NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Voxelotor for treating haemolytic anaemia caused by sickle cell disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using voxelotor 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: February 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using voxelotor in the NHS in England.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: 19 March 2024
- Fourth evaluation committee meeting: 4 April 2024
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Voxelotor with or without hydroxycarbamide is not recommended, within its marketing authorisation, for treating haemolytic anaemia caused by sickle cell disease in people 12 years and over.

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

Why the committee made these recommendations

There is an unmet need for effective treatments for sickle cell disease, and health inequalities affect people with the condition. Usual treatment for haemolytic anaemia caused by sickle cell disease includes hydroxycarbamide (also known as hydroxyurea) or regular blood transfusions. For this evaluation, the company positioned volexotor as a second-line treatment. This does not include everyone who it is licensed for.

Clinical evidence suggests that people who have voxelotor are more likely to have an increase in haemoglobin levels compared with people who have usual treatment. Although this is likely to be beneficial, how well voxelotor works is uncertain because:

- the key trial was short, so it is uncertain what the benefits are in the long term
- the people in the trial did not reflect the people who would have second-line treatment with voxelotor in the NHS, because they were not able to have regular blood transfusions and did not have to have had hydroxycarbamide previously.

The cost-effectiveness estimates for voxelotor are also uncertain. This is because some assumptions used to estimate the cost effectiveness were not supported by clinical evidence. Voxelotor has the potential to partially address the health inequalities associated with sickle cell disease and the unmet need for effective treatments, so a cost-effectiveness estimate that is higher than the usual maximum for a positive decision could be considered acceptable. But, the cost-effectiveness estimates for the company's proposed second line positioning varied widely owing to high uncertainty regarding key assumptions in the economic model. It was agreed that greater uncertainty around clinical effectiveness estimates could be accepted as a reasonable adjustment for the substantial disadvantage identified for people with sickle cell disease. However, even taking this into account, the most plausible cost-effectiveness estimates are beyond what NICE considers an acceptable use of NHS resources.

It is not possible to consider use of voxelotor with managed access because the company has not provided a managed access proposal. So, voxelotor is not recommended.

The committee has requested further clarification and analyses for the fourth evaluation committee meeting to ensure that potential avenues for patient access are fully explored.

2 Information about voxelotor

Marketing authorisation indication

2.1 Voxelotor (Oxbryta, Pfizer) is indicated for 'treatment of haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of voxelotor is £5,917.81 for a 90-pack of 500 mg tablets (excluding VAT; BNF online accessed February 2024). The company has a commercial arrangement, which would have applied if voxelotor had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, 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 In sickle cell disease (SCD), a gene mutation causes red blood cells to become irreversibly sickle shaped. These cells are then broken down in a process called haemolysis, which causes haemolytic anaemia, resulting in low haemoglobin levels. The patient experts explained that the symptoms of haemolytic anaemia in SCD include pain, fatigue, weakness, tachycardia, dizziness and confusion. Sustained haemolytic anaemia can affect the function of multiple organs, causing organ damage, strokes, sight loss and other symptoms, which substantially affects quality of life. The patient experts described how normal everyday activities can be difficult for people with haemolytic anaemia. They explained that some symptoms can lead to sickle cell crises, which needs hospital treatment multiple times a year. This can have a considerable impact on work and education, as well as on carers. The pain resulting from SCD has a major impact on quality of life. There can be constant background pain making day-to-day life uncomfortable, in addition to episodes of excruciating debilitating pain that has been described as more painful than childbirth. Maintaining social relationships and employment can be difficult because of the complications resulting from SCD. For most people with SCD, the clinical course of the disease is uncertain. This can be a source of anxiety

for people with SCD and their parents or carers. The patient experts also explained that SCD is not widely understood, including among healthcare professionals, which can result in poor care and further anxiety. The clinical experts explained that some of the long-term morbidities in SCD are directly related to the degree of haemolytic anaemia. One clinical expert highlighted that a potential complication related to low haemoglobin levels is cerebral damage in children and young people with SCD. They considered that increasing haemoglobin levels in people with haemolytic anaemia would mean fewer hospital admissions, reduced risk of symptoms and organ damage, improved mental health and less time off work or education. However, the committee noted this association was not reflected in the HOPE trial (see section 3.5). The patient experts also explained how SCD has a substantial impact on people with the condition from an early age, and on their carers. They explained that transitioning from childhood into adulthood can be particularly challenging, including learning how to manage the condition themselves. They also commented that navigating work and social life is particularly difficult for people with SCD. In response to the first draft guidance consultation, the clinical and patient experts further highlighted that people with SCD face health inequalities and there is an unmet need for this population. The committee acknowledged the substantial difficulties and health inequalities faced by people with SCD. It recognised that SCD is a serious condition that can affect the body across multiple organ systems, can impact the mental wellbeing of people with the condition and their carers, and is associated with considerable morbidity.

Clinical management

Treatment options

3.2 Usual treatment for SCD includes ensuring adequate hydration, preventing infections and treating pain, with or without hydroxycarbamide. Regular blood transfusions may also be considered. The patient experts explained it is also important to avoid triggers when managing SCD.

These include cold weather, stress and physical activity. They gave an example that temperature variance between rooms in a house can lead to crises and so it is important to ensure the house is a consistent temperature throughout. The patient and clinical experts explained that there are limited treatment options for SCD. A patient expert described their experience of taking hydroxycarbamide for 20 years after starting it as a child. Initially it was effective, but as they got older and their weight increased, the dose of hydroxycarbamide also increased up to a maximum amount. When they reached adulthood, hydroxycarbamide was no longer as effective, even at the maximum dose. Hydroxycarbamide also cannot be used during pregnancy or by people trying to conceive. The patient and clinical experts commented that there is a lack of innovation and investment in treatments for SCD and an unmet need for an effective and well-tolerated treatment that can be taken over a lifetime. The clinical experts also commented that it is unknown if voxelotor has an impact on fertility because there is no long-term data or trial data. The company explained there is no data on voxelotor's impact on male fertility and only some real-world evidence of voxelotor use in pregnancy. The committee noted the All-Party Parliamentary Group's 'No One's Listening' report which highlighted health inequalities experienced by people with SCD and inadequate investment in the condition. The committee concluded that there is an unmet need for effective treatments and that health inequalities affect people with SCD. It noted people with SCD would welcome a new treatment that addresses the short-term symptoms and long-term complications of haemolytic anaemia and improves their quality of life.

