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Draft guidance consultation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: January 2023

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using voxelotor in the NHS in England.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: 1st February 2023
- Second evaluation committee meeting: 16 March 2023
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

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

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

Usual treatments for haemolytic anaemia caused by sickle cell disease include hydroxycarbamide (also known as hydroxyurea) or regular blood transfusions. Voxelotor can be taken on its own or with hydroxycarbamide. There is an unmet need for effective treatments for people with sickle cell disease. The condition is more common in people from African, Caribbean, Middle Eastern or South Asian family backgrounds, who tend to have poorer health outcomes than people from other family backgrounds.

The clinical evidence suggests that a higher proportion of people taking voxelotor have increased haemoglobin levels compared with people having usual treatment. However, although there is likely to be some benefit of increasing haemoglobin levels, the impact on long term outcomes is not certain, and the key trial was short.

All of the cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. And the estimates are uncertain because some of the data included in the economic model was not supported by evidence. So, even taking into consideration the unmet need and health inequalities, voxelotor is not recommended.

2 Information about voxelotor

Marketing authorisation indication

2.1 Voxelotor (Oxbryta, Global Blood Therapeutics) 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

2.4 The list price of voxelotor is confidential. 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 Global Blood 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 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 affect 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 need hospital treatment multiple times a year, which 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, which 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. 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. The committee acknowledged the substantial difficulties 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 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, the effectiveness of hydroxycarbamide at its maximum dose reduced. Hydroxycarbamide also cannot be used during pregnancy or in people trying to conceive. So they moved to another treatment option, crizanlizumab, in line with NICE's technology appraisal guidance on crizanlizumab for preventing sickle cell crises in sickle cell disease, and reported this to be helpful so far. The committee was aware that crizanlizumab is not a comparator in this appraisal. The patient and clinical experts commented that there is a lack of innovation and investment in treatments for SCD and there is 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 concluded that people with SCD would

welcome a new treatment that addresses the short-term symptoms and long-term complications of haemolytic anaemia and improves the quality of life of people with SCD.

Population

3.3 The company positioned voxelotor as second-line treatment after hydroxycarbamide consideration in people who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective. The committee was aware that this would mean voxelotor would be used as monotherapy for people who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or as combination therapy in people for whom hydroxycarbamide is considered insufficiently effective. 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. 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 'second line' was chosen after consultation with 9 UK clinicians who stated that 'second line' is the most likely place in therapy that voxelotor will be used in the NHS, after hydroxycarbamide has been offered. 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. The committee concluded that the company's proposed 'second-line'

positioning was not supported by trial evidence, and that the trial population did not represent the company's proposed population in NHS practice or in the company's economic model. It further concluded that the company had not robustly explored the use of voxelotor in populations in which it would be used as a monotherapy or as combination therapy.

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 are unable to take hydroxycarbamide and some people choose not to 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 areas such as contraindications because of pregnancy. The patient experts said that although many of the reasons driving patient choice would be issues such as effects on fertility and pregnancy, 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 chose not to take it for other reasons.

3.5 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 the level of haemoglobin was not specified. The committee understood from this response that clinical practice may change in future, which added more uncertainty about voxelotor's likely line of therapy in the NHS. 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 3.11) 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. The committee further noted the company's proposed positioning was ill-defined and did not match the trial population; in this positioning, voxelotor could be used as monotherapy or combination therapy (see section 3.3). But 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. Although the company's comparator arm included some proportion of these treatments, the committee concluded that, given the uncertainty, further analyses exploring the impact of voxelotor displacing these treatments and voxelotor being used as monotherapy or combination therapy would be needed for robust decision-making.

Clinical effectiveness

Data sources

3.6 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 and 10.5 g/dL. The trial was done in 60 centres in 12 countries. The trial had a 72-week follow-up, during which treatment was given. 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. The clinical expert explained that people with haemoglobin levels below 6 g/dL would be considered highly anaemic and would require treatment in addition to hydroxycarbamide. The committee noted the mean haemoglobin levels at baseline in HOPE were higher than 6 g/dL (the exact mean haemoglobin level is considered confidential by the company so cannot be reported here) and therefore not reflective of a population in whom hydroxycarbamide is not adequately effective. It also noted 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

3.7 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 3.13). However, it acknowledged some uncertainty over whether the benefit may vary depending on the mechanism causing this increase in haemoglobin.

Long-term complications

3.8 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 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 has to 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. 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

3.9 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 drugs. It is a sophisticated 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 to 3.5,

3.7, 3.8, 3.10 to 3.13), many of the advantages of this more sophisticated approach were lost when modelling the cost effectiveness of voxelotor. The added complexity of this model may have led to more uncertainty than using a more traditional modelling approach, by combining more modelling complexity than usual with more uncertain assumptions than usual. 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 3.7, 3.8 and 3.10 to 3.13), population modelled (see section 3.3) and comparators (see sections 3.4 and 3.5).

