Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2438

crizanlizumab 10mg/mL concentrate for solution for infusion (Adakveo®)

Novartis Pharmaceuticals UK Ltd

10 June 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan process.

crizanlizumab (Adakveo®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: for the prevention of recurrent vaso-occlusive crises in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxycarbamide or as monotherapy in patients for whom hydroxycarbamide is inappropriate or inadequate.

In a randomised, double-blind, phase II study, crizanlizumab reduced the annual rate of sickle cell-related pain crises requiring medical attention compared with placebo in patients aged ≥16 years who had a history of two to ten such events in the previous year.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

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 or as monotherapy in patients for whom hydroxyurea / hydroxycarbamide is inappropriate or inadequate.[1]

Dosing Information

The recommended dose of crizanlizumab is 5mg/kg administered by intravenous infusion over 30 minutes at week 0, week 2 and every 4 weeks thereafter. Crizanlizumab can be given alone or with hydroxyurea / hydroxycarbamide.

Treatment should be initiated by physicians experienced in the management of sickle cell disease.[1]

Product availability date

31 October 2021

Crizanlizumab meets SMC orphan criteria.

Crizanlizumab has conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA).[1]

Summary of evidence on comparative efficacy

Crizanlizumab is a selective humanised immunoglobulin G2 (IgG2) kappa monoclonal antibody, which binds to P-selectin, an adhesion molecule expressed on activated vascular endothelial cells and platelets, and over-expressed in the chronic pro-inflammatory state associated with sickle cell disease. Binding of crizanlizumab to P-selectin on the surface of activated endothelium and platelets has been shown to block cellular adhesive interactions and prevent vaso-occlusion.[1,2]

Evidence for crizanlizumab comes from a multicentre, randomised, double-blind, parallel group, phase II study (SUSTAIN) which evaluated the efficacy and safety of crizanlizumab compared with placebo in 198 patients with sickle cell disease. Eligible patients were aged 16 to 65 years with a confirmed medical history or diagnosis of sickle cell disease. They had experienced two to ten sickle cell-related pain crises within the previous 12 months (defined as occurrence of appropriate symptoms, visit to medical facility and/or healthcare professional and pain medication treatment). Patients were randomised equally to receive crizanlizumab 2.5mg/kg (n=66), crizanlizumab 5mg/kg (n=67) or placebo (n=65) by intravenous infusion over 30 minutes on days 1 and 15 and every 4 weeks to week 50 (total of 14 doses). Randomisation was stratified according to number of crises in the previous year (2 to 4 or 5 to 10) and hydroxycarbamide (also known as hydroxyurea) use (yes or no). During the study, patients were generally allowed to receive medicines used as standard of care including analgesics, hydroxycarbamide and/or erythropoietin (provided they had

been receiving them ≥6 months and at a stable dose for ≥3 months and remained stable during the study). Study patients could receive aspirin but no other chronic anticoagulant therapy, including warfarin or heparin. Occasional transfusions were permitted but not chronic or regularly planned transfusions.[2,3]

The primary outcome was the annual rate of sickle-cell related pain crises defined as acute episodes of pain with no known cause of pain other than vaso-occlusive event, which resulted in a medical facility visit and treatment with oral or parenteral opiates or parenteral non-steroidal anti-inflammatory drugs (NSAIDs). Episodes of acute chest syndrome, hepatic sequestration, splenic sequestration and priapism were also considered as crisis events. The primary efficacy analysis was performed on data adjudicated by the central review committee in the intention to treat (ITT) population, which included all randomised patients. A hierarchical statistical testing strategy was applied in the study, including the primary and key secondary outcome (annual rate of days hospitalised) for both doses of crizanlizumab versus placebo with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The primary analysis found that the annual rate of sickle cell-related pain crises was significantly reduced in the crizanlizumab 5mg/kg group compared with placebo. There was no significant difference between crizanlizumab 2.5mg/kg and placebo for the primary outcome or crizanlizumab 5mg/kg versus placebo for the key secondary outcome. Results are presented in table 1 for the licensed dose (5mg/kg) and placebo only.[2,3]

Other descriptive secondary outcomes included: time to first and second sickle cell-related pain crisis; annual rate of uncomplicated sickle cell-related pain crises (defined as an acute episode of pain with no known cause other than a vaso-occlusive event requiring a visit to a medical facility, treatment with a parenteral or oral opiate or parenteral NSAID but not classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism) and annual rate of acute chest syndrome (defined on the basis of a new pulmonary infiltrate involving at least one complete lung segment that was consistent with alveolar consolidation).[2,3]