Population

3.3 In its submission, the company positioned voxelotor as 'second-line treatment after hydroxycarbamide in people who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective'. In response to the first draft guidance consultation, the company updated its proposed

positioning by removing the term ‘unwilling to take hydroxycarbamide’. The committee was aware that this would mean voxelotor would be used as monotherapy when people cannot have or are intolerant of hydroxycarbamide, or as combination therapy when hydroxycarbamide has not worked well enough on its own. It noted that the company’s proposed population was narrower than the marketing authorisation indication, and therefore narrower than the population in the NICE scope (that is, people with SCD). It also noted that the company had not submitted evidence for a possible subgroup of interest identified in the NICE scope, defined as ‘combination treatment with or without hydroxycarbamide’. The HOPE trial included people who had previously taken, were taking and who had never taken hydroxycarbamide (see section 3.5). The EAG noted that 64% of people in the voxelotor arm and 63% in the placebo arm were taking hydroxycarbamide at baseline. The company confirmed that most people continued to take hydroxycarbamide throughout the HOPE trial. The EAG commented that the population in the HOPE trial was not limited to people having voxelotor as second-line treatment, and HOPE did not represent the company’s proposed positioning of voxelotor. The company explained its positioning of voxelotor, as a second-line treatment after hydroxycarbamide has been offered, was chosen after consultation with 9 UK clinicians. The clinicians stated that this is the most likely position for its use in the NHS. The committee recalled that the HOPE trial excluded people who were having regular transfusion therapy. But in the company model, regular transfusion therapy was included at different rates for each arm (see section 3.9). It therefore noted the company’s proposed positioning of voxelotor as a second-line treatment was not aligned to the population in the HOPE trial. So it may be more appropriate for the company to position voxelotor as a first-line treatment option for SCD, in line with its marketing authorisation. The company explained that the British Society of Haematology recommends hydroxycarbamide as a first-line treatment, so it would expect voxelotor to be used as a second-line treatment. The committee

acknowledged the guidelines but felt that this did not prevent the possibility of voxelotor displacing current standard care. In response to the first draft guidance consultation, clinical experts highlighted that voxelotor may be particularly beneficial for a specific subgroup of people with SCD. That is, people with severe anaemia (haemoglobin level below 6 g/dl), who are unable to have transfusions and whose condition has not responded to hydroxycarbamide or who do not tolerate it. The committee asked the company whether there is any evidence for the clinical effectiveness of voxelotor in this subgroup. The company stated it is difficult to generate evidence in this subgroup and was not aware of any available evidence. The committee concluded that the company's proposed second-line positioning was not supported by trial evidence. Also that the trial population did not represent the company's proposed population in NHS practice or the population in its economic model. It further noted that the company had not robustly explored the use of voxelotor in populations aligned with the HOPE trial and the marketing authorisation, in which it would be used as a monotherapy or as combination therapy. The committee also recognised there may be a specific subgroup of people with SCD who might particularly benefit from voxelotor. But, it was not presented with any evidence to allow exploration of the clinical effectiveness and cost effectiveness of voxelotor in these populations. At the third committee meeting, the company's positioning of voxelotor was revisited. The committee recalled that voxelotor had been trialled as an additional treatment to standard care therapy, which for 64% of people in HOPE was hydroxycarbamide, rather than a replacement for regular transfusion therapy. It also noted that the company stated that voxelotor would not be used alongside regular transfusion therapy except for a small proportion of people with SCD. The committee concluded that further clinical input on the appropriateness of the company's positioning of voxelotor would be helpful. However, it acknowledged the health inequalities associated with SCD (see section 3.19) and was willing to appraise voxelotor in line with the company's chosen positioning, while

remaining mindful of the large level of uncertainty. The committee considered that this uncertainty could be reduced with further clinical expert input gained through consultation.

Comparators

3.4 The comparator in the company's cost-effectiveness analysis was established clinical management without voxelotor. It was defined as 1 or more of supportive care, hydroxycarbamide and regular blood transfusions. The clinical experts explained that all people with SCD should be offered hydroxycarbamide as first-line treatment. But some people cannot have hydroxycarbamide or choose not to have it because of the risk of side effects and possible impact on fertility. For this group, the clinical experts said they would consider treatment with voxelotor. The committee noted that people are unlikely to be 'unwilling' to take a clinically effective treatment without reason. It asked the patient experts if this would be better phrased as 'ineligible or intolerant', especially if it related to factors such as contraindications because of pregnancy. The patient experts said that many of the reasons driving patient choice would be issues such as effects on fertility and pregnancy. But, there were some people who would choose not to take it even if it was not contraindicated, because of worries about the potential side effects. Some people also have concerns related to hydroxycarbamide being a cancer treatment. The committee sympathised that these factors could make people reluctant to use hydroxycarbamide, and that this must be especially difficult in the context of having so few treatments available. But it would be unusual to completely rule out a potentially clinically effective and medically indicated comparator for these reasons. The committee concluded that it was important to distinguish between people with medical contraindications to hydroxycarbamide, and people who choose not to take it for other reasons. In response to the first draft guidance consultation, the company updated its proposed positioning by removing the term 'unwilling to take hydroxycarbamide'. The committee asked the clinical experts whether, if voxelotor was recommended, they would

