated with a substantial economic burden on the parent/carer. **Question: Is there any data/evidence available on the impact of MoCD type A on quality of life?** To our knowledge, there is currently no public data / evidence on the impact of MoCD type A on quality of life. **Question: Do you consider that the use of fosdenopterin can result in any potential substantial**	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		health-related benefits that are unlikely to be included in the QALY calculation? We believe that the majority of patient health-related benefits will be accounted for in QALY calculations. However, QALY calculations do not account for carer-related benefits. In this case, the psychosocial health-related benefits for carers should be accounted for.	Thank you for your comment. Comment noted.
	Willink Metabolic Unit, Manchester Centre for Genomic Medicine	**How many people have MoCD type A in England, and how many would be offered fosdenopterin?** The true birth incidence is not known. Around 1-2 children per year are diagnosed in the catchment area of the Manchester metabolic service. **Where do you consider fosdenopterin will fit into the existing care pathway for MoCD type A?** There is no alternative disease-modifying treatment for typical MoCD-A. Everyone with this diagnosis and without existing contraindication will be treated. **Which treatments are considered to be established clinical practice in the NHS for treating MoCD type A?** Supportive care only	Thank you for your comment. Comment noted**.** Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		How effective are the current treatments for the management of MoCD type A? There is currently no effective treatment **How should best supportive care be defined?** Carer support, access to respite care, physiotherapy and occupational therapy, feeding support (tube feeding and gastrostomy, possibly fundoplication and jejunostomy), anticonvulsant medication, dystonia medication, oxygen supplementation, non-invasive ventilatory support, intermittent hospital admission for intercurrent infection or aspiration, access to palliative care. At least one full-time carer will be required 24/7. **Are the tests to establish the correct diagnosis of MoCD Type A standard practice in the NHS?** Yes, but there is limited access **Is there any data/evidence available on how long people live with MoCD type A /the impact of MoCD type A on quality of life?** See published case series and natural history studies	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Misko AL, Liang Y, Kohl JB, Eichler F. Delineating the phenotypic spectrum of sulfite oxidase and molybdenum cofactor deficiency. Neurol Genet. 2020;6(4):e486. Spiegel R, Schwahn BC, Squires L, Confer N. Molybdenum cofactor deficiency: A natural history. J Inherit Metab Dis. 2022 May;45(3):456-469. **Do you consider that the use of fosdenopterin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** See also below: Fosdenopterin treatment will remove the risk of nephrolithiasis and acute ocular complications due to lens dislocation in treated MoCD-A, whether the child has severe neurological impairment or not. **What is the impact of living with MoCD type A when treated with standard care or fosdenopterin for patients and carers?** The impact of daily IV infusions and the requirement to keep a frozen drug at home is significant. This burden has been found acceptable in early treated children but may be too high in late treated children. **Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope? Please identify the nature of the data which you**	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		understand to be available to enable the committee to take account of these benefits. There is a dichotomy of outcomes, depending on the extent of brain disease at the start of treatment, as demonstrated in: 122. Schwahn BC, Van Spronsen FJ, Belaidi AA, Bowhay S, Christodoulou J, Derks TG, Hennermann JB, Jameson E, König K, McGregor TL, Font-Montgomery E, Santamaria-Araujo JA, Santra S, Vaidya M, Vierzig A, Wassmer E, Weis I, Wong FY, Veldman A, Schwarz G. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015;386(10007):1955-1963**.**	
	Sentynl Therapeutics	**How many people have MoCD Type A in England, and how many would be offered fosdenopterin?** There are currently two patients in England with MoCD Type A, both of whom are being treated with fosdenopterin through an early access programme. However, there may be more patients in the UK who would be eligible for treatment if a confirmed genetic diagnosis of MoCD Type A was given. **Where do you consider fosdenopterin will fit into the existing care pathway for MoCD Type A?**	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Fosdenopterin will be a first-line treatment for MoCD Type A, however it is expected that some patients will continue symptomatic treatments concomitantly with fosdenopterin. **Which treatments are considered to be established clinical practice in the NHS for treating MoCD Type A?** There are no licensed treatment options available for MoCD Type A. Current treatments for MoCD Type A only focus on relieving symptoms associated with the disease, or supportive care for the patient.[2-8] Established clinical practice usually consists of AEDs to control seizures, and the use of nasogastric feeding tubes. The most utilised supportive AEDs include phenytoin, nitrazepam, levetiracetam, lorazepam, diazepam, clonazepam, pyridoxine, valproate sodium, midazolam and phenobarbital. Low sulphur diets may provide some benefit in milder cases, however the effectiveness of this has not been established, and this would not be considered SoC.[6] **How effective are the current treatments for the management of MoCD Type A***?* There is a high unmet need for a treatment to prevent the progressive neurodegeneration that MoCD Type A causes, as none currently exist. Current AEDs are employed to reduce the severity and frequency of seizures, but their effectiveness is limited to alleviating short-term symptoms; they do not address the underlying disease process.[3,9] The mechanism of action of	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		AEDs is, variously, targeting the modulation of voltage-gated ion channels (sodium, calcium, and potassium channels), inhibiting γ-aminobutyric acid (GABA), directly modulating synaptic release, or inhibiting synaptic excitation.[10] They do not address the build-up of neurotoxic sulphites in the brain, which is the primary cause of neurodegeneration and structural damage, and ultimately, early mortality in patients with MoCD Type A patients. Diet changes, particularly low sulphur diets, have been used in several case studies to reduce the unusually high levels of sulphite and S-sulphocysteine (SSC) served in patients. However, the benefits of diet on clinical outcomes are limited, and it is not thought to have an impact on modifying the course of disease in severe MoCD.[6] These approaches have shown limited effectiveness in improving the overall prognosis for patients with MoCD. Seizures may persist or remain difficult to control despite medication, and the long-term survival rates for individuals with this condition are still poor. **Are the tests to establish the correct diagnosis of MoCD Type A standard practice in the NHS?** Diagnosis of MoCD Type A usually requires biochemical testing; however, a genetic test is the only way to differentiate between the types of MoCD and confirm MoCD Type A. This is standard practice in the NHS.	Thank you for your comment. Comment noted.

