SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Oxbryta 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of voxelotor.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Light yellow to yellow, oval shaped, biconvex, film-coated tablet of approximately 18 mm × 10 mm, debossed with “GBT 500” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxbryta is indicated for the 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.

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the management of SCD.

Posology

The recommended dose of Oxbryta is 1500 mg (three 500 mg film-coated tablets) taken orally once daily.

If a dose is missed, treatment should be continued on the day following the missed dose.

Paediatric population
The recommended dose of Oxbryta in patients 12 to < 18 years of age is the same as for adults.

The safety and efficacy of Oxbryta in paediatric patients below the age of 12 years have not been established yet. No data are available.

Special populations

Renal impairment
No dose adjustment is recommended in patients with mild to severe renal impairment. Oxbryta has not been evaluated in patients with end stage renal disease (ESRD) requiring dialysis (see section 4.4).

Hepatic impairment
No dose adjustment of Oxbryta is recommended for patients with mild or moderate hepatic impairment. The recommended dose of voxelotor in patients with severe hepatic impairment (Child Pugh C) is 1000 mg (two 500 mg film-coated tablets) taken once daily (see section 4.4).

Method of administration

Oxbryta film-coated tablets should be swallowed whole with water. Oxbryta can be taken with or without food (see section 5.2). Tablets should not be cut, crushed, or chewed because of the unpleasant taste.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious hypersensitivity reactions have been observed in < 1% of patients treated with voxelotor in clinical studies. Clinical manifestations may include generalised rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia (see section 4.8).

If hypersensitivity reactions occur, voxelotor must be discontinued and appropriate medical therapy must be administered. Voxelotor must not be reinitiated in patients who experience these symptoms with previous use.

Severe cutaneous adverse reactions (SCARs)

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, which can be life-threatening or fatal, has been reported in association with Oxbryta (see section 4.8).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Oxbryta should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction such as DRESS with the use of Oxbryta, treatment with Oxbryta must not be restarted in this patient at any time.

Laboratory test interference

Oxbryta administration may interfere with measurement of haemoglobin (Hb) subtypes (HbA, HbS, and HbF) by high-performance liquid chromatography (HPLC). If precise quantitation of Hb species is required, chromatography should be performed when the patient has not received Oxbryta therapy in the immediately preceding 10 days.

Renal impairment

No clinically significant differences in the pharmacokinetics of voxelotor were observed in subjects without SCD with mild to severe renal impairment (see section 5.2). No dose adjustment is recommended. Safety of voxelotor has not been evaluated in SCD patients with ESRD requiring dialysis.

Hepatic impairment

There are limited data on the safety of voxelotor in patients with SCD with different degrees of hepatic impairment. Based on pharmacokinetic data in subjects without SCD, severe hepatic impairment increases voxelotor exposures (see section 5.2). The voxelotor dose in patients with severe hepatic impairment (Child Pugh C) should be adjusted (see section 4.2).

Concomitant strong CYP3A4 inducers

Concomitant use of strong CYP3A4 inducers with Oxbryta should be avoided due to the risk of decreased efficacy of voxelotor (see section 4.5).

SCD genotypes

Most patients (90.5%) in the pivotal Phase 3 study had SCD genotype HbSS (75.2%) or HbS/β^0-thalassemia (15.3%). Therefore, safety and efficacy data on other SCD genotypes are limited.

Elderly

Clinical studies of voxelotor did not include patients > 65 years of age.

Combination therapy with hydroxycarbamide

When Oxbryta is administered in combination with hydroxycarbamide, the prescribing information of hydroxycarbamide should be consulted.

Immunosuppressive effects

Voxelotor decreased the humoral immune response to antigens in both rats and monkeys. Clinical relevance in already immunocompromised patients or in patients treated with immunosuppressive drugs cannot be excluded.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 1500 mg (daily dose), that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on voxelotor

Strong CYP3A4 inducers

Coadministration of strong CYP3A4 inducers may decrease voxelotor exposures and may lead to reduced efficacy.

Coadministration of voxelotor with strong CYP3A4 inducers (i.e., rifampicin, phenobarbital, carbamazepine, phenytoin, and St John’s wort extract) should be avoided.

Other interactions studied

Itraconazole (a strong CYP3A4 inhibitor), omeprazole (acid reducing agent), and hydroxycarbamide had no effect on the pharmacokinetics of voxelotor.

