NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Crizanlizumab for preventing sickle cell crises in sickle cell disease

1 Recommendations

1.1 Crizanlizumab is recommended as an option for preventing recurrent sickle cell crises (vaso-occlusive crises) in people aged 16 or over with sickle cell disease only if the conditions in the managed access agreement are followed.

1.2 This recommendation is not intended to affect treatment with crizanlizumab 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.

Why the committee made these recommendations

Treatments to prevent sickle cell crises include hydroxycarbamide (also known as hydroxyurea), which is taken as a tablet, or regular blood transfusions. Crizanlizumab is a treatment injected into the vein (intravenous, or IV) that people aged 16 or over can take on its own or alongside hydroxycarbamide.

The clinical evidence suggests that people taking crizanlizumab have fewer sickle cell crises in a year than if they have best supportive care with or without hydroxycarbamide. However, because the trial was short and included only a small number of people on the licensed dose of the drug, the long-term benefits are uncertain.

There is also uncertainty about the cost-effectiveness estimates because some of the inputs used in the model do not reflect the clinical evidence. The most likely cost-effectiveness estimate is above what NICE normally considers a cost-effective use of NHS resources. Therefore, the committee could not recommend crizanlizumab for routine use in the NHS.

However, there is an unmet need for effective treatments for people with sickle cell disease. They also face health inequalities because the condition is not well understood, results in disability, and is more common in people of African or African-Caribbean family origin, who tend to have poorer health outcomes than other ethnicities. Access to crizanlizumab may help address these inequalities. Because of this, crizanlizumab is recommended for people with sickle cell disease and recurrent vaso-occlusive crises if more data is collected using a managed access agreement, to address the uncertainties in the evidence. This recommendation will be reviewed based on the data collected.

2 Information about crizanlizumab

Marketing authorisation indication

2.1 Crizanlizumab (Adakveo, Novartis) is indicated 'for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics.

Price

2.3 The list price of crizanlizumab is confidential. The company has a commercial arrangement (a managed access agreement including a commercial access agreement). This makes crizanlizumab available to

the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The company's positioning of crizanlizumab is appropriate for the population with recurrent vaso-occlusive crises (VOCs), and in line with the marketing authorisation (issue 1, see technical report page 2).
- Based on the positioning of crizanlizumab in the treatment pathway, the relevant comparators are hydroxycarbamide (also known as hydroxyurea) and regular blood transfusions. Allogeneic stem cell transplant is not a relevant comparator (issue 1, see technical report page 2).
- The results of the SUSTAIN trial are likely to be generalisable to the target population in England. But the uncertainty around how applicable the SUSTAIN trial results are for those who do not seek medical treatment for VOCs cannot be resolved (issue 3, see technical report page 4).
- People are unlikely to have crizanlizumab alongside regular blood transfusions to prevent recurrent VOCs (issue 5, technical report page 7).

The committee discussed the following issues (issues 2, 4, 5, 6 and 7), which were outstanding after the technical engagement stage.

New treatment option

People with sickle cell disease who have recurrent VOCs would welcome a new treatment option

3.1 VOCs happen when sickle-shaped red blood cells block blood vessels (vaso-occlusion) in different parts of the body. It means not enough oxygen is delivered to tissues and organs, causing ischaemic injuries and excruciating pain. If someone has 2 or more crises a year, they are said to have recurrent VOCs. The patient experts explained that, while they have learnt to avoid common trigger factors, VOCs are unpredictable in terms of when they happen and how severe they are. Recovery can take days to weeks, depending on the cause of the crisis. The patient experts described how this unpredictability can be emotionally distressing, and how it can suddenly prevent them from being able to work or do other planned activities. They explained that severe episodes can often require treatment in hospital, and the build-up of complications over time and resulting organ damage significantly affects their quality of life. Treatments to prevent VOCs in adults include hydroxycarbamide or regular blood transfusions. One patient expert explained that, although hydroxycarbamide had effectively reduced the severity of their crises, they stopped treatment because of the potential toxicity associated with its long-term use. The clinical expert explained that, because hydroxycarbamide is a chemotherapy drug, people often prefer not to take it because they are concerned about serious side effects. Hydroxycarbamide may also affect male fertility and prenatal development during pregnancy. The patient experts explained that there have been no new treatments for sickle cell disease for several decades. There is an unmet need for an effective and well-tolerated treatment that can be taken over a lifetime to reduce VOCs. The committee noted comments received during consultation highlighting that hydroxycarbamide and blood transfusions are not always effective in people with severe disease. Crizanlizumab would be an option for these people, who would otherwise

