NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Fosdenopterin for treating molybdenum cofactor deficiency type A

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

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

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

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

Issue date: September 2024

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using fosdenopterin in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 10 October 2024
- Second evaluation committee meeting: 07 November 2024
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Fosdenopterin is not recommended, within its marketing authorisation, for treating molybdenum cofactor deficiency (MoCD) type A in people of all ages.

1.1 This recommendation is not intended to affect treatment with fosdenopterin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

MoCD type A is a rare genetic condition that can appear shortly after birth. It causes the build-up of sulfites in the body and the brain, which leads to seizures, feeding difficulty, loss of muscle control and poor survival. Standard care includes treatments that manage symptoms, such as antiseizure medicines.

Clinical trial evidence suggests that fosdenopterin increases the time before people are unable to eat and how long they live compared with standard care. But the trials were very small and did not compare fosdenopterin with other treatments, so the results are highly uncertain.

There are also uncertainties in the economic model, including that it:

- only captures evidence for 1 person with late-onset MoCD type A treated with fosdenopterin; most of the evidence was from people with early-onset MoCD type A
- does not fully capture all the outcomes relevant to MoCD type A
- does not include quality-of-life data from people with MoCD type A

Even when considering the condition's severity, its effect on quality and length of life, and the size of benefit with fosdenopterin, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources for highly specialised technologies. So, fosdenopterin is not recommended.

2 Information about fosdenopterin

Marketing authorisation indication

2.1 Fosdenopterin (Nulibry, Sentynl Therapeutics) is indicated for 'the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for fosdenopterin.

Price

2.3 The list price of fosdenopterin is £1,205.51 per 9.5 mg vial (excluding VAT; company submission accessed September 2024). The list-price treatment cost per person for the first year is estimated to be £529,158. The list-price treatment cost per person for the fifth year is estimated to be £1,056,748. The costs take people's weight into account.

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

3 Committee discussion

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

The condition

Details of condition

3.1 Molybdenum cofactor deficiency (MoCD) type A type is a rare genetic condition that can appear shortly after birth, with symptoms appearing within 28 days of birth for most people. The condition is caused by defects to the gene that makes molybdenum cofactor. Without molybdenum cofactor, an enzyme called sulfite oxidase does not function properly to process sulfites. This causes the build-up of sulfites to toxic levels in the body and in particular the brain, leading to seizures and severe brain abnormality. Without treatment, people who have the condition have a median survival of around 4 years.

The company classified 2 types of MoCD type A: early and late onset. It noted that early-onset MoCD type A occurs within the first month of life, and can cause more severe with symptoms such as seizures and feeding difficulty. Late-onset MoCD type A normally occurs within the first 2 years of life, and usual symptoms include developmental delay and uncontrolled muscle movements. The clinical expert noted that the aforementioned use of early and late onset is misleading, and that classifying the condition based on a strict cut-off of 28 days from birth may not be appropriate (see section 3.9). They highlighted that late-onset MoCD type A is uncommon. They also explained that clinicians prefer the terms typical and atypical MoCD type A because these capture the nature of the condition more precisely. They added that typical MoCD type A symptoms usually present within 28 days of life, but noted that some people may have sustained brain injury before birth. The clinical expert cited a recently published consensus guidelines for MoCD type A, which describe how fetal seizures may be noticed during late pregnancy as ‘increased hiccupping’. Other symptoms of typical MoCD type A include acute encephalopathy (brain disorder), feeding difficulties and irritability. They explained that the usual symptoms of atypical MoCD type A include loss

of muscle control and movement disorder, but that seizures and ongoing brain damage may also occur.

The clinical expert highlighted that they were aware that around 70 people have or have had MoCD type A in the UK over about 30 years. They also said that that the rate of MoCD type A has been increasing slightly in more recent years. The committee acknowledged the clinical expert's opinion and concluded that describing MoCD type A as typical and atypical was a reasonable approach. It thought that it was not appropriate to apply a strict cut-off of 28 days from birth for people with typical MoCD type A.