continue to use hydroxycarbamide at first line, and which treatments voxelotor would displace. The clinical experts stated that they would not offer voxelotor and hydroxycarbamide together as an initial treatment. And that for now they would continue to offer hydroxycarbamide before voxelotor, apart from for a small subset of people with very low haemoglobin levels, although they didn't specify the level of haemoglobin. The committee understood from this response that clinical practice may change in future, which added more uncertainty about voxelotor's likely treatment positioning in the NHS (see section 3.3). And so the most appropriate comparator was also uncertain. The committee noted that there was also a therapeutic benefit from regular transfusion therapy (see section 3.12) and that the company had proposed that voxelotor would reduce the need for regular blood transfusions. This suggested that regular blood transfusion was also a potential comparator, but this was excluded in the HOPE trial (see section 3.5). In response to the first draft guidance consultation, the company outlined that an indirect treatment comparison between voxelotor and regular blood transfusions would be useful. But it explained that this was not feasible because of lack of data. The EAG agreed with the company. The committee further noted the company's proposed positioning was ill-defined and did not match the trial population because in this positioning, voxelotor could be used as monotherapy or combination therapy (see section 3.3). The eligible population and therefore the comparator for voxelotor monotherapy and combination therapy remained unclear. Taking everything into account, the committee concluded that the most appropriate comparator was uncertain. But it was likely to be either hydroxycarbamide or regular transfusion therapy or a mix of both, and this may differ depending on whether voxelotor is used as monotherapy or in combination.

Clinical effectiveness

Data sources

3.5 The clinical evidence was based on HOPE, a phase 3, double-blind, randomised, placebo-controlled trial of voxelotor compared with placebo. The population was people with SCD who had a haemoglobin level of between 5.5 g/dl and 10.5 g/dl. The trial was done in 60 centres in 12 countries over 24 weeks. It had a 72-week follow up, during which people had treatment. Hydroxycarbamide was allowed in both arms of the trial. Acute rescue transfusions were also allowed, but people having regular blood transfusions were excluded. The primary outcome was the percentage of people with a greater than 1 g/dl increase in haemoglobin at 24 weeks. In the voxelotor 1,500 mg arm of HOPE, 51.1% of people had a greater than 1 g/dl increase in haemoglobin at week 24 compared with 6.5% in the placebo arm. This difference was statistically significant. No treatment effect was observed with voxelotor on the exploratory endpoints reflecting disease burden, which included quality of life, rate of opioid use and percentage of people who required rescue transfusions of red blood cells. The clinical expert explained that people with haemoglobin levels below 6 g/dl would be considered to have severe anaemia and would need treatment in addition to hydroxycarbamide. The committee noted the mean haemoglobin levels at baseline in HOPE were 8.6 g/dl in both arms, so were higher than 6 g/dl and not reflective of a population in whom hydroxycarbamide is not effective enough. In response to the first draft guidance consultation, the company explained that hydroxycarbamide is not indicated for the treatment of haemolytic anaemia and so haemoglobin levels alone are not used to determine whether hydroxycarbamide is effective. The committee concluded that the population in HOPE did not represent the company's proposed NHS practice population or the population in the company's economic model (see section 3.3).

Treatment effect

3.6 The HOPE trial showed a statistically significant difference for voxelotor compared with standard care in the number of people who had an increase in haemoglobin of at least 1 g/dl at week 24. The committee

noted that this was a surrogate outcome, and considered whether it was meaningful for people with haemolytic anaemia in SCD. The patient experts commented that this increase in haemoglobin for people with SCD could provide a considerable benefit. They explained that the lifestyle of people with SCD is determined by the level of anaemia, and an increase of at least 1 g/dl in haemoglobin may improve symptoms and function. One patient expert advised that when their haemoglobin increased in general, they were able to work full time rather than part time, and were able to exercise more and live a healthier lifestyle (the amount of haemoglobin increase was not stated). The clinical experts also shared their experience of using voxelotor in the early access to medicines scheme. They explained the clinical effect of an improvement in haemoglobin with voxelotor occurs within 1 to 2 weeks. They said that for people with SCD, an increase of 1 g/dl in haemoglobin would likely substantially improve symptoms and quality of life. And this effect would be expected to occur across the range of haemoglobin levels seen in SCD, for example, it raises baseline haemoglobin so people are better able to tolerate any exacerbations of disease. They acknowledged that the measured haemoglobin concentration simplifies complex changes in the make-up of circulating blood, which differ according to the reason for a haemoglobin rise (for example, whether it is caused by transfusion, voxelotor or natural variation of the disease). The committee concluded that an increase in haemoglobin of 1 g/dl is likely to be beneficial for people with SCD, despite there being no significant change in quality of life shown in the trial evidence (see section 3.14). However, it acknowledged some uncertainty over whether the benefit may vary depending on the mechanism causing this increase in haemoglobin.

Long-term complications

3.7 The HOPE trial provided data over 72 weeks, and the HOPE open-label extension trial provided data over a further 48 weeks. The EAG noted that HOPE did not provide evidence for the long-term impact of voxelotor on the development of SCD complications. HOPE also showed no significant

difference between voxelotor and placebo for some short-term outcomes, including the proportion and total number of vaso-occlusive crises, health-related quality of life and the proportion of people requiring an acute transfusion. The company explained that HOPE was not designed for this. The clinical experts noted it was difficult to determine whether voxelotor will reduce long-term complications and there is currently no clinical evidence for this. But they explained that long-term complications of SCD can be a result of either vaso-occlusion or chronic haemolytic anaemia. Because voxelotor increases haemoglobin levels, they expected voxelotor would reduce the risk of long-term complications caused by haemolytic anaemia. The clinical experts also noted that there is a lot of 'silent damage' caused by haemolytic anaemia in SCD, with the chronic nature of the disease resulting in end-organ damage. They reported that there is increasing evidence that having chronic haemolytic anaemia affects areas such as cardiac function (because the heart must work harder) and bone density. The committee acknowledged the challenges of providing long-term evidence that voxelotor reduced long-term complications. But it was aware that the NICE manual for health technology evaluations states that when using a surrogate outcome, there should be good evidence that the relative effect of a technology on the surrogate endpoint is predictive of its relative effect on the final outcome. This evidence would preferably come from randomised controlled trials, or if that is not possible, epidemiological or observational studies. In response to the first draft guidance consultation, the company highlighted that the link between lower haemoglobin levels and poorer outcomes is biologically plausible and is demonstrated across epidemiological studies. It noted this corresponds to a level 2 surrogate relationship according to the NICE manual for health technology evaluations. The committee recognised it was clinically plausible that voxelotor could reduce long-term complications in SCD, but because of the lack of evidence, there were high levels of uncertainty around the nature and extent of any effect.