Effect of voxelotor on other medicinal products

CYP3A4 substrates

Voxelotor increased the systemic exposure of midazolam (a sensitive CYP3A4 substrate). The observed exposure increase of the CYP3A4 substrate midazolam was 1.6-fold in healthy subjects at a voxelotor sub-therapeutic dose (observed voxelotor C_{max} 7.0 - 8.0 microgram/mL and AUC 126.3 - 148.9 microgram·hr/mL). The effect at the full dose level of voxelotor is expected to be larger. Coadministration of voxelotor with sensitive CYP3A4 substrates with a narrow therapeutic index (i.e.,

alfentanil, sirolimus, and tacrolimus) should be avoided. If concomitant use is unavoidable, consider dose reduction of the sensitive CYP3A4 substrate(s).

CYP2B6 substrates

In vitro studies indicated that voxelotor acts as an inhibitor and inducer of CYP2B6 (see section 5.2). The clinical relevance is currently unknown, and caution is recommended when co-administering voxelotor with sensitive substrates of CYP2B6 such as bupropion and efavirenz.

CYP2C8, CYP2C9, and CYP2C19 substrates

Voxelotor is an *in vitro* inhibitor of CYP2C8, CYP2C9, and CYP2C19 at maximal systemic concentrations. There was no observed change on the exposures of S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) in healthy volunteers at a sub therapeutic voxelotor dose (observed voxelotor C_{max} 7.0 - 8.0 microgram/mL and AUC 126.3 - 148.9 microgram·hr/mL). The effect at the full dose level of voxelotor is currently unknown. Caution is recommended when co-administering voxelotor with sensitive substrates of CYP enzymes.

Transporter-mediated drug interactions

In vitro studies indicated that voxelotor may act as an inhibitor of OATP1B1, OAT3 and MATE1 transporters (see section 5.2). Therefore, caution is recommended when co-administering voxelotor with sensitive substrates of these transporters, especially for those substrates with a narrow therapeutic index.

Concomitant use of voxelotor with digoxin (a P-gp substrate) did not alter digoxin to a clinically relevant extent. Voxelotor is not an inhibitor of bile salt export pump (BSEP). It is not known if voxelotor affects the oral absorption of breast cancer resistance protein (BCRP) substrates.

Oral contraceptives and other steroidal agents

Specific interaction studies with oral contraceptives have not been performed. However, based on the results of *in vitro* studies, a negative impact of voxelotor on contraceptive efficacy is not expected.

Other interactions studied

Voxelotor did not change the systemic exposure of caffeine (CYP1A2 substrate) and metoprolol (CYP2D6 substrate).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of voxelotor in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure**,** it is preferable to avoid the use of Oxbryta during pregnancy.

Breastfeeding

It is unknown whether voxelotor/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of voxelotor in milk and subsequent uptake in pups (for details see section 5.3). A risk to the newborns/infants cannot be excluded. Voxelotor should not be used during breast-feeding.

Fertility

No human data are available on the effect of voxelotor on fertility. In rats, effects on sperm motility and morphology were observed. These effects did not, however, affect the reproductive performance (see section 5.3). Relevance to human is not known.

4.7 Effects on ability to drive and use machines

Oxbryta has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include headache (31.8%), diarrhoea (22.7%) and abdominal pain (22.7%). Serious adverse reactions include headache (1.1%) and drug hypersensitivity (1.1%). Permanent discontinuation due to an adverse reaction occurred in 2.3% of patients.

Dose modifications (dose reduction or dosing interruption) due to an adverse reaction occurred in 13.6% of patients who received voxelotor in the pivotal study. The adverse reactions requiring dose modification included rash (4.5%), diarrhoea (3.4%), headache (2.3%), nausea (2.3%), abdominal pain (1.1%), and drug hypersensitivity (1.1%).

Severe cutaneous adverse reactions (SCARs): drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with Oxbryta treatment (see section 4.4).

Tabulated list of adverse reactions

Table 1 lists adverse drug reactions that occurred in patients treated with voxelotor 1500 mg during a 72-week, randomized, double-blind, placebo-controlled pivotal Phase 3 study (n=88), as well as adverse reactions from postmarketing experience.

