SMC2626

voxelotor film-coated tablets (Oxbryta®)

Pfizer Ltd

10 May 2024

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 medicine process

voxelotor (Oxbryta®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.

SMC restriction: as a second line treatment for haemolytic anaemia in patients with SCD who are intolerant, ineligible or have an inadequate response to, hydroxycarbamide.

In a double-blind phase III study, voxelotor compared with placebo, increased the proportion of patients achieving an improvement in haemoglobin (Hb) levels.

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.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Voxelotor inhibits polymerisation of the mutant form of Hb, sickle haemoglobin (HbS), which is present in sickle cell disease (SCD), by binding to HbS and stabilising the oxygenated form. Increasing the ratio of oxygenated HbS to deoxygenated HbS, inhibits polymerisation of deoxygenated HbS and thereby limits the damage that HbS polymers cause to red blood cells (RBC). Voxelotor inhibits RBC sickling and improves RBC deformability. Voxelotor is taken orally once daily.[1, 2]

1.2. Disease background

Sickle cell disease is a rare genetic (autosomal recessive) disorder, which occurs more commonly in people of African, Caribbean, Middle Eastern or South Asian descent. It is characterised by mutations in the gene for the Hb beta subunit, which produce a mutated form: HbS. When HbS is deoxygenated in the venous capillaries of peripheral tissues it can polymerise to produce HbS polymers that injure the RBC causing a sickle shape, with reduced deformability, impaired flow round the body and a tendency to rupture (haemolyse). Patients suffer haemolytic anaemia, leading to the release of products that damage the vascular system. Many patients suffer from vaso-occlusive crisis (VOC) with acute and chronic pain and other vascular complications, with much higher rates of stroke than the general population. Acute chest syndrome (ACS), characterised by fever and/or respiratory symptoms, is another common cause of hospital admission for SCD patients, and they can have acute anaemia events such as splenic sequestration crisis and aplastic crisis. Infections, such as streptococcus pneumoniae and gram-negative bacteria, pose a danger to SCD patients. Also, they may suffer renal and pulmonary complications, including pulmonary hypertension, and can have involvement of the eye, heart, skin, gastro-intestinal system and gallbladder. Bones may be affected with avascular necrosis of femoral or humeral head. Children can have growth and development delays. Sickle cell disease is associated with substantial reductions in quality of life and life expectancy.[2, 3]

1.3. Company proposed position (if appropriate)

The company has requested that SMC consider voxelotor when positioned as a second line treatment for haemolytic anaemia in patients with SCD who are intolerant, ineligible or have an inadequate response to, hydroxycarbamide.

1.4. Treatment pathway and relevant comparators

First-line treatment comprises hydroxycarbamide (also known as hydroxyurea) and when this is unsuitable or an inadequate treatment option, regular RBC transfusion can be used for prevention when there is a high risk of severe complications such as stroke, ACS or very frequent and severe VOC.[4-7] Allogenic haematopoietic stem cell transplantation (HSCT) can cure SCD, but is associated with risks characteristic of transplantation of cells from another person.[2] In November 2023, exagamglogene autotemcel (Casgevy®) was licensed for treatment of patients ≥12 years of age who have SCD with recurrent VOC and who are suitable for HSCT but do not have a matched donor, it is not currently available for use.

1.5. Category for decision-making process (if appropriate)

Eligibility for interim acceptance decision option

Voxelotor received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency (MHRA). The indication was for the treatment of haemolytic anaemia in adult and paediatric patients 12 years and older with SCD. Voxelotor can be administered alone or in combination with hydroxycarbamide.

Eligibility for a PACE meeting

Voxelotor meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the HOPE study[2, 8] detailed in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	HOPE[2, 8]
Study design	Double-blind phase III study
Eligible patients	Patients, age 12 to 65 years, with SCD (homozygous HbS, sickle haemoglobin C disease, haemoglobin S beta-thalassemia, or other genotypic variants of SCD). Hb 5.5 to 10.5 g/dL and, in past 12 months, 1 to 10 VOC.
Treatments	Voxelotor 1,500 mg, voxelotor 900 mg or placebo orally once daily for 72 weeks.
Randomisation	Stratified by hydroxycarbamide use (yes or no); geographic region (North America, Europe, or other); and age (adolescent [12 to 17 years] or adult [18 to 65 years]). Patients were equally assigned to each treatment group.
Primary outcome	Patients with Hb response, increase from baseline >1.0 g/dL, at week 24.
Secondary outcomes	• Change from baseline in Hb at week 24 • Percentage change from baseline in unconjugated bilirubin at week 24 • Percentage change from baseline in reticulocyte percentage at week 24 • Percentage change from baseline in LDH at week 24.
Statistical analysis	Control of type I error for secondary outcomes by hierarchy was inadequate as the order was informed by interim analyses. Therefore, p-values not reported.