Effects on quality of life

3.2 Patient experts noted in their submissions that MoCD type A markedly affects the daily life of people with the condition and their carers. They highlighted that it was hard having to adjust their lives to becoming full-time carers and learning how to give the various treatments needed throughout the day. The patient experts noted that, often, people would need to take numerous medicines to control their symptoms (including for seizures). They highlighted that, while some people may not have seizures, others can have 10 to 60 seizures per day. They also noted that some children would not be able to have food by mouth, so would need have nasogastric tubes fitted to have food. The committee heard that:

- sometimes people with MoCD type A may not need antiseizure medicines or nasogastric feeding
- some children with MoCD type A:
  - may be non-verbal
  - may not have full control of their bowels and may need a nappy beyond the expected age
- children with MoCD type A would need:
  - help with dressing

- cleaning of central lines needed for some treatments (for example, fosdenopterin).

The committee noted that some parents do not think that these care needs will change with age for people having treatment. The clinical expert noted that brain damage can substantially affect quality of life and result in a higher care burden. The committee understood that a patient organisation submission included a survey exploring the experience of carers of people with MoCD type A. The survey confirmed that the clinical expert's opinion reflected the experience of people who responded to the survey. The committee concluded that MoCD type A markedly affects quality of life and that there is an unmet need for people with the condition.

Clinical management

Treatment options

3.3 There are no treatment options for MoCD type A aimed at targeting the underlying condition. Standard of care is aimed at managing symptoms such as seizures and loss of muscle control. The company proposed that fosdenopterin would be started when people are suspected of having MoCD type A (a presumptive diagnosis). Then, a genetic test would be done to confirm if they have the condition. People confirmed as having MoCD type A would continue having fosdenopterin and people with a negative genetic test would stop treatment. The clinical expert noted that people diagnosed early and started on fosdenopterin treatment early could be prevented from the severe neurodisability and brain damage associated with MoCD type A. They explained that the treatment restores normal biochemistry and, if used early enough, can lead to better outcomes. They added that not every person necessarily needs antiseizure treatment. But brain damage can occur before treatment, so long-term symptoms may occur regardless of fosdenopterin treatment. The clinical expert highlighted that speed of diagnosis is dependent on familiarity with MoCD type A in a particular hospital. If a hospital is familiar

with the condition, biochemical tests can be done within 24 hours to make an initial decision. This means that starting treatment the next day is possible. Then, genetic confirmatory test can then done afterwards. If the hospital is not familiar with MoCD type A, tests to diagnose it may be the second- or third-line tests done. This can delay diagnosis. The committee concluded that fosdenopterin provides a treatment option for people with MoCD type A and speed of diagnosis is an important factor for outcomes.

Comparators

3.4 NICE's final scope for this evaluation included established clinical management without fosdenopterin as the relevant comparator. The committee understood that this largely constituted antiseizure medicines. The company explained that it had included the 10 most common antiseizure medicines used in its clinical trials as the relevant comparators (standard care). The committee understood that fodenopterin would be used in addition to current standard treatment, including antiseizure medicines, and that fosdenopterin is a life-long treatment. The committee recalled that sometimes some people may not need antiseizure medicines (see section 3.2). It asked the clinical expert if seizures are a common occurrence in this population. The clinical expert explained that most people with MoCD type A need treatment for seizures, but that seizures may not necessarily present immediately. The committee concluded that the company's proposed description of standard care was appropriate.

Clinical effectiveness

Data sources and results

3.5 The clinical evidence submitted by the company came from 3 fosdenopterin trials (MCD-501 [4 people], MCD-201 [8 people], and MCD-202 [3 people]). These were pooled and compared with a natural history study (MCD 502 [37 people]). The trials included people with MoCD type A. The company provided results for both the full analysis set (FAS, that is, all people having or not having treatment) and the genotype-