Adverse reactions reported with voxelotor are listed by system organ class and preferred term. Within each system organ class, adverse reactions are listed under frequency categories. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon

(≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available clinical study data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse reactions

System organ class	Adverse reactions[a]	Frequency category
Immune system disorders	Drug hypersensitivity	Uncommon
Nervous system disorders	Headache	Very common
Gastrointestinal disorders	Diarrhoea Abdominal pain[b] Nausea	Very common
Skin and subcutaneous tissue disorders	Rash[c]	Very common
	Pruritus	Common
	Drug reaction with eosinophilia and systemic symptoms (DRESS) Angioedema[d]	Not known

a. Adverse reactions were NCI Grades 1 or 2 except for Grade 3 diarrhoea (n=1), nausea (n=1), rash (n=1), rash generalized (n=3) and hypersensitivity (n=1).

b. Abdominal pain includes abdominal pain, abdominal pain upper, and abdominal pain lower.

c. Rash includes rash, urticaria, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash papular.

d. Angioedema includes swelling of eyelid, face oedema, lip swelling, and periorbital swelling.

Description of selected adverse reactions

Gastrointestinal (GI) disorders
In the pivotal Phase 3 study, the most commonly reported GI adverse reactions were diarrhoea, abdominal pain and nausea with diarrhoea and nausea showing a dose-dependent effect. The majority of reported GI events were Grade 1 or 2 and were manageable without the need for dose interruption, reduction or treatment discontinuation and resolved with continued use. Gastrointestinal adverse reactions resulting in dose reductions occurred in 4.5% of patients. Diarrhoea was the most common adverse reaction and was reported in 22.7%, and 11.0% of patients in the voxelotor 1500 mg, and placebo groups, respectively. There was 1 (1.1%) report of Grade 3 diarrhoea. A serious adverse reaction of nausea resulting in hospitalization occurred in 1 (1.1%) patient in the voxelotor 1500 mg group.

Drug hypersensitivity
In the pivotal Phase 3 study, 1 patient (1.1%) experienced drug hypersensitivity on Study Day 40. Observed symptoms included generalized morbilliform rash, urticaria, mild shortness of breath, mild facial swelling, pyrexia, headache, and diarrhoea. Elevated eosinophils were noted. Symptoms abated after voxelotor was withheld, and recurrence was observed after reintroduction of voxelotor. Event resolved with antihistamine and oral corticosteroids.

Rash
In the pivotal Phase 3 Study, rash was reported in 14.8% and 11.0% of patients in the voxelotor
1500 mg and placebo groups, respectively. The majority of rash events were similar in appearance (consistent with typical maculopapular drug eruptions) and distribution, were not associated with extradermal symptoms, and were clinically manageable with or without

treatment including oral antihistamines or topical corticosteroids. Exposure-response analysis did not reveal a statistically significant dose- or exposure-response relationship.

Paediatric population

The safety profile observed in paediatric patients 12 to < 18 years of age treated with voxelotor in the clinical studies was similar to that seen in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There was one report of overdose in the pivotal Phase 3 study where a patient took a total of 3000 mg of voxelotor at one time. There were no adverse reactions associated with this event.

In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, ATC code: B06AX03

Mechanism of action

Voxelotor is a haemoglobin S (HbS) polymerisation inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to red blood cells (RBCs). By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerisation. Voxelotor inhibits RBC sickling and improves RBC deformability.

Pharmacodynamic effects

The pharmacodynamic effect of voxelotor treatment demonstrated a dose-dependent increase in Hb oxygen affinity as determined by the change in p20 and p50 (partial pressure of oxygen

at which Hb oxygen saturation of 20% or 50% is achieved) that was linearly correlated with voxelotor exposure leading to inhibition of HbS polymerisation. The impact of the anti-polymerisation effect is to reduce measures of haemolysis (indirect bilirubin) with a concomitant decrease in percent reticulocyte count and an increase in Hb consistent with improvement in haemolytic anaemia.

Cardiac electrophysiology
At plasma concentrations approximately 2-fold above therapeutic concentrations, voxelotor does not prolong QT interval to any clinically relevant extent.