Table 1: Results of primary and secondary outcomes using primary analyses in the ITT population of SUSTAIN[2,3]

			Difference versus placebo	
	Crizanlizumab 5mg/kg (n=67)	**Placebo (n=65)**	**Percentage difference (95% CI)**	**Median of differences* (95% CI)**
Primary outcome				
Median annual rate of sickle cell-related pain crises	1.63	2.98	-45% p=0.01	-1.01 (-2.00 to 0.00)
Secondary outcomes				
Median annual rate of days hospitalised	4.00	6.87	-42%, p=0.45	0.00 (-4.36 to 0.00)
Median time to first sickle cell-related pain crisis, months	4.07	1.38	HR 0.50 (0.33 to 0.74)	NR
Median time to second sickle cell-related pain crisis, months	10.32	5.09	HR 0.53 (0.33 to 0.87)	NR

Median annual rate of uncomplicated sickle cell-related pain crises	1.08	2.91	-63%	NR

CI=confidence interval; HR=hazard ratio; NR=not reported; *Hodges-Lehman estimator of location shift

However, due to uncertainties in the statistical methods for estimating the treatment effect and the handling of missing data using simple annualisation, additional analyses were performed using negative binomial regression and different imputation methods. The European Medicines Agency considered that data based on investigator assessed sickle cell-related pain crises using negative binomial regression and imputation based on "jump to reference" for crizanlizumab patients (crizanlizumab patients stopping study treatment would behave like placebo patients) and "missing at random" for placebo patients were the most appropriate to estimate the benefit of crizanlizumab. This estimate was considered conservative and more in-line with the ITT principle. Using this method, results were reported differently as the mean annual rate of sickle cell-related pain crises and a predicted rate ratio.[1,2] Details are presented in table 2 and found a smaller relative treatment effect compared with placebo which did not reach statistical significance.

Table 2: Results of primary and secondary outcome re-analysed using investigator data, negative binomial regression and conservative imputation method[1,2]

	Crizanlizumab 5mg/kg (n=66)[A]	**Placebo (n=65)**	**Predicted rate ratio (95% CI)**
Primary outcome			
Mean annual rate of sickle cell-related pain crises	3.62	4.95	0.74 (0.52 to 1.06)
Secondary outcomes			
Mean annual rate of days hospitalised	18.24	24.53	0.77 (0.40 to 1.51)
Mean annual rate of days hospitalised due to sickle cell-related pain crises	17.31	24.41	0.72 (0.36 to 1.45)
Time to first sickle cell-related pain crisis, months	3.78	1.15	HR 0.54 (0.36 to 0.81)
Mean annual rate of uncomplicated sickle cell-related pain crises	3.39	4.79	0.72 (0.49 to 1.05)

[A] one outlier patient was excluded from this analysis; CI=confidence interval; HR=hazard ratio

Quality of life was assessed using the brief pain inventory as a secondary outcome; this is a standardised self-reported questionnaire which assesses the intensity of pain and the degree to which pain interferes with function. The Short form 36 version 2 health survey (SF-36v2) was assessed as an exploratory outcome. The SF-36v2 is a standardised self-reported questionnaire which assesses general health on two main domains (physical health and mental health) and eight scales. There were no treatment differences found between crizanlizumab 5mg/kg and placebo in the least square mean change from baseline to week 52 for both of these outcomes.[2,3]

Summary of evidence on comparative safety

In the SUSTAIN study, any treatment-emergent adverse event (AE) was reported by 86% (57/66) of the crizanlizumab 5mg/kg group and 89% (55/62) of the placebo group and these were considered treatment-related in 41% and 24% respectively. In the crizanlizumab 5mg/kg and placebo groups respectively, patients reporting a serious AE were 26% and 27% and patients discontinuing therapy due to an AE was 3.0% and 4.8% respectively.[2,3]

The most frequently reported treatment-emergent AEs of any grade in the crizanlizumab 5mg/kg and placebo groups respectively were: headache (17% and 16%), back pain (15% and 11%), nausea (18% and 11%), arthralgia (18% and 8.1%), pain in extremity (17% and 16%), urinary tract infection (14% and 11%), upper respiratory tract infection (11% and 9.7%), pyrexia (11% and 6.5%), diarrhoea (11% and 3.2%), musculoskeletal pain (12% and 9.7%), pruritus (7.6% and 4.8%), vomiting (7.6% and 4.8%) and chest pain (1.5% and 1.6%).[3]