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		Is there any data/evidence available on how long people live with MoCD Type A /the impact of MoCD Type A on quality of life? Most published cases of MoCD Type A show classical presentation during the first postnatal days, including intractable seizures, feeding difficulties, severe encephalopathy, apneas, exaggerated startle reactions, and axial hypotonia and limb hypertonia.[11-13] If the neonatal period is survived, infants continue to have myoclonic and generalised seizures and develop severe dystonic spastic cerebral palsy.[14] In the absence of treatment, patients usually die within the first years of life.[2] Mortality data are limited for MoCD Type A patients in England, however international data shows that mortality is high due to intercurrent lower respiratory *tr*act infections and seizures, with a median survival of 3 years.[15] **Do you consider that the use of fosdenopterin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation***?* The use of fosdenopterin will result in substantial health-related benefits that will not be included in the QALY calculation. The impact of caring for a patient with MoCD Type A, when treated with SoC include reduction in productivity, levels or	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

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		work and financial stability, as well as quality of sleep for carers. In addition to this, carers may experience anxiety and depression due to the worry of their child being so unwell, and the high possibility that they may die soon. It is unlikely that this will be included in the QALY calculation. The primary indicated benefit of treatment with fosdenopterin is improved patient survival. MoCD Type A is also characterised by the incidence of seizures, difficulty feeding, and compromised mobility. Treatment with fosdenopterin is primarily anticipated to impact survival but is also expected to limit the progression of these symptoms (i.e., a stabilisation in the incidence of seizures, a reduced need for nasogastric feeding and a higher likelihood of gross motor skill preservation), which is correlated to the time of treatment. This means that parents will potentially be somewhat relieved of their caregiving duties when the child is able to attend school. **What is the impact of living with MoCD Type A when treated with standard care or fosdenopterin for patients and carers?** Patients with MoCD are unable to communicate effectively or move without assistance, [2,15] impacting their ability to participate in normal activities. Although no studies have been conducted to assess health-related quality of life and caregiver burden specifically for MoCD Type A, it is reasonable to infer that both those affected by the	Thank you for your comment. Comment noted.

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		condition and their carers will experience a significant impact on their HRQoL. **Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** As mentioned above, the company suggest including feeding status, neuroimaging results and biomarker data as outcomes. Further clarification is required on the 'severity of disease' suggestion. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which fosdenopterin will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;	Thank you for your comment. Comment noted.

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		• could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. Informal caregivers are typically women and play a major role in chronic disease management These women must support their children physically, mentally, and emotionally, which adds to their own burden and furthers the disparity in burden experienced by women carers compared to caregivers of all genders.[16] The introduction of fosdenopterin would help to relieve this burden and hopefully decrease some of the disparities in gender equality associated with caring for those with a mostly fatal, severely disabling chronic disease. 1. Mayr S, May P, Arjune S, Havarushka N, Lal D, Schwarz G. Forecasting the incidence of rare diseases: An iterative computational and biochemical approach in molybdenum cofactor deficiency type A [Abstract # 567]. *Journal of Inherited Metabolic Disease.* 2019;42(S1):290. 2. Mechler K, Mountford WK, Hoffmann GF, Ries M. Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. *Genet Med.* 2015;17(12):965-970. 3. Hansen LK, Wulff K, Dorche C, Christensen E. Molybdenum cofactor deficiency in two siblings:	

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		mutation and review of the literature. *Pediatrics.* 2005;116(3):757-766. 13. Zhang X, Vincent AS, Halliwell B, Wong KP. A mechanism of sulfite neurotoxicity: direct inhibition of glutamate dehydrogenase. *J Biol Chem.* 2004;279(41):43035-43045. 14. JL. J. Molybdenum cofactor deficiency and isolated sulfite oxidase deficiency. In: McGraw-Hill;, ed. *The Metabolic and Molecular Bases of Inherited Disease.*2001. 15. Spiegel R, Schwahn BC, Squires L, Confer N. Molybdenum cofactor deficiency: A natural history. *Journal of Inherited Metabolic Disease.* 2022;45(3):456-469. 16. Rico-Blázquez M, Quesada-Cubo V, Polentinos-Castro E, et al. Health-related quality of life in caregivers of community-dwelling individuals with disabilities or chronic conditions. A gender-differentiated analysis in a cross-sectional study. *BMC Nursing.* 2022;21(1).	
Additional comments on the draft scope	Birmingham Women's and Children's Hospital NHSFT	I don't know if this assessment needs to consider the wider scope of how fosdenopterin will be given to patients who are in other hospitals. For example patients on holiday who end up in a hospital that is not a treating centre. Or who require procedures in another hospital to their treating	Thank you for your comment. Comment noted.

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		centre. AS this is an IV treatment – would caregivers be permitted to administer this on the ward to their child? Can it be stored in DGH pharmacies? It's not quite the same as enzyme replacement infusions that are only given weekly or fortnightly where a dose could be omitted.	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Neonatal and Paediatric Pharmacy Group (NPPG)