matched analysis set (GMAS, that is people having treatment genotype-matched to people not having treatment). The key outcome measure reported by the company was overall survival. For the FAS, the median overall survival was not reached for the fosdenopterin group but was 50.7 months for people having standard care. The company reported better survival probability for people having fosdenopterin compared with standard care (hazard ratio [HR] 5.5, 95% confidence interval [CI] 1.44 to 21.04). For the GMAS, the median overall survival for fosdenopterin was not reached and was 47.8 months for people having standard care (HR 7.1, 95% CI not reported). The company submitted additional results on feeding status. These suggested that, compared with placebo, fosdenopterin increased the time before non-oral feeding was needed (75 months, 95% CI 0.2 to not estimable compared with 10.5 months, 95% CI 4.9 to 53.6). The company also reported results of seizure control. It reported that the odds ratio of seizures being absent or resolved compared with being controlled or present was 1.216 (95% CI, 0.337 to 4.387) for fosdenopterin compared with standard care in the FAS. For the GMAS, the odds ratio was 1.461 (95% CI, 0.368 to 5.808). The committee noted that the impact of fosdenopterin on seizures was highly uncertain because the confidence intervals were wide and they crossed 1. The EAG explained that the primary issue related to the small trial population. It was also concerned about the high number of censoring events in the overall survival results, which could have made interpreting the trial results more difficult. The committee noted that very few people in the clinical trials (fosdenopterin: 1 of 15, standard care: 4 of 37) had late-onset MoCD type A. It also noted that there was limited evidence for the use of fosdenopterin in this population (see section 3.9). The committee concluded that the size and nature of the trials the results were uncertain but suggested that fosdenopterin could improve survival outcomes compared with standard care.

Generalisability and uncertainty in the trials

3.6 The EAG noted that the fosdenopterin trials were all single-arm trials. This increased uncertainty, given that the population included in the clinical trial was already small. It also noted difficulty understanding the flow of people during the trials. It was unclear whether people were presumptively diagnosed with MoCD type A and started on treatment with fosdenopterin before having a confirmatory genetic test (see section 3.13). The EAG highlighted that the company used results from 2 different data cuts, July 2019 and October 2021, for its economic and clinical analyses. The company explained that it did not have full access to the individual patient level data because the clinical trials were done by a different company. The EAG noted that the population addressed in the company's model was in babies, children and young people with MoCD type A. But it was concerned that 1 person in the comparator arm was diagnosed at month 484 (40 years). This meant that, before their diagnosis, they had the same risk of death and ability to feed orally as the general population, which could have biased the results. The committee had concerns about how generalisable the fosdenopterin trials were to UK clinical practice. It asked the clinical expert if they considered the trials were generalisable. The clinical expert noted that the trials were not reflective of the UK MoCD type A population. This was because, in their experience, about 90% of people with the condition are from South Asian ethnic backgrounds. But, in the trials, around 70% of people who had fosdenopterin were from White ethnic backgrounds. But the clinical expert said they had not seen any evidence to suggest that treatment efficacy would differ between ethnic groups. The committee understood that MoCD type A is linked with a high incidence of consanguinity rather than with being from a South Asian ethnic background (see section 3.19). The clinical expert explained that the number of people who had seizures (fosdenopterin 71%, standard care 92%) and feeding difficulties (fosdenopterin 64%, standard care 84%) at baseline was similar to that in UK clinical practice. The committee

concluded that the generalisability of the trials was uncertain but, in the absence of further data, the trials were sufficient for decision making.

Economic model

Company's modelling approach

3.7 The company submitted a 2-state survival model capturing people alive or dead. It did so because it considered improvement in overall survival to be the primary benefit of treatment with fosdenopterin. It also expected treatment to stabilise seizure, reduce the need for nasogastric feeding and to stabilise mobility. But the company noted that, because of a lack of data, it could not capture these additional benefits in distinct health states. The model applied a lifetime horizon of 100 years, a cycle length of 4 weeks, and discounts costs and quality-adjusted life years (QALYs) at 3.5%. Utilities from Dravet syndrome (a severe form of epilepsy that starts in childhood) was applied in the model as a proxy for MoCD type A utilities (see section 3.10). The committee concluded that the company's model was sufficient for decision making but highlighted that there was substantial uncertainty associated with it because it:

- did not capture all the relevant outcomes for MoCD type A (see section 3.8)
- used a proxy condition as a source of utility values (see section 3.10).