be left without treatment. The patient experts explained that fewer VOCs would mean fewer GP visits and hospital admissions, a reduced risk of organ damage, improved mental health and less time off work. The committee concluded that people with sickle cell disease would welcome a new treatment that reduces the frequency of VOCs and improves their quality of life.

Comparators

The relevant comparators are hydroxycarbamide and regular blood transfusions

3.2 Standard treatment to prevent VOC is generally best supportive care (for example avoiding trigger factors and maintaining general physical and psychological health) with or without hydroxycarbamide (also known as hydroxyurea). Regular blood transfusions may be considered for a small number of people for whom hydroxycarbamide is inappropriate. The company assumed that people would not have treatment with crizanlizumab alongside regular blood transfusions to prevent VOC. The committee noted that, because crizanlizumab had no effect on haemoglobin or measures of haemolysis in the SUSTAIN trial (the main clinical trial; see section 3.3), combining it with blood transfusions could potentially benefit people with sickle cell disease. The clinical expert highlighted that they were not aware of any data to support combined use. They explained that, because regular blood transfusions substantially reduce the number of sickled red blood cells, this reduces the need for crizanlizumab because of its mechanism of action. The clinical expert described how people can have adverse effects from blood transfusions, such as iron overload, and that clinicians prefer not to combine treatments that may further increase the risk of adverse events. The committee concluded that hydroxycarbamide and regular blood transfusions are the only relevant comparators. It agreed that, although there is a lack of

evidence, it was unlikely that people would have crizanlizumab alongside regular blood transfusions to prevent VOCs.

Clinical effectiveness evidence

People on crizanlizumab have significantly fewer sickle-cell-related pain crises than people on placebo

3.3 The clinical evidence came from SUSTAIN, a double-blind, randomised multicentre trial of crizanlizumab compared with placebo. SUSTAIN treatment centres were in the US, Brazil and Jamaica. The trial had a 52-week follow up, during which treatment was given. Use of hydroxycarbamide alongside crizanlizumab was permitted in both arms of the trial, but people having regular blood transfusions were excluded. The primary outcome for SUSTAIN was the annual rate of sickle cell-related pain crises. These were defined as acute episodes of pain caused by a VOC that resulted in a visit to a medical facility and treatment with pain relief medication. The median annual rate of sickle cell-related pain crises was significantly lower for the licensed dose of crizanlizumab (1.63) than for placebo (2.98; p=0.01). Overall and serious adverse event incidence was comparable across arms.

Immature SUSTAIN trial data

Limitations in the trial data mean the long-term clinical effectiveness of crizanlizumab is uncertain

3.4 The company submission highlighted the limitations of the SUSTAIN trial, including the small sample size (n=65 for placebo, n=67 for the 5 mg/kg crizanlizumab dose) and short duration (52-week treatment phase and 6-week follow up evaluation phase). This did not allow differences in long-term outcomes such as mortality or rare events that occur with low annual frequency, such as acute chest syndrome, to be determined. The SUSTAIN trial also did not provide information on the effect of crizanlizumab in people who do not seek medical treatment for VOCs and

instead manage them at home. The committee concluded that the limitations in the trial data mean that the long-term clinical effectiveness of crizanlizumab is uncertain.