The most frequently reported serious AEs in the crizanlizumab 5mg/kg and placebo groups respectively were: pyrexia (3.0% and 1.6%) and pneumonia (4.5% and 4.8%).[3]

The summary of product characteristics (SPC) notes that patients should be monitored for signs and symptoms of infusion-related reactions and of interference with automated platelet counts, which can lead to unevaluable or falsely decreased platelets counts. Refer to the SPC for details.[1]

Summary of clinical effectiveness issues

Sickle cell disease is a group of rare genetic disorders caused by a single mutation in the beta-globin gene. The presence of a single sickle cell gene known as sickle cell trait is protective against malaria in endemic regions and is more common in people of African or Caribbean background. Sickle cell disease only occurs in children who inherit a sickle cell gene from each parent and there are different genotypes depending on the second beta-globin variant. All result in mutant haemoglobin, which is less soluble and prone to polymerisation on deoxygenation, causing rigid and distorted, crescent-shaped red blood cells that can leading to vaso-occlusion. Resulting vaso-occlusive events can cause acute and chronic pain crises mainly in the chest, back, hands, feet and joints and can also cause organ damage. Acute chest syndrome is a major cause of mortality. If untreated, the majority of patients become functionally asplenic in early childhood, increasing their risk of infections. Chronic haemolysis also leads to anaemia, jaundice, cholelithiasis, and delayed growth and sexual maturation. Those with the highest rates of haemolysis are at risk of pulmonary artery hypertension, stroke, chronic renal failure and leg ulcers. Therefore, patients with sickle cell disease have chronic morbidity and a reduced life expectancy (42 to 53 years in men and 48 to 58 years in women). Current management includes early diagnosis, education and preventative measures and treatments before symptoms or organ damage occurs. Preventative measures such as maintaining hydration, avoiding temperature extremes and physical exhaustion may reduce crises. Supportive treatment options include anti-inflammatory medicines, analgesics and massage to manage episodes of pain, antibiotics to manage fever and suspected infections and red blood cell transfusions to manage severe complications (including acute chest syndrome

and stroke).[2,4,5] Hydroxycarbamide is the only other medicine licensed for use in the treatment of sickle cell disease.[6,7] It can reduce vaso-occlusive crises and the need for transfusions but not all patients are willing or are able to take it and despite its use some patients still experience crises. The only cure for sickle cell disease is a haematopoietic stem cell transplant but this is only suitable for a minority of patients.[2,4] Crizanlizumab meets SMC orphan criteria for this indication.

Key strengths

- There is evidence from the double-blind, randomised, phase II study (SUSTAIN), in which crizanlizumab (5mg/kg) reduced the annual rate of sickle cell related pain crises compared with placebo. Results based on the primary analysis were statistically significant. In an additional analysis, accounting more conservatively for the substantial level of drop out, the results only numerically favoured crizanlizumab. Results of secondary outcomes, such as the annual rate of days hospitalised due to vaso-occlusive events and annual rate of uncomplicated vaso-occlusive events, also numerically favoured crizanlizumb over placebo but were not assessed for significance.[2,3]

- The treatment effect of crizanlizumab appeared consistent across pre-specified subgroups, including patients who were and were not receiving concomitant hydroxycarbamide, which is relevant to patients eligible for crizanlizumab in clinical practice.[2,3]

- Crizanlizumab is the first monoclonal antibody to bind to P-selectin and to be licensed for the prevention of recurrent vaso-occlusive crises in patients with sickle cell disease aged ≥16 years.[1,2] Clinical experts consulted by SMC considered that crizanlizumab fills an unmet need in patients with sickle cell disease.

- The introduction of crizanlizumab would offer an additional treatment for patients who are receiving hydroxycarbamide or an alternative for patients who cannot or do not want to take hydroxycarbamide. Clinical experts consulted by SMC considered that crizanlizumab is a therapeutic advancement offering an additional well-tolerated treatment option for these patients and that its place in therapy would be in addition or as an alternative to hydroxycarbamide.