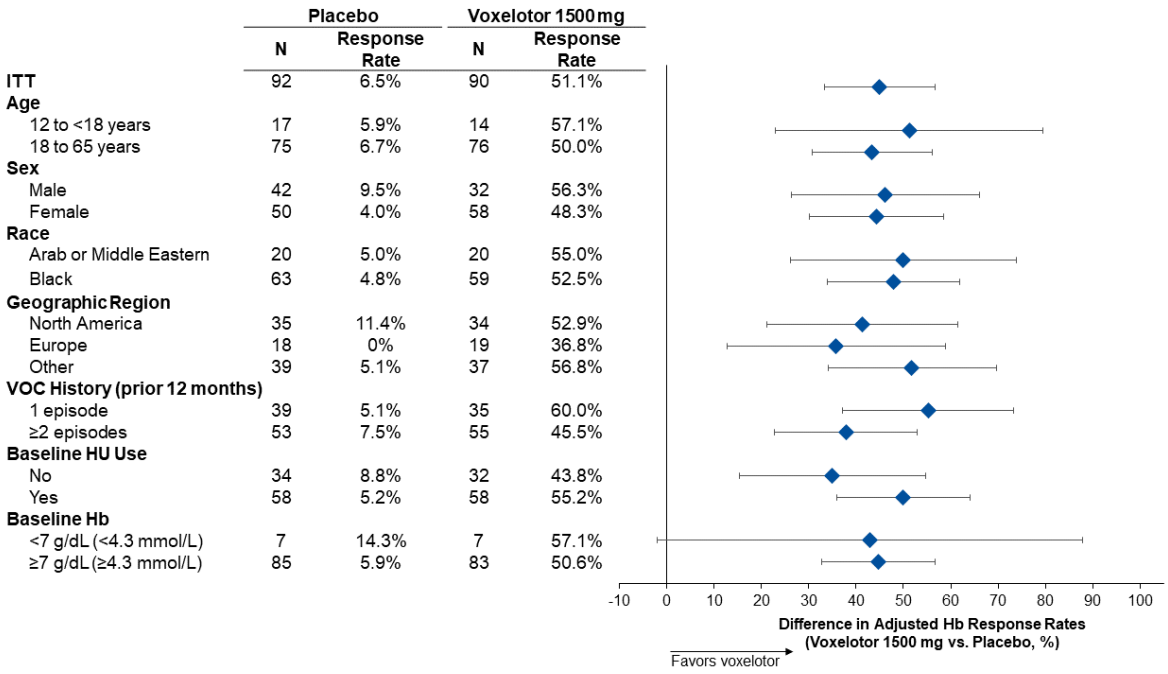
Clinical efficacy and safety

The efficacy and safety of voxelotor in patients with SCD was evaluated in a randomised, double-blind, placebo-controlled, multicentre study (EudraCT2016-003370-40). In this study, 274 patients were randomised to daily oral administration of voxelotor 1500 mg (N=90), voxelotor 900 mg (N=92), or placebo (N=92). Patients were included if they had baseline Hb ≥ 5.5 g/dL (3.41 mmol/L) to ≤ 10.5 g/dL (6.52 mmol/L) and 1 to 10 vaso-occlusive crisis (VOC) events within 12 months prior to enrolment. Otherwise eligible patients on stable doses of hydroxycarbamide for at least 90 days were allowed to continue hydroxycarbamide therapy throughout the study. Randomization was stratified by patients already receiving hydroxycarbamide (yes, no), geographic region (North America, Europe, Other), and age (12 to < 18 years, 18 to 65 years). Key exclusion criteria included patients who (1) were receiving regular RBC transfusions, (2) received RBC transfusions within 60 days, (3) received erythropoietin within 28 days of enrolment, (4) had known active hepatitis A, B, or C or who were known to be human immunodeficiency virus (HIV) positive (5) had severe renal insufficiency, (6) had uncontrolled liver disease, (7) were pregnant, or (8) were breast-feeding.

Seventy-five percent of patients had HbSS genotype, 15% had HbS/β^0-thalassemia, 4% HbS/β^+-thalassemia, 3% HbSC, and 3% other sickle cell variants. The majority were receiving hydroxycarbamide therapy (65%). The median age was 24 years (range: 12 to 64 years); 46 (17%) patients were 12 to < 18 years of age. Median baseline Hb was 8.5 g/dL (5.28 mmol/L) (5.9 to 10.8 g/dL [3.66 to 6.70 mmol/L]). One hundred and fifteen (42%) had 1 VOC event and 159 (58%) had 2 to 10 events within 12 months prior to enrolment. Of the 274 patients, 75 (27.4%) discontinued the study early. The main reasons for discontinuation were withdrawal of consent (10.2%) and adverse events (8.4%).