Model's ability to capture outcomes

3.8 The EAG raised concerns about the simplicity of the company's model. It noted that the model was based on overall survival and did not capture all the relevant outcomes for MoCD type A, including developmental status, mobility, feeding status and seizure. So, the impact of fosdenopterin on these outcomes could not be tested in the model. The EAG explained that it had requested further data from the company at clarification including data for people's ability to feed orally. It used this data to make changes to the model. The EAG preferred to assume that:

- people having fosdenopterin and feeding orally would have similar outcomes to the general population
- people unable to feed orally would have similar outcomes to the standard-care population.

These assumptions affect utilities (see section 3.11) and carer burden (see section 3.12). The committee recalled the clinical expert's opinion about the impact of brain damage on outcomes (see section 3.2). It asked the company whether it had data on the number of people in the trials who had sustained brain damage. The company responded that there were only neuroimaging results for some people. It also noted that each of the clinical trials had defined outcomes related to brain damage differently, which could have made interpreting the results difficult. The committee asked the company whether it had done any analysis defining the cohorts by whether they had sustained brain damage. The company responded that the population was very small, so it did not want to further subdivide the data. But it estimated that around 50% of people in the prospective group likely had sustained brain damage. The clinical expert explained that, once a person has had a brain injury caused by MoCD Type A, it is difficult to get the full benefit of the treatment. They noted that people with a sibling who had MoCD type A were more likely to be diagnosed and started on treatment early. This could reduce their chances of further brain damage. The committee asked the clinical expert whether it was plausible to differentiate the severity of people with MoCD type A based on their ability to feed orally. The clinical expert explained that the ability to feed orally was an appropriate proxy for disease severity. But they noted that this would not capture outcomes such as seizures and loss of muscle control. The committee concluded that it would have preferred the model to capture relevant outcomes such as brain damage, seizures and feeding status. In the absence of this, it accepted the approach to apply ability to feed orally as a proxy for outcomes for people having fosdenopterin.

Model population

3.9 In its base case, the company considered fosdenopterin for everyone, that is, both the early- and late-onset populations (see section 3.1). It defined early-onset MoCD type A as being when symptoms start within 28 days of birth. The EAG noted that, in the included trials, most people in the fosdenopterin (14 of 15) and standard-care groups (33 of 37) had early-onset MoCD type A. It explained that including the 1 person with late-onset MoCD type A (1 of 15) who had fosdenopterin did not affect the model results. The EAG highlighted that more late-onset data was needed to be able to model this group. So, its base case only included the early-onset population. During technical engagement, the company submitted a case study (Lund et al, 2024) that discussed treatment of 2 people with late-onset MoCD type A who had treatment with fosdenopterin. The company noted that people with late-onset MoCD type A are less likely to have sustained brain damage and are more likely to respond to treatment. The EAG highlighted that the case study may provide supportive evidence for using fosdenopterin in late-onset MoCD type A. But it thought that, the company's model still did not include further data to support this. The committee asked the company whether it could describe the outcomes of the person with late-onset MoCD type A who had fosdenopterin in the clinical trials. The company explained to the committee that this person had developmental delay in their second year of life, which led to diagnosis and treatment with fosdenopterin. The clinical expert explained that there was limited data to provide evidence for this group. They added that they are aware of 1 person with late-onset MoCD type A who started treatment on day 55. But they had no evidence to quantify the treatment benefit for this person. The committee recalled the EAG's concern that 1 person in the standard-care group had been diagnosed at age 40 years. Before that, they could have had the same risk of survival as the general population (see section 3.6). It was concerned that limited evidence had been presented to fully support the efficacy of fosdenopterin in the late-onset population defined by the company (see section 3.5). The

committee concluded that the model population should reflect the efficacy data, that is, the early-onset population.

Source of utility values

3.10 The company did not collect quality-of-life data in any of its clinical trials. It used data from a study of quality of life in people with Dravet syndrome (Lagae et al. 2018) to generate proxy sex- and age-adjusted utility values for its modelling. Dravet syndrome is a severe form of epilepsy that typically starts during childhood. The company explained that it did this because:

- no data on quality of life for MoCD type A was available
- Dravet syndrome represented a proxy seizure-based condition that was relevant and provided data for children of similar age range.