Economic model

Company's modelling approach

3.8 The company submitted a discrete event simulation model to estimate the cost effectiveness of voxelotor compared with standard care for treating haemolytic anaemia in SCD. Possible events in the model occurred on a time-to-event basis. The committee considered that, methodologically, a discrete event simulation model was a valid approach to estimate the cost effectiveness of medicines. It is a flexible approach that allows the incorporation of disease history and competing risks, and the committee appreciated the company's efforts in developing this. But given the highly uncertain assumptions feeding into the model (see sections 3.3 and 3.4, and sections 3.6 to 3.14), many of the advantages of this more sophisticated approach were lost when modelling the cost effectiveness of voxelotor. At the first committee meeting, the committee concluded that the company's modelling approach added uncertainty to the results. It suggested the company could consider either a more straightforward modelling approach, or use its existing model to more fully explore the uncertainties in the underlying assumptions (see sections 3.6 to 3.14), population modelled (see section 3.3) and comparators (see section 3.4). In response to the first draft guidance consultation, the company did not update its modelling approach. But, it did provide scenario analyses varying the rate of regular transfusion therapy with standard care (see section 3.10) and the utility benefit associated with a 1 g/dl increase in haemoglobin (see section 3.14). The EAG noted that although these scenario analyses were useful, they did not resolve the uncertainty in the underlying assumptions. The committee noted that the scenario analyses helped to quantify the uncertainties to an extent. But it concluded that there remained substantial uncertainty around some of the inputs used in the economic model because they were not supported by clinical trial evidence. The EAG noted that real-world evidence might help reduce these uncertainties. The committee recalled that the company did not provide an evidence submission or economic model for a population

aligned with voxelotor's marketing authorisation. The company also did not provide clinical trial evidence for voxelotor in its proposed second-line positioning (see section 3.3). The committee concluded that the company's economic model and proposed second-line positioning did not reflect the population in the HOPE trial. Being mindful of health inequalities in SCD (see section 3.19), the committee was willing to appraise voxelotor in line with the company's chosen positioning, despite the large level of uncertainty (see section 3.3).

Regular transfusion therapy

3.9 The company model included considerably different rates of regular transfusion therapy at baseline for the voxelotor and standard care arms (the exact proportions of people needing regular transfusions in both arms are considered confidential by the company so cannot be reported here). The company explained that there was no clinical trial data to inform the rates and so the estimates for both arms were generated from a modified Delphi panel exercise with 9 English clinicians specialising in SCD. The proportion in the standard care arm was derived from a weighted average of the responses. The proportion in the voxelotor arm was derived from a consensus among the 9 clinicians. The EAG was concerned about this methodology. It thought the company should have at least assumed the same rate in both arms or, preferably, modelled the risk of needing regular transfusion therapy at baseline. The committee was not clear why rates of regular transfusion therapy varied substantially at baseline in the model, given the lack of supporting evidence. The company explained this was based on results from the modified Delphi panel. The committee was aware the section 3.3 of the NICE manual for health technology evaluations states that evidence generated by expert elicitation is subject to risk of bias and high uncertainty. In the company's response to the first draft guidance consultation, it explained the difference in the regular transfusion therapy rates between the 2 arms. It said this was because people in the voxelotor arm had voxelotor after hydroxycarbamide treatment, instead of regular transfusion therapy. The company added

that it was not a result of people already having regular transfusion therapy switching to voxelotor. The committee noted that the different proportions of people having regular transfusion therapy in each arm at baseline was a main and substantial driver of the cost-effectiveness estimates. It also recalled that acute one-off rescue transfusions were allowed in the HOPE trial but regular transfusion therapy was excluded (see section 3.3), so there was no trial evidence for the proportion of people who have regular transfusion therapy with voxelotor or standard care. The committee was concerned that the evidence used to inform the proportions of people having regular transfusion therapy in the model was uncertain. The committee noted it had not seen any clinical evidence that the proportion of people who have regular transfusion therapy differed between voxelotor and standard care. It was also concerned that the company had used 2 different approaches when choosing the values for the 2 arms. This resulted in the value for voxelotor being based on the lower end of the range given by the Delphi panel (because the company asked for a range, and also asked for clinical consensus on the most likely value in that range). Corresponding assumptions for the standard care arm were based on an average of the range (in its submission the company did not report whether it had asked for consensus on the most appropriate value in that range). In response to the first draft guidance consultation, the company explained that the same opportunity was given to discuss and review their answers in the standard care arm, but a consensus was not reached. So it used a weighted mean of the range for the rate of regular transfusion therapy with standard care. The committee noted the company explanation, but it was aware of the large variance in the estimates provided by the modified Delphi panel. It concluded the methodology and results from the modified Delphi panel exercise were uncertain and the company's use of these results to inform the model resulted in uncertain assumptions that were favourable for voxelotor.

Regular transfusion therapy with standard care

3.10 In response to the first draft guidance consultation, the company provided results from an expert consultation done with 9 UK haematologists. The consultation took place between March and April 2023 and set out to estimate the rate of regular transfusions that people have with standard care. The consultation estimated a higher rate of regular transfusions than the rate used in the company base case. The company also provided an estimated rate of regular transfusion therapy with standard care based on consultation with UK clinicians from 2020. This was lower than the rate used in the company base case (the exact rates are considered confidential by the company so cannot be reported here). The company explained that the regular transfusion therapy rate with standard care from the modified Delphi panel in the company base case is a reasonable estimate, placed between the different clinical expert estimates. The EAG acknowledged the difficulties in estimating the regular transfusion rate with standard care and felt that the company preference for the rates from the modified Delphi panel was reasonable based on the data presented. The committee noted the estimate from the modified Delphi panel was highly uncertain. But, it considered the alternative rates provided by the company helped to reduce this uncertainty. The committee concluded that although the rate of regular transfusion therapy with standard care remained uncertain, the most plausible rate based on the evidence presented is that from the company's modified Delphi panel. Nevertheless, this did not negate its concerns over the differential rates used for standard care and voxelotor (see section 3.9).