The company's model

The company's updated model does not resolve the uncertainty about the change in VOC rate over time after crizanlizumab treatment

3.5 The eligibility criteria in the SUSTAIN trial included 2 to 10 VOCs in the previous 12 months, and patients were randomised based on VOC rate (2 to 4 or 5 to 10) and by concomitant hydroxycarbamide use (yes or no). The company's original Markov model included 3 main health states: no VOCs, 1 or 2 VOCs, 3 or more VOCs, and a death health state. But the committee understood that, because of the trial's eligibility criteria, SUSTAIN could only provide information about people who had 2 or more VOCs at baseline. The ERG considered that the baseline health state occupancy in the model should reflect the patient population in the trial. The company's model structure meant that transition probabilities could not be accurately estimated because it is not known how patients with less than 2 VOCs would transition after the first year in the model, given the 1-year cycle length and duration of the trial. The company explained that, because it had trial results at 1 year, it wanted to show that there was a gradual change over that year. It did this by applying a half-cycle correction to the 1-year cycle length. This meant the distribution of patients at baseline did not match SUSTAIN, and the committee discussed that a monthly cycle length may have been more appropriate. Patients were randomly redistributed to each health state at the end of each cycle, but in the same proportions observed in SUSTAIN so the overall distribution remained the same. The clinical expert explained that because VOCs are unpredictable it is common for people with moderate disease (around 20% to 30%) to fluctuate between a year when they have one hospital admission and a year when they have multiple admissions.

However, the committee heard that, with an effective treatment, the clinical expert would expect a trend towards occupying the lower frequency VOC health states beyond the random fluctuations of crises. They explained that the way in which VOC states are classified in the SUSTAIN trial does not reflect clinical practice. The company provided an updated model in response to the appraisal consultation document, which aimed to resolve the committee's concerns about the model structure. This included changing to a monthly cycle length and updating the baseline VOC health state occupancy to match the baseline position of patients in the SUSTAIN trial. The company explained that the baseline health state distribution was estimated using individual patient data from the SUSTAIN trial and included patients with only 2 or more VOCs, in line with the trial eligibility criteria. The ERG noted that the company's updated model continued to use annualised VOC rates to reallocate patients to health states once every 12 cycles, using the same distribution observed at the end of SUSTAIN over the entire model horizon. The committee was concerned that the updated model did not resolve the uncertainty about the change in VOC rate over time after treatment with crizanlizumab compared with placebo. The committee agreed that it would have preferred for the health states in the model to have matched how patients were stratified according to VOC rate in the SUSTAIN trial. It also considered that VOC state occupancy should have been estimated monthly within SUSTAIN, in line with the updated cycle length, to determine crizanlizumab's treatment benefit over time. The committee concluded that the company's updated model structure does not resolve the uncertainty about the change in VOC rate over time after treatment with crizanlizumab.

Patient weight from SUSTAIN should be used in the model

3.6 In the economic model, SUSTAIN trial data was used to inform the treatment effect of crizanlizumab on the frequency of VOC in people with recurrent VOC. Because of the short duration of the SUSTAIN trial, the

Hospital Episodes Statistics (HES) database was used to estimate the risk of acute sickle cell disease-related complications or death associated with varying frequency of VOC. In the company's original base case, baseline patient characteristics used in the model for age (mean 37.1) and gender distribution (63% female) were taken from the HES database. Body weights (55 kg for females, 65 kg for males) from NICE's guideline on sickle cell disease, which were based on expert opinion, were used to calculate an average patient body weight of 58.7 kg (adjusted for the proportion of females from the HES data). The company considered that using these data sources was consistent with the natural history data in the model and reflected the characteristics of people with sickle cell disease in the UK. The ERG noted that the HES database and the NICE guideline were representative of all patients with sickle cell disease, not just those who had recurrent VOC. Therefore, the data may include patients who would not have crizanlizumab in clinical practice because they are not eligible according to the marketing authorisation. The ERG considered that patient characteristics should come from SUSTAIN, the main source of treatment efficacy. The committee discussed whether people would have crizanlizumab at a younger age than in the SUSTAIN trial, because this would make them less likely to develop complications later in life if the treatment was effective. The clinical expert explained that sickle cell disease is an inherited condition that is often symptomatic from childhood. Intervening earlier would prevent longer-term complications and organ damage, and minimise its psychological and social effects. The committee noted that the marketing authorisation excluded people under 16 so recommendations for this group were outside its remit. The clinical expert suggested that the ratio of females to males in people with recurrent VOC is likely to be around 50:50 in clinical practice. They explained that children with sickle cell disease tend to have a lower weight because of their chronic ill health and increased metabolic rate. The clinical expert suggested that people with a higher frequency of VOC might be slightly underweight because of their ill health and more frequent