Regular transfusion therapy

3.10 The company model included 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 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 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 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 receive regular transfusion therapy with voxelotor or standard care. It was concerned that the evidence used to inform the proportions of people receiving regular transfusion therapy in the model was uncertain. The committee noted it had not seen any clinical evidence of a difference in the proportion of people who have regular transfusion therapy 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 lowest 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) whereas the comparator arm was based on an average of the range (the company did not report whether it had asked for consensus on the most appropriate value in that range). This resulted in assumptions that were more favourable for voxelotor. Finally, the committee noted that whether the rates of regular transfusion were equal between the 2 arms or not had a substantial impact on the incremental cost-effectiveness ratios (ICERs). It was not clear whether the underlying proportion of people who have regular transfusion therapy in the 2 arms would have an impact too. The committee concluded that given the extremely high uncertainty of this value, and its impact on the cost-effectiveness results, the company could explore the impact of alternative assumptions. This could include scenarios in which both arms are equalised at different proportions, and a range of differences in the proportion of regular transfusion therapy across the 2 arms.

3.11 The company also 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 it 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 receive 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, an increase in haemoglobin is likely to be higher than the company estimate. The committee recognised the uncertainty relating to the haemoglobin increase after a transfusion. However, based on the evidence it was presented and clinical expert opinion, it concluded that it is more plausible to assume a haemoglobin increase after a transfusion from the Symphony data. However the committee noted it would also like to see an indirect treatment comparison between voxelotor and regular transfusion therapy to determine the impact on haemoglobin.

Time-to-event probabilities

3.12 To estimate future complications in the model such as acute renal failure, arrythmias, gallstones, heart failure, stroke and vaso-occlusive crises, 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 in HOPE of 24 years, and a 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). That is, 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. The committee agreed that the time-to-event analysis using HES-CPRD data may not be applicable to 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

3.13 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 3.7). 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 3.7). 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 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, such as SF-36, which has a longer recall period than EQ-5D). It concluded 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.

Costs

Resource use

3.14 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 have to have a blood transfusion before surgery to increase their haemoglobin levels. 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

QALY weighting

3.15 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 that is 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 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). 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 also highlighted that the average age of people in the model was 35, which meant that the assessment of disease severity had not captured the lifelong burden of disease before entry into the model. The methods guide 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), but 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 of the marketing authorisation or the HOPE trial, for example the marketing authorisation and the HOPE trial populations were younger than the model population. The committee encouraged the company to investigate whether it could make its model more adequately capture the population that would receive this treatment in NHS practice.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.16 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 cost-effectiveness estimates from the company were above the range that NICE considers an acceptable use of NHS resources, and the EAG estimate was substantially above the range. The committee recalled the considerable uncertainty around the evidence for multiple model parameters. It particularly highlighted the uncertainty of the evidence base for the proportion of people needing regular transfusion therapy in the model. It also commented that the population in the company model was not aligned with the HOPE trial population or the population in which the

company positioned voxelotor in the NHS (see section 3.3). As a result of these uncertainties, the committee concluded that the company and EAG cost-effectiveness estimates were unreliable and not suitable for decision making. The committee was disappointed that it had not been given robust enough analyses to adequately assess the cost effectiveness of voxelotor, given the historic challenges associated with SCD.

Suggested further analyses

3.17 The committee agreed that the model in its current format was not suitable for decision making. This was because it was populated with uncertain data that did not reflect the population that would be expected to receive this treatment in NHS practice, meaning that the clinical and cost-effectiveness were not robustly assessed. It may be beneficial for the company to use a more straightforward modelling approach or use its existing model to more fully explore the uncertainties in the underlying assumptions. But even if the company continues to use its existing model, it could explore the uncertainties around the proposed positioning of voxelotor (see section 3.3), the comparators (see sections 3.4 and 3.5) and the parameters in the model (see sections 3.7, 3.8, and 3.10 to 3.13) using data that it can validate more robustly. Or, where this is not possible, test the impact of alternative assumptions, and use more conservative approaches to mitigate the uncertainty. This would include comparing voxelotor directly with hydroxycarbamide alone, regular transfusion therapy alone, and different mixes of the 2 treatments. The following assumptions would be appropriate for future modelling:

- some utility benefit associated with an increase in haemoglobin level of 1 g/dL
- a haemoglobin increase after regular transfusion therapy from Symphony.

Other factors

Equality issues

3.18 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 family backgrounds, and as a group these people tend to have poorer health outcomes than people from other family backgrounds.
- 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 family backgrounds, and recognised that these groups experienced worse health outcomes and barriers to treatment. It also noted the All Party Parliamentary Group's inquiry 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 concluded that it was willing to take health inequality into account in its decision making (see section 3.20).

Innovation

3.19 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 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 that 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.

Conclusion

Recommendation

3.20 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 3.18). It concluded that in principle it would be willing to accept an ICER slightly higher than is usually acceptable if voxelotor addressed such health inequalities. But it noted that departing from NICE's usual range needs to be done with caution, as 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 population included in the model did not represent the HOPE trial population or the

company's proposed NHS population. It also noted that the evidence provided for multiple parameters in the model was highly uncertain. So, despite being willing to be flexible, it concluded that the most plausible ICER was both highly uncertain and above the range that NICE considers an acceptable use of NHS resources and not suitable for decision making. Therefore, it concluded that voxelotor could not be recommended for routine use.

Managed access

3.21 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. It considered that voxelotor could be promising new medicine, with potential resolvable uncertainty, and may be a candidate for managed access. Although the company expressed they would be open to discussing the possibility of managed access, it had not made 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 resolve the uncertainties in the model. The committee was therefore unable to consider a recommendation with managed access.

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.

Nigel Gumbleton

Technical lead

Carl Prescott

Technical adviser

Kate Moore

Project manager

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