Regular transfusion therapy with voxelotor

3.11 In its response to the first draft guidance consultation, the company did not provide alternative assumptions for the rate of regular transfusion therapy with voxelotor in the model. The EAG highlighted that the rate of regular transfusion therapy accounted for a substantial proportion of the total treatment costs in the standard care arm, compared with the vastly reduced proportion of total treatment costs in the voxelotor arm (the exact proportions of total treatment costs in both arms are considered

confidential by the company so cannot be reported here). In the absence of further evidence, the EAG provided scenario analyses to explore the uncertainty. In these scenarios, the rate of regular transfusion therapy with voxelotor was based on values from the company's modified Delphi panel. The EAG used the highest value provided in the modified Delphi panel and an average of the lowest and highest value. It also provided a scenario in which the rate of regular transfusion therapy with voxelotor was equal to the rate with standard care. The committee recalled that the HOPE trial excluded regular transfusion therapy and so the results from HOPE could not show a difference in the proportion of regular transfusion therapy between the arms (see section 3.5). It recognised it may have been suitable to exclude regular transfusion therapy in the HOPE trial because of the risk of confounding, because the primary outcome of HOPE was the percentage of people with a greater than 1 g/dl increase in haemoglobin (see section 3.5). This meant there was no clinical trial evidence to support the rates of regular transfusion in the model, including whether it was appropriate to assume different rates of transfusion at baseline with voxelotor compared with standard care (see section 3.9). There was also no observed treatment effect relating to requirement of rescue transfusions of red blood cells in HOPE (see section 3.5). The committee noted that in the scenario analyses provided by the EAG, varying the rate of regular transfusion therapy with voxelotor had a substantial effect on the cost-effectiveness estimates. It was aware the company did not present clinical evidence for the rate of regular transfusions with voxelotor and the value provided by the company was highly uncertain because it was generated from a small number of clinical expert opinions in the modified Delphi panel. It also noted that the company provided other possible sources for the rate of regular transfusion therapy with standard care. This helped reduce the uncertainty. But, it did not provide other possible sources for the rate of regular transfusion therapy with voxelotor. The committee noted the rate of regular transfusion therapy with voxelotor was a major driver of the

cost-effectiveness results and that the values were not based on clinical trial evidence but on clinical opinion from only 1 source, the modified Delphi panel. The committee was aware that the NICE manual for health technology evaluations states that evidence generated by expert elicitation is subject to risk of bias and high uncertainty. It determined that the rate of regular transfusion therapy with voxelotor from the modified Delphi panel was highly uncertain and that assuming a differential rate between voxelotor and standard care, without alternative, more certain evidence was not suitable for decision making because of the profound impact on cost effectiveness and resulting consequences of decision error. It recalled it had not seen any clinical evidence that the proportion of people who have regular transfusion therapy differed between voxelotor and standard care (see sections 3.5 and 3.9). Therefore, the committee concluded, in the absence of further evidence, it should be assumed that the rate of regular transfusion therapy with voxelotor is equal to the rate with standard care from the modified Delphi panel. The committee recognised that alternative evidence to inform a differential rate of regular transfusion therapy with voxelotor compared with standard care would be helpful for decision making. This evidence could possibly be provided from real-world evidence, or through the collection of longer-term data in the NHS through a managed access agreement, and would ideally be categorised into different possible reasons for people having regular transfusion therapy, focusing on where people receive it to treat haemolytic anaemia alone in line with the marketing authorisation for voxelotor. However, it noted that it was presently unable to explore this further because the company had not provided a managed access proposal.

Haemoglobin benefit after regular transfusion therapy

3.12 In its submission, the company assumed in its model that after regular transfusion therapy, people have an increase in haemoglobin compared with baseline (the exact increase in haemoglobin used is considered confidential by the company so cannot be reported here). This was based

on analysis of real-world evidence from the Symphony database in the US 28 days after a transfusion (the exact increase in haemoglobin from Symphony is considered confidential by the company so cannot be reported here). The company received clinical advice that regular transfusion therapy involves a transfusion every 6 weeks and that any increase in haemoglobin declines 3 weeks after a transfusion. So the company halved the value from Symphony. The EAG commented that the value from Symphony was for haemoglobin levels 4 weeks after transfusion. So a haemoglobin increase at 3 weeks should be at least as high as the value at 4 weeks. It therefore preferred to use the value from Symphony for the increase in haemoglobin in people who have had a transfusion. The clinical expert commented that they would expect people with SCD who have regular transfusion therapy to have a therapeutic benefit and an improvement in their quality of life after a transfusion. They also explained that after a transfusion, the increase in haemoglobin is likely to be higher than the company estimate. In response to the first draft guidance consultation, the company highlighted that it would expect the mean change in haemoglobin after transfusions in Symphony to be higher than in the UK. It explained that the UK uses automated red cell exchange therapy more frequently than the US which uses top-up transfusions. It commented that automated red cell exchange therapy does not increase overall haemoglobin concentration as much as top-up transfusions. So the mean change in haemoglobin from the US Symphony database is likely to be higher than that in the UK. But the company did update its model to assume a haemoglobin increase after a transfusion based on the Symphony data. The committee recognised the uncertainty relating to the haemoglobin increase after a transfusion. But, based on the evidence it was presented and clinical expert opinion, the committee concluded that the amount of haemoglobin increase after a transfusion should be based on the Symphony data.