hospital admissions. Additional analyses from US data provided by the company at technical engagement indicated that a small proportion of patients with recurrent VOCs (n=729) had an average body weight of 73.6 kg, which was higher than the company's base case. The committee noted that this was lower than the average body weight for the total population of people with sickle cell disease of 84.2 kg (n=11,788). The committee acknowledged that prolonged ill health may affect patient weight, particularly during VOCs, but agreed that it would still expect people's body weight to be greater than in the company's base case. It understood that a higher average patient body weight (60 kg to 80 kg) would increase the dose and number of vials of crizanlizumab needed and subsequent drug wastage. The committee noted that in the HES database most patients had very few or no VOCs per year and the gender distribution was more evenly split in the subgroup of patients with recurrent VOCs than in the company's model. It discussed how in SUSTAIN the mean patient age was lower, the gender distribution ratio was closer to 50%, and body weight was higher than in the company's base case. The committee agreed that using patient characteristics from the SUSTAIN trial would maintain the internal validity of the trial results. It noted that the company considered the trial population to be generalisable to those expected to have crizanlizumab in the NHS. The committee agreed with the ERG's preference to use the age and gender distribution from the HES database to maintain the link between age and gender mix, and complications and mortality estimated from HES data. The committee agreed however that the inputs from the HES database may not reflect the population who would receive crizanlizumab in clinical practice. The committee understood that using patient characteristics from SUSTAIN significantly increased the company's base-case incremental cost-effectiveness ratio (ICER). The company updated its base-case assumptions in line with the committee preferences by using patient weight from SUSTAIN in the model. The committee concluded that patient weight from SUSTAIN should be used in the model.

Hydroxycarbamide use that most likely reflects NHS clinical practice should be used in the model

3.7 In the company's original base case, hydroxycarbamide use in the crizanlizumab and standard care arms was assumed to be 14.2%, based on the UK National Haemoglobinopathy Registry annual report 2018 to 2019. The ERG noted that the National Haemoglobinopathy Registry includes all patients with sickle cell disease and that hydroxycarbamide use is likely to be higher in people with recurrent VOCs. It considered that the higher use of hydroxycarbamide from SUSTAIN should be used in the model. The clinical expert explained that the SUSTAIN trial included sites in the US, where hydroxycarbamide use is higher than the UK. The committee discussed how it would be expected that all people with sickle cell disease would have been offered or had hydroxycarbamide for at least 6 months before being considered for crizanlizumab. This is line with guidance from the British Society for Haematology. It is also in line with the company's positioning of crizanlizumab as either an add on to hydroxycarbamide, if it does not adequately reduce VOCs, or as a single treatment if hydroxycarbamide is inappropriate. The clinical expert said that, in people with homozygous sickle cell disease, hydroxycarbamide use is around 30% in people with recurrent VOCs. The committee heard that the clinical expert might expect approximately 50% of people taking hydroxycarbamide to still be on first-line treatment after 6 months. The committee initially considered that hydroxycarbamide use from SUSTAIN should be used in the model, but acknowledged that there is uncertainty around the proportion of people who would have concomitant hydroxycarbamide in England. The company updated its base-case assumptions for hydroxycarbamide use to 30% to reflect the clinical expert's opinion. The committee noted that the company's response to technical engagement included details from an advisory board with UK clinical experts who estimated that hydroxycarbamide use varied between 10% and 50%. The committee heard from the clinical expert that there is some variation in hydroxycarbamide use across England. However, they

explained that, for the population that would be considered eligible for crizanlizumab, including people with a high VOC rate, it is usually around 30% in clinical practice. The committee considered that 30% hydroxycarbamide use was in the middle of the range outlined by the company's advisory board, and most likely reflects use in the population who would receive crizanlizumab in the NHS. It concluded that the hydroxycarbamide use that most likely reflects NHS clinical practice should be used in the model.