Abbreviations: SCD=sickle cell disease; HbS=sickle haemoglobin ; dL = decilitre; LDH = lactate dehydrogenase; Hb = haemoglobin; VOC = vaso-occlusive crisis.

The primary outcome, Hb response (increase from baseline >1 g/dL) at week 24, was achieved by significantly more patients receiving the licensed dose of voxelotor (1,500 mg) compared with placebo as detailed in Table 2.2. There was inadequate control of type 1 error, therefore, p-values are not detailed for secondary outcomes.[2]

Table 2.2: Primary and secondary outcomes of HOPE study at week 24.[2, 9, 10]

	Voxelotor 1,500 mg (n=90)	Placebo (n=92)
Hb response, n (%)*	46 (51%)	6 (6.5%)
Difference (95% CI)	45% (33%, 57%), p<0.001	
LSM change in Hb (g/dL)	1.1	-0.1
Difference (95% CI)	1.2 (0.9, 1.6)	
Percent change in unconjugated bilirubin	-29%	-2.8%
Difference (95% CI)	-26% (-35%, -17%)	
Percent change in reticulocyte percentage	-18%	6.8%
Difference (95% CI)	-25% (-38%, -12%)	

Percent change in lactate dehydrogenase	-4.6%	3.0%
Difference (95% CI)	-7.5% (-17%, 2.8%)	

* primary outcome. Abbreviations: CI = confidence interval; g/dL = grams/decilitre; Hb = haemoglobin; LSM = least square mean.

In analyses at week 72, within the voxelotor 1,500 mg and placebo groups, 69% (61/88) and 77% (70/91) of patients had a post-baseline VOC event, with 219 and 293 VOC events, respectively, corresponding to adjusted incidence rates of 2.4 and 2.8 events per year.[2]

In an ongoing open-label extension study (HOPE OLE) 178 patients who completed 72 weeks in the HOPE study received voxelotor 1,500 mg once daily. At the data cut-off 31 December 2020, there were 100 patients (56%) ongoing in the study, with 44% (78/178) and 12% (21/178) of patients having completed 72 and 96 weeks of treatment in the extension study, respectively. The effects of voxelotor on Hb and haemolysis markers showed durability. In the modified intention-to-treat population, incidence rates for VOC with voxelotor 1,500 mg; voxelotor 900 mg then 1,500 mg; and placebo then voxelotor 1,500 mg were 1.1, 1.0 and 1.7 events, respectively.[2, 11]

2.2. Evidence to support the positioning proposed by the submitting company

The company has requested that SMC considers voxelotor when positioned as a second line treatment for haemolytic anaemia in patients with SCD who are intolerant, ineligible or have an inadequate response to hydroxycarbamide. They assumed that most patients in the HOPE study were in this category because two-thirds were taking hydroxycarbamide when they decided to enter a clinical study, suggesting that their current management of SCD was not optimal. Pre-specified analysis of the primary outcome by baseline hydroxycarbamide use are detailed in Table 2.3.[2, 8]

Table 2.3: Subgroup analysis of primary outcome by baseline hydroxycarbamide use.[2, 8]

Baseline hydroxycarbamide	Voxelotor 1,500 mg		Placebo		Difference (95% CI)
	N	Hb Response	N	Hb response	
Yes	58	55%	58	5.2%	50% (36%, 64%)
No	32	44%	34	8.8%	35% (15%, 55%)

CI = confidence interval; Hb = haemoglobin.