The company noted that the utility estimates were likely conservative (that is, would not favour fosdenopterin) because people with MoCD type A have more seizures. The EAG made several corrections to the company's base case. These included applying adult utility values reported in Lagae et al. for people 18 years and over who were having standard care. The EAG acknowledged the paucity of data. But it noted that proxy utilities from Dravet syndrome may not accurately match the quality of life for people with MoCD type A. It highlighted that this further increased uncertainty. The committee asked the clinical expert about their familiarity with Dravet syndrome and whether it represented a good source of utility values. The clinical expert responded that they had experience with treating people who had sustained brain damage but not Dravet syndrome specifically. They explained that Dravet syndrome does not capture symptoms such as loss of muscle control and involuntary movements. But, in their view, it is a moderately good proxy for quality of life. The committee concluded that there was high uncertainty associated with using utility values from a different condition. But it thought that data from Dravet syndrome was reasonable in the absence of further evidence.

Utility assumption beyond year 1 for fosdenopterin

3.11 In its base case, the company used its calculated Dravet syndrome utility values for the standard-care arm (see section 3.10). For the fosdenopterin arm, it assumed that, after treatment for 1 year, people would have the same quality of life as the general population. It did so because it expected people having early treatment with fosdenopterin to have comparable long-term utilities with the general population. The EAG disagreed with this approach. It noted that no evidence was submitted by the company to support its assumption. Also, it was concerned that the utility values for people having fosdenopterin were overestimated. The EAG preferred to differentiate quality of life based on ability to feed orally (see section 3.8). It assumed that people having fosdenopterin:

- who are able to feed orally would have utilities midway between the standard-care population and general population
- who are unable to feed orally would have the same utilities as the standard-care population.

The company did not agree with the EAG's approach, noting that non-oral feeding was related to speed of diagnosis and treatment. It highlighted that the EAG did not capture other quality-of-life factors such as seizures. During technical engagement, the company submitted an additional scenario analysis linking utility values with seizures. The EAG explained that it was unclear how the subset of people having fosdenopterin (8 of 11) and SOC (8 of 37) were selected for inclusion in the company's analysis. But the resulting utility values when either oral feeding or seizure status was linked with utility values suggested people having fosdenopterin do not have similar quality of life to the general population. It noted that, ideally, the utility values would be dependent on both seizures and oral feeding. The committee asked the clinical expert about the plausibility of the company's assumption that people having fosdenopterin would have general population quality of life after treatment for 1 year. The clinical expert explained that it was implausible. They

highlighted that MoCD type A can be severe for many people and that they can have neurological disorders such as those seen in people with cerebral palsy. So, people with MoCD type A would need care and would not have a quality of life similar to the general population. The committee concluded that, based on the evidence presented, it was not plausible to assume general population utility after treatment for 1 year.

Carer burden

3.12 The company applied a caregiver disutility (-0.14), in its base case. It also assumed that people having standard care would need 1.8 carers throughout their life to give care corresponding to 14.8 hours per day. It took these estimates from NICE's technology appraisal guidance on fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis and on fenfluramine for treating seizures associated with Dravet syndrome. For people having fosdenopterin, the company assumed that they would only need 1 carer until age 5 years, and none after that. The EAG noted that the company did not fully capture care in places such as special needs school. It highlighted that this should be included within the scope for personal social services. The EAG also noted that fosdenopterin is given intravenously through a catheter every day. It added that some people having treatment would be unable to feed orally beyond age 5 years, so would likely need care after this age. The company responded that people who have treatment early would have care needs similar to those of the general population. It added that any care would fall within regular parenting hours. The clinical expert explained to the committee that people who can feed orally may need less support but would likely need some support beyond age 5 years. The committee understood that the carers of some people with MoCD type A thought that their children would always need care. In some of these children, diagnosis was as early as 3 days after birth, and the children had started having treatment by day 4. The committee was aware that the EAG's base case assumed a differentiated care burden for people having fosdenopterin based on their

ability to feed orally. People feeding orally were assumed to need less care (1 carer) until age 18 years and none after that. But people unable to feed orally were assumed to need care similar to that of the standard-care population (1.8 carers). The committee concluded that the EAG's approach of differentiating carer needs by feeding status was plausible.