Key uncertainties

- There is uncertainty in the size of the treatment effect associated with crizanlizumab. Approximately a third of study patients discontinued study treatment early and although the proportions and time to discontinuation were similar across the treatment groups, it is not clear if this was affected by disease status or lack of efficacy of study treatment. The robustness of the results and the size of the treatment benefit based on the primary analysis are uncertain due to the statistical methods and the simple imputation used to account for discontinuing patients and differed when alternative methods were used.[2,3]

- In the SUSTAIN study, a small number of patients received the licensed dose of crizanlizumab 5mg/kg (n=67) and few of these were aged 16 to 18 years (n=3). In addition, the duration of treatment was limited to 52 weeks, which is considered short to assess the treatment effect on rarer events, including acute chest syndrome, and mortality in a chronic condition.

- The safety profile of crizanlizumab has raised few concerns so far but the available safety data are limited especially for the commercially available formulation. The 52-week duration of the SUSTAIN study is also short to determine the long-term safety of chronic P-selectin inhibition.[2]
- The definition of sickle cell related pain crises / vaso-occlusive crises used in the SUSTAIN study meant that only patients with sickle cell disease who sought medical treatment for crises were enrolled. The primary outcome also assessed the rate of crises using this definition. There are no data on the use of crizanlizumab in patients who manage a crisis at home; most pain crises are believed to be managed at home and therefore the SUSTAIN study may not have fully captured the benefit of treatment with crizanlizumab. In addition, study patients had two to ten vaso-occlusive crises requiring medical treatment in the previous 12 months. There is no evidence to support the use of crizanlizumab in patients who suffered more than ten or less than two crises in the previous 12 months.[2,3]
- Approximately 62% of study patients were receiving concomitant hydroxycarbamide and this may be higher than the proportion who do in clinical practice. Study patients were not allowed to receive regular transfusions and this may affect the generalisability of results to patients who do receive regular transfusions as part of their standard of care. The efficacy and safety of crizanlizumab in patients who do receive regular transfusions is unknown.

MHRA specific obligations

- To further confirm the efficacy and safety of crizanlizumab, the company should submit the results of the primary analysis of a phase III (CSEG101A2301, STAND) study of crizanlizumab with or without hydroxycarbamide in adolescent and adult sickle cell disease patients with vaso-occlusive crises (due by December 2025).
- To further confirm the efficacy and safety of crizanlizumab, the company should submit the final results of the phase II CSEG101A2202 (SOLACE) study of crizanlizumab with or without hydroxycarbamide in sickle cell disease patients with vaso-occlusive crises (due by December 2025).[2]

The specific obligations may address some of the key uncertainties in the clinical evidence presented. The availability of results from the phase II, SOLACE study could provide reassurance on the efficacy and safety of the commercially available formulation of crizanlizumab, which was not used in the key SUSTAIN study. Results from the phase III, STAND study could provide further placebo-controlled evidence using the commercially available formulation of crizanlizumab in a larger study population, including a higher proportion of adolescent patients. The STAND study will also assess the effects of crizanlizumab on vaso-occlusive crises managed at home as well as in a healthcare setting (secondary outcome). However, patients receiving regular transfusions will also be excluded from STAND so the uncertainty of treatment effect in these patients will not be addressed.[2,8,9]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of crizanlizumab, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Sickle cell disease is a severe and life-long genetic condition. Painful crises are a common feature and these episodes can be frequent and unpredictable with the most severe episodes requiring hospitalisation for treatment and analgesia. These crises can also have severe, life-threatening complications. As a result, sickle cell disease has a severe impact on patients' health and well-being and affects all aspects of daily activities including education or work**.** In addition, serious health inequalities and poor acute care has resulted in some patients managing pain crises at home.

- Crizanlizumab may fill an unmet need and address some of the health inequalities in this group of patients. The only medicine currently available to reduce sickle cell disease-related crises in Scotland is hydroxycarbamide. It is not effective for everyone and some are unable or unwilling to take it. Crizanlizumab offers a novel treatment option that can be taken with or without hydroxycarbamide.

- Crizanlizumab would offer a step forward in managing the condition and may reduce the number of crises, relieving the severe pain and distress and the associated risks. It may improve the experience of care and wellbeing of patients who experience fewer unpredictable pain crises, allowing them to participate more fully in daily and social activities, including school and work. It may reduce the need to seek emergency care to manage crises, which have previously led to poor experiences. This in turn may improve their quality of life, mental health and independence.