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the EuroQol EQ-5D-5L and Clinical Global Impression of Change (CGI-C) questionnaires. Within the voxelotor 1,500 mg and placebo groups, 74% (39/53) and 47% (24/51) of patients were assessed by investigators as moderately or very much improved at week 72 compared with baseline.[2, 10]

2.4. Supportive studies

A retrospective analysis of observational data from the US Symphony Health Solutions Integrated Dataverse Database was presented. It included patients with SCD, ≥12 years old, who initiated voxelotor between November 2019 and June 2021 and had activity recorded in the preceding year. Analyses were conducted in subgroups of patients who had an outcome of interest (for example, Hb level or VOC) in the three months prior to voxelotor initiation. Mean follow-up was 3.9 months. Results are supportive of the clinical study evidence, as detailed in Table 2.4. [12]

Table 2.4: Annualised rates of outcomes in Symphony study.[12]

Outcome	N	3 months before voxelotor	After voxelotor initiation
Annualised mean Hb, g/dL (95% CI)	74	7.8 (7,5, 8.2)	8.9 (8.5, 9.4)
IR transfusion (95% CI)	190	7.0 (6.4–7.5)	3.3 (2.6–4.1)
IR VOC (95% CI)	1,065	10.9 (10.4–11.4)	8.4 (7.7–9.0)
IR VOC-related hospitalisation (95% CI)	609	7.2 (6.9–7.6)	4.8 (4.3–5.3)
IR all-cause hospitalisation (95% CI)	749	7.4 (7.0–7.7)	4.6 (4.2–5.1)

Abbreviations: CI = confidence interval; Hb = haemoglobin; IR = mean annualised incidence rate; VOC = vaso-occlusive crisis.

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

The economic analysis is supported by an indirect comparison of voxelotor with regular RBC transfusion therapy as detailed in Table 2.5.

Table 2.5: Summary of indirect treatment comparison

Criteria	Overview
Design	Naïve
Population	Patients with sickle cell disease
Comparators	Voxelotor; regular transfusion therapy
Studies included	HOPE; Symphony Health Solutions Integrated Dataverse Database ad hoc analysis
Outcomes	Change in Hb over time
Results	Voxelotor: individual patient level data, mean values in groups with and without concomitant hydroxycarbamide are considered confidential by the company. Regular transfusion therapy results are considered confidential by the company.

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

3. Summary of Safety Evidence

To reduce confounding by SCD comorbidities, adverse events in the HOPE study were categorised as non-SCD-related or SCD-related. Adverse effects unrelated to SCD in the voxelotor 1,500 mg and placebo groups were reported by 97% (85/88) and 90% (82/91) of patients, respectively, and these were serious in 28% and 25% of patients. Rates of SCD-related adverse events were 78% and 80%, respectively, and these were serious in 52% and 53% of patients. Overall, adverse events led to dose reductions in 15% and 7% of patients in the respective groups and to study drug discontinuation in 13% and 8%.[13]

Most non-SCD-related adverse events were reversible and mild or moderate. Within the voxelotor 1,500 mg and placebo groups these commonly included headache (32% and 25%); diarrhoea (23% and 11%); arthralgia (22% and 14%); nausea (19% and 10%); pyrexia (15% and 7.7%) and rash (15% and 11%).[13] Adverse events related to SCD included sickle cell anaemia with crisis, a term that included VOC and pain crisis (76% and 79%); priapism (13% and 2.4%); osteonecrosis (0 and 1.1%); acute chest syndrome (ACS) and pneumonia (18% and 14%), which comprised ACS (14% and 6.6%) plus pneumonia (6.8% and 10%). The regulatory authority has recommended that rates of some SCD-related adverse events, which occurred at higher rates in the voxelotor groups (ACS and priapism) are to be monitored through pharmacovigilance activities.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the HOPE study, voxelotor 1,500 mg (licensed dose), compared with placebo increased by 45% the proportion of patients achieving an increase in Hb > 1g/dL at week 24. It appeared to be associated with reductions in markers of haemolysis.[2, 8]
- Voxelotor is the first medicine licensed for treatment of haemolytic anaemia in SCD.[1] The other medicine used to treat this condition, hydroxycarbamide, is licensed for prevention of recurrent painful VOC including ACS, although British Society of Haematology (BSH) guidelines recommend broader use.[4, 5]
- The company presented observational data that were supportive of the clinical study data.