Presumptive treatment cost

3.13 Fosdenopterin can be used for people suspected of having MoCD type A before the condition is confirmed by genetic testing. The company's model assumed that people in the fosdenopterin and standard-care groups had already had their condition confirmed. The EAG noted that the company's model did not capture the cost of presumptive treatment, that is, from the time of starting treatment but before a genetic confirmation of the condition. The company explained to the committee that the presumptive treatment period is not substantial because fosdenopterin is a life-long treatment. It noted that it had done some analysis to explore the impact of presumptive treatment costs and that this increased the incremental cost-effectiveness ratio (ICER) by about 1%. The EAG noted that it was unclear from the company's submission what proportion of people having treatment presumptively would later have a negative genetic test result. It did a scenario analysis exploring that 10% to 95% of people would have a negative test after presumptively starting treatment. The EAG analysis assumed people would have presumptive treatment for either 7 or 28 days. The committee noted that the EAG's analysis represented the maximum fosdenopterin acquisition cost that the NHS would be expected to cover. It asked the clinical expert what proportion of people who start treatment would later have a negative test. The expert did not have a precise figure but estimated that around 50% was reasonable. They explained that confirmation of MoCD type A could often be within 2 weeks but there could be some delays. The committee recalled that the speed of genetic testing can be affected by a hospital's familiarity with MoCD type A (see section 3.3). So, it preferred to assume that people would

have presumptive treatment for at least 28 days to account for differences in familiarity of the condition. The committee concluded that the cost of presumptive treatment should have been captured in the company's model for 28 days, using the most reliable data if available, or the clinical expert's estimates (50%).

Lifetime treatment wastage

3.14 Fosdenopterin vials (9.5 mg) need to be used within 4 hours once open. The dose used by people is individualised based on their weight. This means any unused vials would need to be disposed of. The EAG noted that, because of the lack of options in vial sizes and the storage needs, a substantial amount of the treatment would be wasted throughout a person's lifetime. It estimated that in the first 5 years of a person's life, around 37% of fosdenopterin would be wasted. The company responded that it did not have any plans to introduce smaller vial sizes. The committee was aware that the model already captured the cost of treatment wastage. It concluded that having smaller vial sizes would have reduced wastage and markedly improved the cost-effectiveness estimates.

QALY weighting

3.15 NICE's health technology evaluations manual specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is revealed through the number of additional QALYs gained and by applying a 'QALY weight'. The committee noted that a weight of between 1 and 3 in equal increments can be applied when the QALY gain is between 10 and 30 QALYs. It noted that some of the company's and EAG's analyses showed QALY

gains within this range. The committee understood that carer QALYs are not normally included in the QALY weighting calculation and that the company's and EAG's analyses also did not include this. The committee recalled that there were multiple uncertainties with the clinical data and the economic modelling. But it considered the high unmet need for people with MoCD type A. Taking into account its preferred assumption (see section 3.17), it concluded that a QALY weight of 1.005 should be applied.

Other considerations

3.16 The company and EAG differed on 3 further assumptions, which the committee was aware had a small to negligible impact on the cost-effectiveness estimates. The company assumed that people having fosdenopterin would only also have 1.0 antiseizure medicine. The EAG preferred to use an estimate of 2.2, which was the lower end estimate used in the Dravet syndrome systematic literature review submitted by the company. The clinical expert explained that MoCD type A is not characterised solely by seizures, but estimated that people with MoCD type A would have 2 to 3 antiseizure medicines, on average. The dose of fosdenopterin is calculated based on a person's weight and the company used weight estimates from 3 different sources combined. The EAG made adjustments to smoothen the weight data, which the company accepted during technical engagement. To reflect the improvement in developmental status after having treatment, the EAG also preferred to assume people having fosdenopterin would be in the twenty-fifth percentile of the weight distribution,. The company's preferred percentile is considered confidential and cannot be reported here. The company assumed that everyone with MoCD type A would need a review by a metabolic physician twice yearly. The EAG's clinical expert noted that such reviews would likely be specific to taking fosdenopterin so should be excluded from the standard-care group. The committee considered these assumptions and had the following conclusions:

- 2.2 antiseizure medicines should be applied based on the systematic literature review results and the clinical expert's opinion
- a twenty-fifth percentile weight distribution should be used for modelling weight to capture the improvement in having treatment with fosdenopterin
- a metabolic physician review should only be included for modelling fosdenopterin.