There is limited evidence of a prolonged treatment benefit while on treatment and after stopping treatment with crizanlizumab

3.8 The company assumed a constant lifetime treatment effect while on treatment with crizanlizumab in its base case. The committee concluded that no evidence was presented to show a prolonged treatment benefit with crizanlizumab after the 52-week trial duration. Duration of treatment efficacy was a key driver of the cost-effectiveness results, particularly if any waning of the treatment benefit is taken into consideration. The committee noted that, because there is limited long-term data on the efficacy of crizanlizumab, the uncertainty around a prolonged treatment effect could not be resolved. The company's base case also assumed that crizanlizumab's treatment benefit continues for 2 years in all people after stopping treatment. This was based on results from SUCCESSOR, a retrospective chart review of patients who completed the SUSTAIN trial, which reported data from the 52 weeks after SUSTAIN finished, when patients did not have crizanlizumab. The company highlighted that patients who had the licensed dose of crizanlizumab in the SUSTAIN trial who were then followed up in SUCCESSOR had a similar mean annual VOC rate to the SUSTAIN trial. The ERG considered that a gradual waning of treatment effect over the 2 years was more likely, and that this would be the same as 1 year of full treatment effect post-discontinuation. In its base case, it reduced the post-discontinuation benefit to 1 year (in people who completed 1 year of treatment) to align with the data available

from SUCCESSOR. The committee discussed how the SUCCESSOR data was uncertain because of the small number of patients who had the licensed crizanlizumab dose (n=15). The data was also uncertain because the patients who agreed to further follow up could have been those who had the best outcomes on treatment. Both of these could bias the results in favour of crizanlizumab. It noted that the SUCCESSOR study included the per-protocol population of the SUSTAIN trial, who had at least 12 of the 14 planned study doses of crizanlizumab. The clinical expert suggested that, because crizanlizumab may reduce inflammation of the endothelium, its treatment effect might continue after stopping the drug. However, they said that this was speculative and would depend on how long the drug stays in the blood after stopping treatment. The committee discussed how the evidence from SUCCESSOR did not provide direct evidence of an ongoing treatment effect after stopping treatment. It acknowledged that it may be possible for a short carryover of treatment effect based on the pharmacokinetic and pharmacodynamic data from the SUSTAIN trial. The company updated its base-case assumptions in line with the committee's preference to remove any efficacy after stopping treatment with crizanlizumab in the model. The committee concluded that, although it was possible that there is some treatment benefit after stopping treatment with crizanlizumab, there is very little evidence to support this.

A single utility value from SUSTAIN should be used for all VOC health states, with per-event utility decrements applied

3.9 The utility values for the VOC health states in the company's model were from an unpublished analysis of a 3-year US registry study (LEGACY) with an additional utility decrement applied for individual VOCs and complications of sickle cell disease. The value for the utility decrement for VOC events was from a longitudinal study of health-related quality of life in people in the UK with sickle cell disease (Anie et al. 2012). Utility decrements for other sickle cell disease complications were taken from a