Time-to-event probabilities

3.13 The company's model included estimates of future complications, such as acute renal failure, arrythmias, gallstones, heart failure, stroke and vaso-occlusive crises. To do this, the company linked haemoglobin levels from HOPE with SCD complications using data derived from the UK Hospital Episode Statistics Clinical Practice Research Datalink (HES-CPRD) database. This database provides data on people using primary and secondary healthcare. The company also provided a scenario analysis using the US Symphony data. The EAG noted that the HES-CPRD database only provided data for 2,106 people and that the population was not aligned with the HOPE trial inclusion criteria. That is, the HES-CPRD database included people who had 3 or more confirmed secondary care interactions for SCD before baseline haemoglobin measurement, and not all of the people included had a vaso-occlusive crisis during the previous 12 months (the exact percentage of people is considered confidential by the company and so cannot be reported here). In HOPE, all the participants had at least 1 vaso-occlusive crisis during the 12 months before enrolment. The committee noted that the mean age in the HES-CPRD database was higher than the median age of 24 years in HOPE, and higher than the licensed population that was 12 years and over (the exact mean age in HES-CPRD is considered confidential by the company so cannot be reported here). So, the HES-CPRD database may not be representative of the age in HOPE or the licensed population. The EAG was also concerned about the company's methods of generating time-to-event probabilities. It explained that the company used 1 index haemoglobin level at a specific time point to determine the time-to-event probabilities. The EAG explained it would prefer an analysis that shows how changes in haemoglobin levels affect the probability of experiencing a complication. In response to consultation, the company applied the inclusion criteria for vaso-occlusive crises events from HOPE to the HES-CPRD database, to better match the HOPE trial population. The EAG commented that the company revision better aligns to the HOPE trial population, but it does not address the uncertainty around nature and

extent of raising haemoglobin levels on long-term SCD complications. The committee agreed that the updated company time-to-event analysis using HES-CPRD data better matched the HOPE trial population. It also reflected on its previous conclusion that although there may be some impact of reducing haemoglobin on future complications, this relationship was highly uncertain. It concluded that this added further uncertainty to the model.

Utility values

Source of utility values

3.14 In the HOPE trial there was no significant difference in EQ-5D score between the voxelotor and standard care arms at 72 weeks. The company stated that, although it was not necessarily challenging the use of the EQ-5D as a tool for SCD, it was concerned that it may not have been used effectively in the trial. At technical engagement, the company had also stated that there was little research testing the validity of the EQ-5D for SCD. It noted there was missing EQ-5D data from HOPE at 72 weeks, and that baseline EQ-5D values in HOPE were higher than expected for people with SCD. It also commented that the impact on long-term complications on quality of life was not captured in HOPE. Instead of using direct HOPE trial data, the company used an analysis of EQ-5D data from the Patient Journey Survey of people with SCD to assess the relationship between haemoglobin levels and quality of life. Using linear models of utility as a function of haemoglobin, the company estimated a utility benefit per 1 g/dl increase in haemoglobin and applied this benefit in the model for both arms (the exact utility benefit is considered confidential by the company so cannot be reported here). The patient and clinical experts also commented that the EQ-5D may not capture the true quality of life in people with SCD. They noted that it is a chronic, lifelong condition and so it can be difficult for people with SCD to put into perspective how much the disease impacts their life. The committee recalled the clinical expert's expectation that there would be an improvement in haemoglobin

within 1 or 2 weeks after treatment with voxelotor (see section 3.6). The committee noted that EQ-5D values from earlier in the HOPE trial did not show a significant difference between the arms. Furthermore, it noted that the European Medicines Agency stated 'no beneficial effect of the treatment was observed between groups on endpoints that reflect disease burden and patient wellbeing'. However, the committee recalled the patient expert's statement that an increase in haemoglobin of 1 g/dl could have a substantial impact on quality of life (see section 3.6). It also acknowledged that the experts considered that the trial may not have accurately captured quality of life in SCD, which caused uncertainty. The committee recognised the uncertainty in the clinical evidence. But it noted this could be reduced by exploring alternative approaches, such as:

- reviewing whether the EQ-5D scores from HOPE consist of unusually high numbers
- obtaining EQ-5D scores from other sources (for example, vignettes), or
- exploring an alternative health-related quality-of-life measure (for example, SF-36, which has a longer recall period than EQ-5D).

In response to consultation, the company attempted to exclude EQ-5D scores from HOPE that were higher than general population scores at baseline. But, it explained the data set was too small and not qualitatively different from what had already been presented. It highlighted an improvement in quality of life associated with voxelotor as demonstrated by improvements in the Clinical Global Impression of Change from HOPE. In the voxelotor arm, 74% of people were described as 'very much improved' or 'moderately improved' compared with 47% of people in the placebo arm. It also did a literature review to explore alternative approaches to capture the impact of a 1 g/dl increase in haemoglobin on quality of life. The literature review identified studies in disease areas other than SCD, such as chronic kidney disease, iron deficiency anaemia and anaemias related to cancer. It provided a range of utility benefit between 0.0114 and 0.109 associated with a 1 g/dl increase in

haemoglobin. The company explained that the range identified from the literature review reinforced the uncertainty around the utility benefit associated with a 1 g/dl increase in haemoglobin. So to explore the uncertainty, it provided scenario analyses using utility benefits of 0.028, 0.075 and 0.109 associated with a 1 g/dl increase in haemoglobin. Because its base-case utility value fell within the range identified in the literature review, the company maintained its original base-case utility value. The committee recognised that an increase in haemoglobin of 1 g/dl was likely to be associated with an improvement in quality of life for people with SCD and therefore a utility benefit in the model. But it noted the exact utility benefit was highly uncertain. It recalled that the HOPE trial showed no statistically significant difference in EQ-5D between the 2 arms. It noted the dimensions of EQ-5D include activities of daily living and self-care which were identified by the patient expert as benefits from reduced fatigue after treatment with voxelotor. So quality-of-life benefits of voxelotor should have been detected within the EQ-5D measurements in the HOPE trial. It also recalled comments from the patient and clinical experts that a 1 g/dl increase in haemoglobin may have a substantial impact on the quality of life of someone with SCD. The committee noted the scenario analyses provided by the company and EAG, which confirmed changing the utility value in the model had a minor impact on the cost-effectiveness results. The committee also noted it had not been presented with other plausible utility values for a 1 g/dl increase in haemoglobin specifically in people with SCD. The committee concluded that the utility benefit in the company base case from the Patient Journey Survey of people with SCD is suitable for decision making. It reached this conclusion based on:

- no other plausible utility values being presented for a 1 g/dl increase in haemoglobin in people with SCD
- the minimal impact on cost effectiveness and
- the clinical and patient expert testimonies.