- The availability of an additional effective treatment may relieve the unpredictable burden of the disease on family and carers. While hospital administration is needed for crizanlizumab, the short predictable administration is not expected to be a treatment burden as family and carers may already support patients by accompanying them to hospital visits for blood tests and monitoring.

Additional Patient and Carer Involvement

We received a patient group submission from Sickle Cell Society UK, which is a registered charity. Sickle Cell Society UK has received 3% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Sickle Cell Society UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

For their submission, the company provided a cost utility analysis within crizanlizumab's full licenced indication. The analysis compared crizanlizumab, at a dose of 5mg/kg and as an add-on treatment to standard of care (SOC), with SOC alone. Treatment in both arms could include hydroxycarbamide. This was confirmed as the appropriate comparison by clinical experts consulted by SMC. Hydroxycarbamide was assumed to be prescribed to 30% of patients in Scotland based on clinical opinion received by the company.

The utilised Markov model followed a cohort of patients across a 55-year time horizon with monthly model cycles. Within the model, patients could occupy one of three health states based on the frequency of VOCs per annum – '<1 VOC', '≥1–<3 VOC', or '≥3 VOC'. Additionally, there was a death state, and patients could experience a number of sickle cell disease complications – acute chest syndrome, sepsis, gallstones, cardiac events, cellulitis, leg ulcers, osteomyelitis, priapism and pulmonary hypertension. Adverse events of treatment were not included in the modelling.

Initial occupancy of the health states was matched to the baseline frequency of VOC reported by participants of the SUSTAIN study[3]. Data on the effectiveness of crizanlizumab at reducing VOC relative to placebo were also taken from the SUSTAIN study, using the primary analysis in the ITT population. The results in the placebo arm were assumed to be representative of patients receiving SOC alone. Instead of using transition probabilities, every 6 months, patients were reallocated across the VOC states in proportions matching those observed during the study. This assumed that there was no treatment waning effect as long as a patient continued to take crizanlizumab. A discontinuation rate for crizanlizumab was included in the model, based on observed data. Upon discontinuation, a patient was assumed to lose all treatment benefits, and be subject to redistribution based on the SOC only proportions at the end of that 6 month period. The frequency of VOC was modelled by multiplying the number of people in each state by the expected number of VOC.

Given the size and duration of the SUSTAIN study, the company reported that it provided insufficent data on mortality and complications, therefore these inputs were informed through analysis of the Hospital Espiode Statistics (HES) database. Survival analysis was used to generate time-variant mortality and complication functions, adjusted for the age and gender distribution of the starting cohort, as well as the frequency of VOC.

The company reported that while utility data were collected from the SUSTAIN study, it was inadequate to capture the day-to-day utility of someone with sickle cell disease at risk of VOC. Instead, the company opted to use utility values extracted from the LEGACY study, a three-year prospective observational study of sickle cell disease patients in the USA.[10] The resulting utility values, representing day-to-day quality of life, reduced as the annual frequency of VOC increased. These were subsequently subject to age adjustment. The disutility for a VOC incident was modelled separately and taken from a British study that measured utility values at the point of hospitalisation for a VOC, discharge and then again a week later, Anie et al (2012).[11] Based on those values the disutility of a VOC was estimated to be 0.007. The disutility of complications were sourced from the literature.

The model included costs for crizanlizumab acquisition (including wastage) and administration. Hydroxycarbamide is an oral formulation, and so only an acquisition cost was included. A major costing element was the use of exchange transfusions for the prevention of VOC. Only those in the SOC arm were assumed eligible to receive these transfusions. The clinical plausibility of this is uncertain. Based on analysis of the HES database a proportion of patients in the SOC arm were assumed to receive transfusions every six weeks with an administration cost of £2,549. Patients were assumed to utilise haematologist visits at a rate of 1 per year for those with fewer than 3 VOC per annum and 3 visits per year for those with 3 or more VOC per year. Each instance of VOC was assumed to cost £1,619, based on the costs of hospitalisation and an assumed rate of transfusions to alleviate the VOC, which could be given to all patients regardless of whether they were treated with crizanlizumab or not. Disease complications were each costed separately based on NHS reference costs.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish either the PAS price or list price results.