range of published sources. The company considered that, because health-related quality of life data in SUSTAIN was collected at set time points and not specifically when a VOC occurred, the data may have not fully captured the expected impact of VOCs on quality of life. The company also considered that the trial was too short to show an overall change in health-related quality of life related to sickle cell disease complications and long-term organ damage. It therefore preferred to use the LEGACY study, with its longer follow up. The ERG noted that the company's approach to estimating utility values may overestimate the impact of individual VOCs on health-related quality of life. It considered that it was not appropriate to account for sickle cell disease complications and long-term organ damage through the health state utility value for the VOC groups. This was because they are already accounted for separately in per-event utility decrements. Because patients are randomly distributed between health states, the committee discussed how it would be unlikely that patients moving from a more severe to less severe health state would recover from long-term organ damage. The committee understood that the utility values derived from the SF-36 data of patients who completed SUSTAIN were similar for each health state but noted slightly higher utility values for states with more VOCs. The committee did not think this was plausible, so agreed with the ERG's approach of applying a single utility value across all 3 VOC health states to capture health-related quality of life between VOC events (as a weighted average from SUSTAIN), with additional per-event decrements applied for each individual VOC and complication. This significantly increased the company's base-case ICER. Most of the SF-36 questionnaires were administered outside of a recall period that included a VOC event. However, the committee noted that some patients in SUSTAIN had a VOC within the recall window of the SF-36 survey so the company could have estimated the VOC utility decrement from SUSTAIN. The company did not provide any new evidence to support its preferred approach to deriving utility values in response to the appraisal consultation document. At the second

committee meeting the clinical expert noted that people with recurrent VOCs are unlikely to all have the same utility values. The committee noted that because the ERG's preferred method of estimating utilities included a decrement for each VOC, it was satisfied the differences between VOCs had been adequately captured. The committee concluded that the ERG's method for estimating utility values was more appropriate than the company's method. This is because it reduced the risk that VOC events are double counted and better represented health-related quality of life in people with recurrent VOCs.

Drug wastage should be included in the model

3.10 The company's original base case assumed drug wastage for each administration of crizanlizumab. In response to the appraisal consultation document, the company's revised base case assumed no drug wastage in the model. The company explained that this change was because it assumed there would be vial sharing in clinical practice, and that this had been validated by its clinical expert. The committee heard how crizanlizumab would likely be administered in a specialist centre which would mean that it may be possible to minimise some wastage. It discussed that, based on the patient weight from the SUSTAIN trial and the recommended licensed dose of crizanlizumab, drug wastage is expected because only 1 vial size is available. The committee considered that crizanlizumab could be prepared in an aseptic pharmacy facility before being administered and then stored for up to 24 hours. It noted that this process may be time consuming and costly. The committee discussed how someone may not be able to attend their infusion appointment after crizanlizumab had been prepared, which would further increase the likelihood of drug wastage. It recognised that vial sharing may be complex and problematic for crizanlizumab because the dose administered depends on a person's weight, and monthly infusions would need to be scheduled. The committee considered that drug wastage was highly likely

with each administration of crizanlizumab. It concluded that drug wastage should be included the model.

Cost-effectiveness estimates

The company's updated base case does not reflect the committee's preferred assumptions

3.11 In response to consultation, the company incorporated the following assumptions into its base case:

- patient weight from SUSTAIN
- patient age and gender mix from the HES database (to maintain the link between age and gender mix and complications and mortality estimated using HES data)
- hydroxycarbamide use at 30% to reflect NHS practice
- removing post-discontinuation efficacy
- using differential utility values for each VOC health state from LEGACY, with per-event utility decrements applied
- no drug wastage assumed for each administration of crizanlizumab.

The committee noted that the company's updated base case did not include its preferred assumptions on:

- using the ERG's approach to calculate a single utility value (based on SUSTAIN) for all 3 health states with per-event decrements for individual VOCs and complications
- including drug wastage for each administration of crizanlizumab.

The committee discussed the results of its preferred analysis, which were commercial in confidence. It noted that the deterministic ICER was slightly more than £30,000 per quality adjusted life year (QALY) gained. It also noted that the ICER could be substantially higher because of the immature SUSTAIN trial data, uncertainty around the

model input parameters and remaining issues with the model structure. The committee was aware that crizanlizumab's cost effectiveness was highly sensitive to changes in certain parameters in the company's base case, which were associated with uncertainty. These included age, weight and gender distribution, hydroxycarbamide use, duration of treatment effect during and after stopping treatment, and the choice of utility values.