4.2. Key uncertainties

- There is a lack of robust evidence that voxelotor improves complications of SCD, such as VOC, ACS and priapism, with the latter two being assessed in ongoing pharmacovigilance activities due to increased rates of these reported as adverse events with voxelotor. In the HOPE study the rates of VOC were similar across the treatment groups, as were the rates of adverse events of sickle cell anaemia with crisis, which includes VOC and pain crisis.[2, 8]
- The company suggested that the Symphony real world evidence (RWE) study indicated improvements in VOC with voxelotor. However, the analysis was limited by retrospective data collection, short follow-up (mean 3.9 months) and selection of a subgroup of patients who had a VOC within three months prior to voxelotor initiation. This could potentiate regression to mean effects that may occur with treatment initiation during a period of disease exacerbation. It is possible that temporal changes in intensity of resource utilisation, which affected data collection, may have confounded comparisons of pre- versus post-voxelotor and the COVID-19 pandemic may also have had an impact.[12]
- Voxelotor is not indicated for the prevention of complications such as stroke, VOC and ACS. Patients who are receiving prophylactic treatment (such as regular transfusion therapy) may not be suitable for voxelotor as any haemolytic anaemia may be resolved by their existing prophylactic therapy.
- The company has requested that SMC consider voxelotor when positioned as a second line treatment for haemolytic anaemia in patients with SCD who are intolerant, ineligible or have an inadequate response to, hydroxycarbamide. In practice, patients within this group who do not require regular transfusion therapy for prophylaxis of complications but are given it to treat haemolytic anaemia may be identified as the relevant population. As the HOPE study excluded patients who were receiving regular transfusions (for prophylaxis or treatment of anaemia),[2, 8] this may limit the application of results to the target population in practice.
- The naïve indirect comparison of voxelotor with regular transfusion therapy has the limitations characteristics of this type of analysis. Also, there was no information on the indication for regular transfusion therapy and no baseline demographic information. It is unclear whether there are substantial differences compared with the HOPE study patients. The methods of calculating pre- and post-transfusion Hb for patients who had repeated

transfusions was not clear. The comparison may not be a robust estimate of the relative effects of voxelotor versus regular transfusion therapy on Hb in the relevant patient population.

- The mechanism of action of voxelotor, stabilisation of oxygenated Hb, could potentially impact the clinical relevance of the primary outcome, increase in Hb of 1 g/dL, if there is reduced release of oxygen from Hb in peripheral tissues. The regulatory review noted that this was investigated in exercise studies that did not provide conclusive reassurance.[2]
- In the HOPE study, type I error for secondary outcomes was not protected, since the multiplicity procedure was informed by, and protocolised after, interim analyses; the population for the interim analyses was part of the final analysis population; and the ordering of the secondary endpoints was changed after the interim analysis. Therefore, no p-values for the secondary endpoints are reported.

4.3. Ongoing studies

Ongoing observational studies are unlikely to address the uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC note that voxelotor in the treatment of SCD fills an unmet need for an additional treatment option for patients for whom hydroxycarbamide is ineffective, unsuitable or not tolerable. They considered that voxelotor is a therapeutic advancement and note that it would be used in practice, as monotherapy or in combination with hydroxycarbamide, for these patients.

4.5. Service implications

Clinical experts consulted by SMC expect no or minimal service implications.

5. 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 voxelotor, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Sickle cell disease (SCD) is a chronic, debilitating condition that affects many systems, is associated with increased risk of blood clots and is often characterised by chronic anaemia, fatigue and frequent, acutely painful, potentially fatal crisis that have an immense psychological impact. It substantially impairs the patients' ability to participate in education, work and social activities, with marked absences preventing them from learning and developing to their potential and from forming friendships and relationships. Patients have significantly reduced quality of life and life expectancy.

- After the first-line treatment, hydroxycarbamide, there are limited options: anaemic patients require regular blood transfusions that need regular hospital visits and venous access, which can become difficult or impossible. They may lead to development of antibodies, infections, iron overload. For patients who are not able to receive these,

symptomatic best supportive care is the only option and there is a substantial unmet need in this setting for additional effective therapies.