Within the context of the model, crizanlizumab increased health related quality of life by increasing the occupancy of the <1 VOC state, relative to the other states. Additionally there was a gain from a reduced incidence of VOC and complications. Crizanlizumab had higher acquisition and administration costs. Those costs were partially offset by lower transfusion costs, lower hospitalisation costs for VOC, lower monitoring costs and lower complication costs.

Strengths of the economic case were assessed as being:

- The model had an intuitive structure, although one which deviated from an independently conducted review of sickle cell disease treatments in the US.[12]
- The clinical evidence came from a randomised trial that directly compared crizanlizumab with placebo on a background of SOC, which could include hydroxycarbamide.
- The company provided a broad set of results that facilitate understanding on how the economic case has been constructed.

Limitations of the economic case were assessed as being:

- The clinical evidence was based on a small study with limited follow up.
- As noted in the clinical section, there was uncertainty over the size of crizanlizumab's treatment effect, based on differing approaches to analyzing the data from the SUSTAIN study. The submitting company reported that sensitivity analysis did not show the size of the treatment effect to be a significant driver of the economic results. However, treatment effect size was not tested sufficiently in that analysis.
- The proportion of patients receiving hydroxycarbamide in Scottish practice was informed by

clinical opinion received by the company, however, it remained a source of uncertainty.

- The means by which patients moved through the model was unusual and appears to suffer from a number of potential limitations that could abstract it from reality. Movement between VOC states can only take place every 6 months, and the company assumed the treatment effect of crizanlizumab is constant across time.
- The company excluded a number of factors from the modelling, believing them as insignificant to the economic case, such as adverse events and low cost elements of treatment. While these were assessed as being minor elements, it was still viewed as a deviation from best modelling practice.
- The dose, and therefore cost, of crizanlizumab is dependent upon body weight. Weight was incorporated into the model as a deterministic mean, in effect assuming all patients had the same total dosage. Account for a distribution in body weight would lead to some patients having a higher dose, increasing the average treatment cost. This would increase the ICER. Further, the average weight of a sickle cell disease patient in Scotland is uncertain. If this was higher than assumed in the base case, this would also increase the ICER.
- The health related quality of life values in the model were uncertain, and the company's choice to source efficacy and utility data from separate studies was not supported by robust justification. Sensitivity analysis showed that the utility values have a large impact upon the outcomes, although the different transformation of the values from the two sources means they were not directly comparable. The company declined to provide additional analysis which would have allowed for a direct comparison, and so the impact of the company's approach was unknown.

The Committee considered the benefits of crizanlizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as crizanlizumab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted crizanlizumab for use on an interim basis in NHSScotland subject to ongoing evaluation and future reassessment.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The British Society of Haematology published "Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease" in May 2018.[5] The guideline states that hydroxycarbamide therapy may decrease the rate of vaso-occlusive crises and hence avoid precipitation of heart failure and death. It recommends that the benefits of hydroxycarbamide should be discussed with patients with homozygous sickle cell anaemia (SS) and sickle cell β^0thalassemia ($S\beta^0$) to enable informed joint decision-making. Treatment with hydroxycarbamide is recommended for patients with SS/$S\beta^0$ to reduce mortality. The guideline also recommends

hydroxycarbamide for patients with SS/Sβ^0 who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, whose disease interferes with daily activities and quality of life and who have a history of severe and/or recurrent acute chest syndrome.

This guideline predates the availability of crizanlizumab.

Additional information: comparators

Hydroxycarbamide is the only other medicine licensed to prevent vaso-occlusive crises in patients with sickle cell disease. However, since crizanlizumab can be used with or without hydroxycarbamide, it is not a direct comparator in all patients.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Crizanlizumab	**5mg/kg by intravenous infusion at week 0, week 2 and every 4 weeks thereafter**	**Year 1: 58,128** **Subsequent years: 53,976**

Costs from BNF online on 22 February 2022. Costs calculated based on an adult weighing 70kg and using the full cost of vials assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 47 patients eligible for treatment with crizanlizumab in year one rising to 48 in year five.

SMC is unable to publish estimates of uptake or the budget impact due to commercial in confidence issues. For the same reason, SMC is unable to provide the budget impact template to NHS health boards.

*Other data were also assessed but remain confidential.**

References

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12. Institute for Clinical and Economic Review. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Evidence Report. March 12, 2020. Available at: https://icer-review.org/topic/sickle-cell-disease/

This assessment is based on data submitted by the applicant company up to and including 14 April 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.