The deterministic ICERs should be used for decision making

3.12 The committee noted that the company's revised base-case probabilistic ICERs were considerably lower than the revised deterministic base-case ICERs. The company considered this to be partly because varying patient weight in the probabilistic sensitivity analysis resulted in fewer vials of crizanlizumab administered for some iterations. The committee discussed how it was unclear why none of the probabilistic sensitivity analyses included a higher patient weight (which requires more crizanlizumab vials) than in SUSTAIN. The ERG explained that, in the company's original submission, certain parameters had not been included in the probabilistic sensitivity analysis, including the proportion of patients in each VOC state and the number of VOC events per health state. When these parameters were included in the probabilistic sensitivity analysis, the probabilistic and deterministic results differed much more substantially. The ERG explained that when patient weight was removed from the probabilistic sensitivity analysis, it still resulted in a large difference between the deterministic and probabilistic ICERs. The committee understood that the ERG was unable to identify the reasons for the discrepancy in the cost-effectiveness results. The committee was concerned that the probabilistic ICERs were highly uncertain. It concluded that in this instance the deterministic results should be used for decision making.

Other factors

Health inequalities were considered in the committee's decision making

3.13 The committee considered potential equalities issues raised by the company, experts and patient groups:

- The patient experts explained that sickle cell disease is not widely understood, including among healthcare professionals, which often results in poor hospital care and stigma around seeking pain relief for crises.
- The committee also heard that, because a significant proportion of patients with sickle cell disease may also be registered disabled because of ill health associated with their disease, for example strokes, chronic leg or foot ulcers and osteonecrosis, there can be problems accessing treatment.
- The committee heard how the condition is more common in people of African or African-Caribbean family origin and that as a group these people tend to have poorer health outcomes than other ethnicities.

The committee noted that these issues had been strongly reiterated in comments received in response to the appraisal consultation document. The committee discussed each of the equality issues raised. It noted that any recommendation for crizanlizumab would be unable to address the issues related to poor hospital care and stigma around seeking pain relief and that these were beyond the remit of a technology appraisal. It discussed potential issues around access to treatments for sickle cell disease in people with registered disabilities. It noted that if crizanlizumab were recommended, healthcare professionals should consider if reasonable adjustments can be made to enable access to crizanlizumab for people who do not receive hospital management of their VOCs or who may have difficulty travelling to hospital because of disability. The committee 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 sickle cell disease is mostly seen in certain minority ethnic populations, and was concerned to hear that consultees said that those populations suffered worse health outcomes and barriers to treatment. The committee concluded that it would consider these issues in its decision making.

The benefits of crizanlizumab are captured in the cost-effectiveness analysis

3.14 The company considers crizanlizumab to be innovative because it is a well tolerated and effective treatment for preventing VOCs in people with sickle cell disease. The committee considered other comments from patient groups highlighting the limited research and development in sickle cell disease compared with other orphan diseases. It acknowledged the limited research into the disease area and noted that crizanlizumab is the first drug to receive a marketing authorisation for treating the disease in several years. The committee recognised that the conditional regulatory approval of crizanlizumab was important to people with sickle cell disease. But it concluded that it had not been presented with evidence of any additional benefits that could not be captured in the QALY.

Conclusion

Crizanlizumab is not recommended for routine use in the NHS

3.15 The committee recalled that the most plausible ICER for crizanlizumab was above £30,000 per QALY gained. It also noted that there were issues with the model structure and that multiple model parameters were highly uncertain, which could lead to a plausible ICER that is considerably higher. NICE's guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS

resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Above a most plausible ICER of £30,000 per QALY gained, the guide to the methods of technology appraisal notes that an increasingly stronger case will need to be identified for supporting the technology as an effective use of NHS resources. NICE's guide to the methods of technology appraisal also states that consideration of the cost effectiveness of a technology is a necessary, but not the sole, basis for decision-making. The committee was willing to be flexible, taking into consideration the significant unmet need for effective treatments in people with sickle cell disease, and NICE's aim of reducing health inequalities (see section 3.13). The committee said that in theory it would be willing to accept an ICER slightly more than what is usually acceptable if it addresses such health inequalities. However, it noted that departing from NICE's usual range needs to be done with caution, as it risks displacing funding from 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). Previously, substantial departures from the usual threshold have been accepted only under policies that were subject to formal public consultation before their adoption. The committee concluded that it was willing to be flexible when considering uncertainty, noting that a conditional marketing authorisation has been granted for crizanlizumab, which requires further data to be collected through several ongoing clinical trials. The committee concluded that, despite applying flexibilities, the ICER was above what NICE normally considers an acceptable use of NHS resources. Therefore, it concluded that crizanlizumab could not be recommended for routine commissioning.