- Voxelotor has a novel mechanism of action and improves anaemia and fatigue in patients with SCD, allowing patients to rely less on others for care and to maintain education, work or social activities. Some patients who have received voxelotor noted a reduced frequency and level of painful episodes including hospitalisation, leading to less disruption of daily living and less anxiety and psychological impact from fear of these episodes. Patients reported improvements with voxelotor in their mental health. They perceive it as a preventative medicine, and it may provide them and their family with hope or reassurance that future crisis are less likely and may mitigate anxiety about premature death during a crisis.

- The clinicians noted that voxelotor could be a valuable option for patients with limited or no effective treatments. They consider that improvement of anaemia with voxelotor may lead to benefits in organ damage and complications of SCD but note that long-term data are needed. It is expected that improvements in patients physical and emotional health may lead to reduced use of healthcare services. It was noted that voxelotor has a convenient oral route of administration and its introduction could be managed within existing services.

- There have been few developments in the treatment of SCD for decades and a recent report ('No One's is Listening: an inquiry into the avoidable deaths and failures of care for sickle cell patients in secondary care' in 2021) detailed inadequate investment in SCD care, research and new treatments, which contrasts with other genetic diseases such as cystic fibrosis. Accessing voxelotor would provide patients with reassurance that they are receiving optimum treatment for their condition.

Additional Patient and Carer Involvement

We received a patient group submission from the Sickle Cell Society UK, which is a registered charity. Sickle Cell Society UK has received 13% 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.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (100 years)
Population	People aged 12 years and older with SCD who are intolerant, ineligible or have an inadequate response to hydroxycarbamide.
Comparators	The comparator was standard of care (SoC) comprising of:

	• Regular transfusion therapy (RTT) with symptomatic care • Hydroxycarbamide with symptomatic care • RTT and hydroxycarbamide with symptomatic care • Symptomatic care alone (neither RTT nor hydroxycarbamide) A weighted treatment mix was applied to the patient cohort to determine the numbers of patients receiving each element of SoC.
Model description	A discrete event simulation (DES) model was used to allow a large number of different outcomes to be modelled using a time-to-event (TTE) approach. This was considered to be the most effective way of modelling the complexity of SCD, accounting for both patient heterogeneity and risk of complications and death as a function of time. The model was run for a cohort size of 50,000 with mean age of 27.6 years upon entry. The model adopted an NHS Scotland and social care perspective.
Clinical data	Key clinical evidence on the efficacy of voxelotor was obtained from the HOPE study.[2, 8] The treatment effect of RTT on haemoglobin levels was obtained from the Symphony RWE database of US patients receiving six or more transfusions per year.[3] No direct evidence versus RTT was available and a formal indirect treatment comparison was not feasible. The comparative effectiveness of voxelotor and RTT were compared within the model via a naïve indirect treatment comparison. Voxelotor discontinuation rates observed in the HOPE study were assumed to reflect what would be expected from clinical practice in the UK. It was assumed that 5% of patients on RTT would discontinue annually.
Extrapolation	The relationship between haemoglobin levels and SCD-related events and complications was derived from an analysis of linked NHS primary and secondary care data (Hospital Episode Statistics - Clinical Practice Research Database, HES-CPRD).[14] The impact of improved haemoglobin on event occurrence was calculated using TTE equations simulated over a time period of 5 years and compared against the Kaplan-Meier estimates for cumulative event occurrence. The link between the covariates evaluated and event occurrence was described sufficiently by an exponential TTE equation, except for VOCs where a log-logistic function was preferred. Voxelotor efficacy was assumed to be unchanged as long as the patient stayed on treatment. Excess mortality rates associated with specific comorbidities were derived from the HES-CPRD database and incorporated into the model. The risk of mortality immediately after certain acute events (acute renal failure, arrhythmias, heart failure and sepsis) was captured in the model through an additional one-off mortality risk.
Quality of life	To derive the baseline utility for the model, the overall population utility was taken from UK general population utility values, adjusted for sex and age to match the HOPE study population. A range of utility decrements were applied to the overall population utility at baseline. A treatment related utility decrement of 0.18 was applied to people receiving RTT. Utility decrements associated with SCD complications ranged from 0.07 to 0.688. Instead of using direct HOPE study 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.[15] Using linear models of utility as a function of haemoglobin, a utility benefit per 1 g/dl increase in haemoglobin was applied to both arms of the model.
Costs and resource use	Acquisition and administration costs for voxelotor and hydroxycarbamide were included in the analysis, as well as RTT and acute transfusion costs. The model assumed one-off costs for acute complications and annual costs for chronic complications. RTT related adverse events and non-SCD related grade 3 or greater adverse

	events were both included. Symptom management costs and monitoring costs were also included in the analysis.
PAS	A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price.