But the committee highlighted this value is very uncertain and understood that health-related quality of life can sometimes be difficult to capture for people with chronic conditions from an early age (see section 3.16). It would have preferred to see alternative health-related quality-of-life values in people with SCD or an alternative quality-of-life measure used in HOPE, such as SF-36.

Costs

Resource use

3.15 The committee noted that in the company model, costs for adverse events associated with SCD were sourced from NHS reference costs 2019/20. It particularly highlighted the costs included in the model for surgical procedures. It recognised that people with SCD who need a surgical procedure must have a blood transfusion to increase their haemoglobin levels before surgery. The committee noted that the costs of blood transfusions were not included in the surgical procedure costs, and so the model may underestimate these costs.

Severity

Quality-adjusted life year weighting

3.16 In its submission, the company explained that haemolytic anaemia in SCD is a severe condition. People with SCD have a range of acute and chronic complications, including progressive organ damage and the associated symptoms and comorbidities. The patient and clinical experts also stated that haemolytic anaemia in SCD is a debilitating condition with symptoms and complications that can negatively impact quality and length of life. The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company provided absolute and proportional quality-adjusted life year (QALY) shortfall estimates in line with NICE's health technology evaluations manual. Absolute QALY shortfall is the future health lost by people with a condition, including quality and length of life, compared with the expected future health of

people without the condition, over their remaining lifetimes. Proportional QALY shortfall represents the proportion of future health that is lost by people with the condition, including quality and length of life. The committee noted that the company's own base case and EAG's absolute QALY shortfall calculation results were below 12, and their proportional QALY shortfall calculation results were below 0.85 (the exact figures are confidential and so cannot be reported here). In response to the first draft guidance consultation, the company accepted that its model did not produce QALY estimates that met the formal quantitative eligibility criteria for severity weighting. But it considered that voxelotor should qualify because the calculation had not fully captured the severity of SCD. The company highlighted that the average age of people in the model was 27.58 years, which meant that the assessment of disease severity had not captured the lifelong burden of disease before entry into the model. It also explained that the QALY loss for people with SCD could be greater than estimated in the model. This is because people who have chronic conditions from an early age have been shown to adapt to their levels of disability. So, paradoxically, they then report better quality of life than would be expected. NICE's health technology evaluations manual clearly stipulates that eligibility for the severity modifier should be based on future rather than past health loss. The committee recognised the impact of the condition (see section 3.1), and it agreed that the model had not fully captured the lifelong nature of the condition. It noted that the characteristics of the population in the company's model did not reflect the populations in the marketing authorisation or the HOPE trial. For example, the populations in the marketing authorisation and the HOPE trial were younger than the population in the model. The committee recognised that SCD can have a substantial impact on people with the condition and their carers. It was disappointed that the model did not adequately capture the population that would have this treatment in NHS practice. It recalled that even the company's own base case did not meet the threshold to allow a

QALY weighting to be applied and so concluded it was unable to apply the 1.2 QALY weighting.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 Because of confidential discounts for voxelotor and other treatments included in the model, the exact cost-effectiveness results are commercial in confidence and cannot be reported here. The company base-case incremental cost-effectiveness ratio (ICER) was below the range that NICE considers an acceptable use of NHS resources, and the EAG's exploratory estimates were substantially above the range. The committee recalled the considerable uncertainty around the evidence for multiple model parameters in the company base case and that some of the assumptions were not supported by clinical evidence. It noted it was not presented with clinical trial evidence for the positioning of voxelotor and that the economic model used clinical opinion for some important inputs. It particularly highlighted the uncertainty of the evidence base for the proportion of people needing regular transfusion therapy in the model. The committee noted that the model was highly sensitive to the rates of regular transfusion therapy and that even a small change in the rates used in the company's base case had a substantial upward effect on the ICER so that it was no longer within the range normally considered a cost-effective use of NHS resources. This was illustrated by the company's and EAG's scenario analyses. Increasing the rate of regular transfusion therapy with voxelotor (see section 3.11) or decreasing the rate of regular transfusion therapy with standard care (see section 3.10) resulted in ICERs that were substantially above the range that NICE considers an acceptable use of NHS resources. The committee also commented that the population in the company model included considerably different rates of regular transfusion therapy in each arm. This was not aligned with the HOPE trial population, in which regular transfusion therapy was excluded (see section 3.5). So the trial population did not represent the company's

proposed population in NHS practice or in the company's economic model (see section 3.3). It recalled that the company's proposed population was narrower than the marketing authorisation (see section 3.3). It also recalled the rate of regular transfusion therapy with voxelotor and that assuming different proportions of people having regular transfusion therapy in each arm at baseline substantially affected the cost-effectiveness results and was highly uncertain (see sections 3.9 to 3.11). There was also no observed treatment effect relating to requirement of rescue transfusions of red blood cells in HOPE (see section 3.5). Because of the substantial uncertainties and potential bias associated with some of the model inputs, the committee concluded that the company's and the EAG's cost-effectiveness estimates were subject to high levels of uncertainty that could not be resolved without providing alternative evidence, which might include further data collection. The committee concluded it was willing to appraise voxelotor in line with the company's chosen positioning, while remaining mindful of the large level of uncertainty (see sections 3.3 and 3.8). The committee also recalled varying the rate of regular transfusion therapy with voxelotor had a substantial effect on the cost-effectiveness estimates (see section 3.11). It was willing to accept further evidence relating to the rate of regular transfusion therapy with voxelotor and considered that it would be beneficial when assessing the cost effectiveness of voxelotor. The committee concluded that this should be provided by the company if available.

The committee's preferred assumptions

3.18 The committee's preferred assumptions mostly aligned with the updated company base case, apart from the rate of regular transfusion therapy with voxelotor:

- utility benefit with voxelotor from Patient Journey Survey of people with SCD
- haemoglobin increase after a transfusion based on Symphony data

- time-to-event analyses using HES-CPRD data
- rate of regular transfusion therapy with standard care from the Delphi panel
- rate of regular transfusion therapy with voxelotor equal to the rate with standard care.