Managed access proposal

A managed access agreement has been proposed by the company

3.16 Having concluded that crizanlizumab could not be recommended for routine use, the committee then considered the company's proposal for ongoing data collection through a managed access agreement, which could help address some of the uncertainties. The company identified 2 sources of evidence that it considered could resolve the committee's uncertainties. The STAND trial is a phase 3 randomised placebo-controlled trial with UK patients. It is examining the efficacy and safety of crizanlizumab, with or without hydroxycarbamide, in patients aged 12 years and over with a history of VOC. The committee noted that the primary analysis of the trial is due to report in 2023. The company considered that the trial would provide data on:

- longer-term efficacy (with data up to 3 years)
- crizanlizumab's impact on the longer-term consequences of sickle cell disease
- duration of treatment effect
- utility values after treatment with crizanlizumab.

Another source of prospective data was the National Haemoglobinopathy Registry. The company proposed that the registry would collect data on people having crizanlizumab in clinical practice, including:

- the frequency of VOCs that lead to hospitalisation while on crizanlizumab
- healthcare utilisation
- age, gender mix and weight of people with sickle cell disease who have recurrent VOCs in the UK
- concomitant hydroxycarbamide use in people with sickle cell disease and recurrent VOCs in the UK.

A managed access agreement could address uncertainties

3.17 The committee agreed that data from the STAND trial and the National Haemoglobinopathy Registry collected through a managed access agreement may be enough to address the current uncertainties in the evidence base for crizanlizumab. It also acknowledged the need to manage the risks to the NHS because of the identified uncertainties. It considered the details of the company's proposed eligibility criteria in the managed access agreement and concluded that they were clinically achievable. The committee recognised the limited data available in people with sickle cell disease and that collecting more data could reduce the uncertainty around crizanlizumab's clinical and cost effectiveness.

Crizanlizumab is recommended for treating sickle cell disease within a managed access agreement

3.18 The high levels of uncertainty about crizanlizumab's long-term clinical effectiveness means that there would be a substantial financial risk to the NHS if the committee was to recommend it for routine use when it may not be cost effective. The committee noted that the risk to the NHS is reduced through the proposed managed access agreement. The committee took into account a range of factors in its decision making, including the unmet need of the disease and health inequalities faced by people with sickle cell disease. The committee was willing to be flexible in its considerations around uncertainty, particularly if access could be managed in a way that reduced the risk to the NHS. The committee was satisfied that further data collection through a managed access arrangement could gather enough evidence on longer-term effectiveness of crizanlizumab. It concluded that crizanlizumab met the criteria to be considered for use with managed access. It recommended crizanlizumab for preventing recurrent VOCs in sickle cell disease patients aged 16 years and older if the conditions in the managed access agreement are followed. When the guidance is next reviewed, the company should use

the committee's preferred assumptions as set out in section 3, unless new evidence indicates otherwise.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within a managed access agreement, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has sickle cell disease with recurrent sickle cell crises and the doctor responsible for their care thinks that crizanlizumab is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within a managed access agreement. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within a managed access agreement, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Review of guidance

5.1 The guidance on this technology will be reviewed when the primary analysis from the STAND trial is available (clinical study report expected December 2025).

Gary McVeigh
Chair, appraisal committee
September 2021

6 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

Each technology appraisal is assigned to a team consisting of 1 technology analyst (who act as technical lead for the appraisal), a technical adviser and a project manager.

Anita Sangha
Technical lead

Alexandra Filby and Victoria Kelly
Technical advisers

Kate Moore
Project manager

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