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

6.2. Results

SMC would wish to present the cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns raised by the submitting company regarding the PAS, SMC is unable to publish these results or results using list prices.

6.3. Sensitivity analyses

In deterministic one-way sensitivity analysis, the parameters with the greatest impact on ICER were the proportion of chronic transfusion in SoC, cost of transfusion and chronic transfusion discontinuation rate. A range of scenario analyses were performed and presented in Table 6.3.

Table 6.3 Scenario analyses results

	Parameter	**Base case**	**Scenario**
1	Discount rate	3.5%	1.5%
2A	Proportion SoC on RTT: market research	AIC	AIC
2B	Proportion SoC on RTT: clinician survey	AIC	AIC
3A	Discontinuations	RTT 5% HC 5%	RTT 25% HC 25%
3B		RTT 5% HC 5%	RTT 25% HC 5%
4	Discontinuations: Voxelotor responders	13.5%	0%
5	Hb evaluation timepoint	24 weeks	72 weeks
6	Treatment waning	None	5% annual reduction in Hb
7A	Utility increase (per g/dL Hb)	AIC	0.028
7B		AIC	0.075
7C		AIC	0.109
8	Caregiver disutility	Included	Excluded
9	Hb increase with RTT	0.7g/dL per RTT	0.35g/dL per RTT
10A	Proportion RTT use in voxelotor arm	AIC	AIC
10B		AIC	AIC
10C		AIC	AIC
10D		AIC	AIC
11	Combined Scenario: 3B+4		
12	Combined Scenario: 7B+4		
13	Combined Scenario: 2A+10C		

14	Combined Scenario: 2A+3C+10B
15	1 yr delayed treatment effect of voxelotor on RTT
16	Combined Scenario: 10D + VOC incidence from HOPE-OLE
17	Combined Scenario: 15 + VOC incidence from HOPE-OLE

Abbreviations: AIC, academic in confidence; Hb, haemoglobin; HC, hydroxycarbamide; HOPE-OLE, HOPE study open-label extension; RTT, regular transfusion therapy; SoC, standard of care; VOC, vaso-occlusive crises.

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

6.3. Key strengths

The application of a DES model is commendable. Time to SCD-related events was modelled on Hb levels informed by a contemporaneous cohort of patients with SCD from the UK. Use of the Hospital Episode Statistics - Clinical Practice Research Database (HES-CPRD) database to fill in gaps in data from clinical trials is also noteworthy, but has limitations as noted below.

6.4. Key uncertainties

The main weaknesses with the economic analysis were:

- The majority of people in HOPE were taking hydroxycarbamide and were expected to maintain a stable dose when starting voxelotor. However the model had a majority of patients on voxelotor monotherapy. HOPE also excluded people who were having RTT, which is inconsistent with the positioning which allows RTT with voxelotor.

- The treatment mix for SoC and voxelotor included in the base case model is not based on clinical evidence or real-world evidence, but on clinical expert views. The model initially included considerably different rates of RTT for voxelotor based on a modified Delphi panel exercise with 9 SCD clinical experts due to the absence of any clinical trial data. Applying different proportions of RTT use in either the voxelotor or SOC arms was explored in the scenario analysis and led to substantial changes to the ICER. To address this concern, the company provided a revised analysis which used real-world evidence from an observational study (Retrospective Real World Oxbryta Data Collection and Analysis Study [RETRO]) showing a higher proportion of patients on RTT with voxelotor.

- There is some uncertainty about the impact of voxelotor in reducing both short and long term complications in SCD due to a lack of clinical evidence. HOPE showed no significant difference between voxelotor and placebo for some short-term outcomes, including the proportion and total number of vaso-occlusive crises and the proportion requiring an acute transfusion. Following NDC, the submitting company provided longer term results of a post-hoc analysis of the HOPE open-label extension study showing numerically lower rates of VOC and RBC transfusions in patients who continued voxelotor. Applying these data to the model improved the cost-effectiveness of voxelotor.