Other factors

Equality issues

3.19 The committee considered potential equality issues raised by the company, experts and patient groups:

- SCD is not widely understood, including among healthcare professionals, which often results in poor healthcare and stigma around seeking pain relief for crises.
- The condition is more common in people from African, Caribbean, Middle Eastern and South Asian ethnic groups, and as a group these people tend to have poorer health outcomes in the UK than people from other ethnic groups.
- There is a high unmet need and limited access to new safe, effective treatments for SCD, which widens health inequalities for the SCD community.

The committee discussed each of the equality issues raised. It noted that any recommendation for voxelotor would be unable to address the issues related to poor healthcare and stigma around seeking pain relief, and that these were beyond the remit of a technology appraisal. It also acknowledged the potential health inequalities faced by people with this condition and was mindful that the principles that guide the development of NICE guidance and standards included the aim to reduce health inequalities. The committee noted that SCD is mostly seen in people from certain ethnic groups, and recognised that these groups experienced worse health outcomes and barriers to treatment. It also noted the All-Party Parliamentary Group's 'No One's Listening' report findings of serious

health inequalities associated with SCD. The committee was hugely grateful to the patient experts for their testimonies about living with the disease. The committee acknowledged that health inequalities affect people with SCD. It concluded that it was willing to take health inequality into account in its decision making by accepting a higher cost-effectiveness estimate than it otherwise would have done, while also accepting the considerable unresolved uncertainty within the clinical evidence that underpinned the economic modelling (see sections 3.3, 3.6, 3.7, 3.8, 3.10, 3.12, 3.13 and 3.14).

Innovation

3.20 The company considers voxelotor to be innovative because it is the only approved treatment that addresses sickle cell haemoglobin polymerisation. Voxelotor is a once daily oral treatment, which has advantages compared with regular transfusion therapy, which needs frequent hospital appointments, can damage veins over time and sometimes needs iron chelation to reduce the risk of iron toxicity. The company also considered that voxelotor will reduce the need for transfusion-related hospital visits. The committee considered comments from patient groups highlighting the limited research and development in SCD compared with other orphan diseases. It agreed there was an unmet need for this population. It also noted its previous conclusion that the model may not have fully captured the severity of the disease. It recalled that the NICE health technology evaluations manual states that the committee should use the most plausible ICER as the primary consideration when making decisions about the acceptability of a technology as a cost-effective use of NHS resources. But, if there are strong reasons to suggest that the health benefits of the technology have been inadequately captured and may therefore misrepresent the health utility gained, this should be taken into account (see section 3.21).

Conclusion

Recommendation

3.21 The NICE health technology evaluations manual states that consideration of the cost effectiveness of a technology is necessary but is not the only basis for decision making. The committee was willing to be flexible, taking into consideration the significant unmet need for effective treatments in SCD, and NICE's aim of reducing health inequalities (see section 3.19). To address health inequalities, it concluded it would accept a higher cost-effectiveness estimate for decision making than it otherwise would have done, despite the considerable unresolved uncertainty. But it noted that departing from NICE's usual range needs to be done with caution, because it displaces funding from what may be more cost-effective treatments elsewhere in the NHS, with an overall net loss of health gain (see the principles that guide the development of NICE guidance and standards). The committee noted that the HOPE trial population did not represent the company's proposed population in NHS practice or in the company's economic model. It noted it was not presented with clinical trial evidence for the company's proposed positioning of voxelotor and that the economic model used clinical opinion for some important model inputs, so the evidence provided for multiple parameters in the model was highly uncertain. It recalled that small changes to these assumptions, specifically rates of regular transfusion, resulted in a substantial increase in the ICERs. The committee was willing to be flexible by:

- accepting greater uncertainty around clinical effectiveness estimates
- accepting a higher cost-effectiveness estimate than it otherwise would have done
- considering potential uncaptured benefits

But despite these flexibilities, the committee's preferred assumptions (see section 3.18) and other scenario analyses that varied the rate of regular transfusion therapy with voxelotor to higher values than that used in the company base case (see section 3.11), resulted in ICERs substantially above the range NICE considers an acceptable use of NHS resources. So, it concluded that voxelotor could not be recommended for routine use.

The committee would welcome scenario analyses from the company that estimate rates of regular transfusion therapy with standard care and voxelotor based on real world evidence.

Managed access

3.22 Having concluded that voxelotor could not be recommended for routine use, the committee considered if it could be recommended with managed access for treating haemolytic anaemia in SCD. The committee recalled that to consider a recommendation with managed access, the committee need a managed access proposal from the company along with a feasibility assessment from NICE. The draft guidance produced after the first committee meeting stated that voxelotor could be a promising new medicine, with potential resolvable uncertainty, and may be a candidate for managed access. Although the company expressed that it would be open to discussing the possibility of managed access, it did not make a managed access proposal for voxelotor. The NHS England Innovative Medicines Fund clinical lead commented that, as a result, it is not clear whether a period of managed access could sufficiently resolve the remaining clinical uncertainties. At the second committee meeting, the company explained it had not submitted a managed access proposal because it believed the additional data provided in response to consultation and an updated patient access scheme had reduced the uncertainties to a level that would permit a positive recommendation. It further explained that the additional data needed to resolve the remaining uncertainties would not be generated through a period of managed access. The committee noted the company's reasons for not submitting a managed access proposal. The committee recalled the rate of regular transfusion therapy with voxelotor and the different proportions of people having regular transfusion therapy in each arm at baseline substantially affected the cost-effectiveness results and were highly uncertain (see sections 3.9 to 3.11). It commented that some of the major uncertainties in the model, in particular the rate of regular transfusion therapy with voxelotor, may have been reduced after a period of managed access. But,

it noted that it had not been presented with a managed access proposal including a feasibility assessment to explore if new evidence could be collected without undue burden on the NHS. After clarifying with the company at the second committee meeting that no managed access proposal had been submitted at any point, the committee concluded that it was unable to consider a recommendation with managed access. It further concluded that it would be willing to consider voxelotor's suitability for managed access at the fourth committee meeting if a proposal was submitted with details on how evidence relating to rates of regular transfusion therapy would be collected.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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

Megan John

Chair, technology appraisal committee D

NICE project team

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

Emily Leckenby
Technical lead

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Kate Moore
Project manager

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