Cost-effectiveness estimates

Company's and EAG's cost-effectiveness estimates

3.17 The exact cost-effectiveness estimates cannot be reported here because there are confidential discounts for fosdenopterin. Both the company's and EAG's base-case ICERs were substantially above the range that NICE normally considers an acceptable use of NHS resources, even when the QALY weighting was applied. The committee noted that there were several uncertainties, including with the model's ability to capture outcomes relevant to MoCD type A. The committee noted the uncertainty around the cost-effectiveness estimates. It thought that this could have been reduced by adapting the model to capture the expected correlation of people's outcomes (brain damage, seizure status and ability to feed orally) with economic outcomes such as utility values and carer burden (see section 3.2, section 3.8, section 3.11 and section 3.12)

The committee's preferred assumptions included:

- using ability to feed orally to differentiate outcomes for people having fosdenopterin (see section 3.8), in the absence of the model being adapted according to the committee's preferred analyses to reduce uncertainty
- using the early-onset population for generating cost-effectiveness estimates in the economic model (see section 3.9)

- applying Dravet syndrome utility values, in the absence of further data (see section 3.10)
- assuming people having treatment with fosdenopterin and able to feed orally have utility values midway between standard care and the general population, and people unable to feed orally have the same utility values as people having standard care (see section 3.11)
- assuming people having fosdenopterin and feeding orally need less care (1 carer), and people having fosdenopterin and unable feed orally have the same care needs as people having standard care (1.8 carers, see section 3.12)
- including the cost of presumptive treatment in the cost-effectiveness estimates (see section 3.13)
- assuming people with MoCD type A would have around 2 antiseizure medicines (see section 3.16)
- assuming people having fosdenopterin are in the twenty-fifth percentile of weight distribution (see section 3.16)
- excluding a metabolic physician review for people having standard care (see section 3.16).

With the committee's preferred assumptions applied, fosdenopterin was substantially above the range that NICE normally considers an acceptable use of NHS resources. So, it was not recommended.

Managed access

Recommendation with managed access

3.18 Having concluded that fosdenopterin could not be recommended for routine use, the committee then considered whether it could be recommended with managed access for treating MoCD type A. It noted that the company had not submitted a managed access proposal, so it could not make a recommendation for managed access at this stage.

Equality

3.19 The clinical expert explained that almost everyone in the UK with MoCD type A are from minority ethnic backgrounds. They noted that there is a high incidence of MoCD type A in people from South Asian ethnic background (see section 3.6). The committee understood that MoCD type A is linked with high incidence of consanguinity rather than with a South Asian ethnic background. The committee noted that issues related to differences in prevalence cannot be addressed in a technology evaluation. In its submission, the company also noted that fosdenopterin could reduce carer burden and that caring may be disproportionately done by women. The committee considered this issue and recalled that it had taken carer burden into account in its decision making (see section 3.12). The patient experts' submission noted that families on low income may not have access to the medical-grade freezer needed to store fosdenopterin. The committee considered this issue but noted that its recommendation does not restrict access to treatment for some people over others. So, it agreed that this was not a potential equalities issue. The committee noted that it was not presented with evidence to support the improved impact of fosdenopterin for any of the groups highlighted.

Conclusion

Recommendation

3.20 The committee concluded that, with its preferred assumptions and QALY weighting applied, the cost-effectiveness estimates for fosdenopterin were substantially above the range considered an acceptable use of NHS resources for a highly specialised technology. So, it did not recommend fosdenopterin for treating MoCD type A.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

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

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

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

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

Raphael Egbu
Technical lead

Christian Griffiths
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