- There is an over reliance on the surrogate relationship between Hb levels and various SCD complications, which even if biologically plausible still calls into question the extent of

reduction in events. The company linked haemoglobin levels from HOPE with data on SCD complications from HES-CPRD. There are concerns that the database population was much wider than the HOPE inclusion criteria which could bias estimates. Whilst the evidence supports an association between haemoglobin levels with clinical outcomes, it does not necessarily demonstrate that an increase in haemoglobin will cause an improvement in clinical outcomes. The level 2 surrogacy evidence presented is unconvincing and level 1 evidence is minimal.

- There is some uncertainty about the utility gains associated with voxelotor. Instead of using direct HOPE study 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. Alternative values from the literature in other disease areas were tested in the scenario analysis, but only had a minor impact on cost-effectiveness. Whilst it is highly plausible that a 1g/dl increase in Hb leads to improved quality of life, quantifying the beneficial effect of voxelotor on endpoints that reflect disease burden and patient wellbeing continues to be an area of empirical uncertainty.

- The cost of blood transfusions were not included in any surgical procedure costs to resolve adverse events. People with SCD requiring surgery must have a transfusion to increase their Hb levels. Hence the model may underestimate adverse event costs but this is not a key driver of cost-effectiveness.

- The model included caregiver disutilities for multiple acute and chronic conditions associated with SCD. Caregiver disutility should ideally be included as part of the scenario analysis rather than the base case. However, it's exclusion has minimal impact on the ICER and is not pertinent to decision making.

7. Conclusion

The Committee considered the benefits of voxelotor in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as voxelotor 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 voxelotor for restricted use in NHSScotland.

8. Guidelines and Protocols

In 2018, the British Society for Haematology (BSH) published 'Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease.'[5]

In 2017, the BSH published 'Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects.'[6]

In 2016, the BSH published 'Guidelines on red cell transfusion in sickle cell disease. Part II: indications for transfusion.'[7]

9. Additional Information

9.1. Product availability date

21 September 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Voxelotor	**1,500 mg orally once daily**	**£71,803**

Costs from BNF online on 31 January 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimates that there will be around 88 patients eligible for treatment with voxelotor each year. The uptake rate was estimated to be 9% in year one (7 patients) and 29% in year five (25 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

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

References

1. Pfizer Limited. Voxelotor film-coated tablet (Oxbryta®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 27 June 2023.
2. European Medicines Agency. European public assessment report for voxelotor (Oxbryta®), Committee for Human Medicinal Products (CHMP) Assessment report, procedure number EMEA/H/C/004869/0000, 16 December 2021.
3. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. Nature reviews disease primer 2018; 4: 18010.
4. Masters Pharmaceuticals. Hydroxycarbamide film-coated tablet (Siklos®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 13 June 2022.
5. Qureshi A, Kaya B, Pancham S, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol 2018; 181: 460-75.
6. Davis BA, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. Br J Haematol 2017; 176(2): 179-91.
7. Davis BA, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. Br J Haematol 2017; 176: 192-209.
8. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med 2019; 381: 509-19.
9. US Food and Drug Administration (FDA). Multi-discipline review of voxelotor, 213137Orig1s000. www.fda.gov.
10. Global Blood Therapeutics. Clinical study report for GBT440-031 (HOPE), 9 September 2020.
11. Achebe M, Hassab H, Alkindi S, et al. Long-term safety and efficacy of voxelotor for patients with sickle cell disease: results from an open-label extension of the phase 3 HOPE trial (Poster). American Society of Hematology Annual Meeting & Exposition 2021; December 11-14, 20212021.
12. Shah N, Lipato T, Alvarez O, et al. Real-world effectiveness of voxelotor for treating sickle cell disease in the US: a large claims data analysis. Expert Review of Hematology 2022; 15: 167-73.
13. Howard J, Ataga KI, Brown RC, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol 2021; 8: e323-e33.
14. Pfizer Ltd. HealthiQ HES/CPRD analysis of SCD patients report. Data on File. 2021.
15. Pfizer Ltd. Data on file. 2021.

This assessment is based on data submitted by the applicant company up to and including **15 April 2024.**

**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.