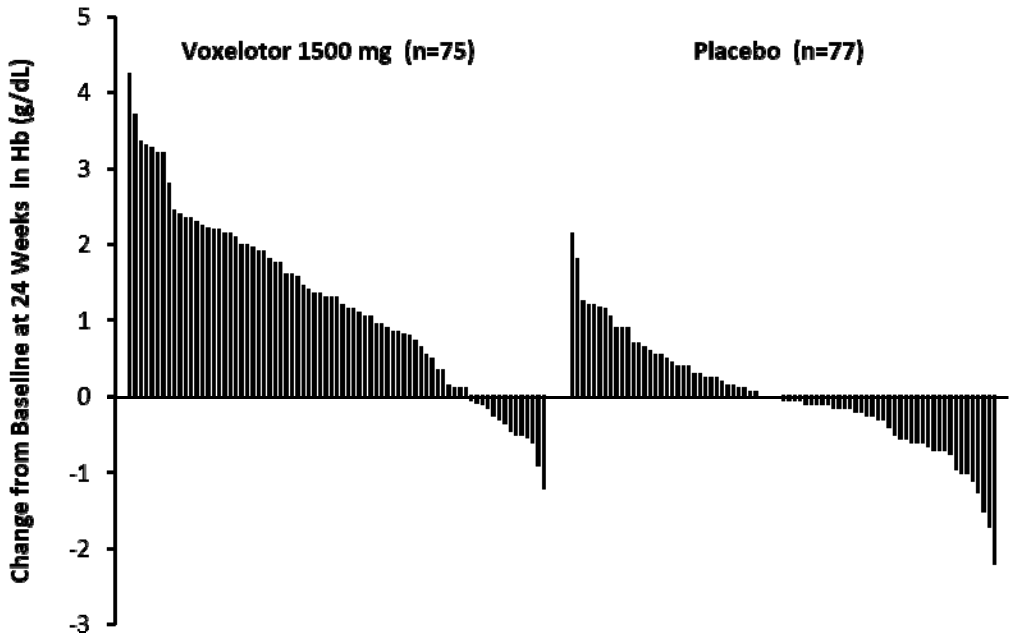
Efficacy was based on the following primary endpoint: Hb response rate defined as a Hb increase of > 1 g/dL (0.62 mmol/L) from baseline to Week 24 in patients treated with voxelotor 1500 mg versus placebo. The response rate for voxelotor 1500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$). No outlier subgroups were observed (Figure 1). The increase in Hb was observed beginning at Week 2 and maintained through Week 72. The distribution of Hb change from baseline for individual patients completing 24 weeks of treatment with voxelotor 1500 mg or placebo is depicted in Figure 2.

Figure 1: Haemoglobin response at Week 24 by subgroup (voxelotor 1500 mg vs placebo) (intent-to-treat [ITT] population)



	Placebo		Voxelotor 1500 mg	
	N	Response Rate	N	Response Rate
ITT	92	6.5%	90	51.1%
Age				
12 to <18 years	17	5.9%	14	57.1%
18 to 65 years	75	6.7%	76	50.0%
Sex				
Male	42	9.5%	32	56.3%
Female	50	4.0%	58	48.3%
Race				
Arab or Middle Eastern	20	5.0%	20	55.0%
Black	63	4.8%	59	52.5%
Geographic Region				
North America	35	11.4%	34	52.9%
Europe	18	0%	19	36.8%
Other	39	5.1%	37	56.8%
VOC History (prior 12 months)				
1 episode	39	5.1%	35	60.0%
≥2 episodes	53	7.5%	55	45.5%
Baseline HU Use				
No	34	8.8%	32	43.8%
Yes	58	5.2%	58	55.2%
Baseline Hb				
<7 g/dL (<4.3 mmol/L)	7	14.3%	7	57.1%
≥7 g/dL (≥4.3 mmol/L)	85	5.9%	83	50.6%

Figure 2: Subject-level change from baseline in haemoglobin at Week 24 in patients who completed 24 weeks of treatment[a,b]



a. Approximately 83% of all randomised patients completed 24 weeks of treatment.

b. In the International System of Units (SI), the Hb range of -3 to 5 g/dL on the Y axis equates to -1.86 mmol/L to 3.10 mmol/L based on a conversion factor of 0.6206.

Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to Week 24 and Week 72 (Table 2).

Table 2: Adjusted mean (SE) change from baseline to Weeks 24 and 72 in haemoglobin and clinical measures of haemolysis (ITT population)

	Week 24		Week 72	
	Oxbryta 1500 mg QD (N=90)	**Placebo (N=92)**	**Oxbryta 1500 mg QD (N=90)**	**Placebo (N=92)**
Haemoglobin g/dL mmol/L	 1.13 (0.13) 0.70 (0.08)	 -0.10 (0.13) -0.06 (0.08)	 1.02 (0.15) 0.63 (0.09)	 0.02 (0.15) 0.01 (0.09)
P-value	< 0.001		< 0.001	
Indirect Bilirubin %	-29.1 (3.5)	-2.8 (3.5)	-23.9 (4.9)	2.7 (4.9)
Percent Reticulocyte Count %	-18.0 (4.7)	6.8 (4.7)	-7.6 (5.5)	11.0 (5.5)

SE = standard error

The total number and annualized incidence rate (IR) of on-treatment VOCs were as follows: 219 events with adjusted IR of 2.4 events/year in the voxelotor 1500 mg group and 293 events with adjusted IR of 2.8 events/year in the placebo group. No statistically significant difference was observed between the treatment groups; however, the study was not designed to detect a difference.

In the pivotal study leg ulcers were observed at baseline: 4 in the voxelotor 1500 mg group, 3 in the placebo group. In the voxelotor group, all 4 patients with leg ulcers at baseline improved after treatment (3 patients had resolution by Week 72 and 1 patient with moderate severity at baseline improved to mild). One patient developed new leg ulcers during treatment. In contrast, in the placebo group, only 1 of the 3 patients with leg ulcers at baseline had improvement and 5 patients developed new leg ulcers.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with voxelotor in paediatric population from birth to < 6 months of age in the treatment of haemolytic anaemia due to SCD. See section 4.2 for information on paediatric use.

The European Medicines Agency has deferred the obligation to submit the results of studies with voxelotor in paediatric population from 6 months of age to < 12 years of age in the treatment of haemolytic anaemia due to SCD, as well as further data from studies in the paediatric population less than 18 years of age. See section 4.2 for information on paediatric use.

Study GBT440 007
Study GBT440 007 is an ongoing Phase 2, multicentre, open-label single- and multiple-dose study designed to evaluate the safety, tolerability, PK, and efficacy of voxelotor in paediatric patients with SCD. Efficacy and safety data from the completed multiple-dose part in patients 12 to < 18 years of age with SCD (HbSS or HbS/β^0-thalassemia) who received voxelotor 900 mg or 1500 mg for 24 weeks are discussed here.

In total, 25 patients received voxelotor 900 mg and 15 patients received voxelotor 1500 mg. The median age in the voxelotor 1500 mg group was 14 years (range: 12-17 years), 33% were male and 73% were Black. Most patients in the 1500 mg group had HbSS genotype (80%) and all used hydroxycarbamide at baseline. Thirty-three percent (33%) had no history of VOC within the 12 months prior to screening and 33% had 1 or 2 VOCs in the 12 months prior to

screening. Median baseline Hb level was 8.8 g/dL (5.46 mmol/L). Eighty-eight percent (88.0%) of patients in the voxelotor 900 mg group and 80.0% of patients in the voxelotor 1500 mg group completed the study with 24 weeks of dosing. One patient in the voxelotor 1500 mg group discontinued due to an adverse reaction (Grade 1 diarrhoea).

Efficacy assessments included clinical measures of anaemia (Hb) and haemolysis (percent reticulocyte count and indirect bilirubin). Consistent with the results of the Phase 3 Study of voxelotor, improvements in Hb were observed as early as Week 2 and were maintained through Week 24: median change in Hb from baseline to Week 20/Week 24 average was 0.7 g/dL (0.43 mmol/L) for the 1500 mg group, decrease in percent reticulocyte count at 24 weeks was -17.4% (-35.6, -36.5) and decrease in indirect bilirubin was -42.8% (-50.5, -15.4) in the voxelotor 1500 mg group. The safety profile was consistent with that observed in the Phase 3 Study.

5.2 Pharmacokinetic properties

Absorption

The median plasma and whole blood T_{max} of voxelotor after oral administration is 2 hours. The mean peak concentrations in whole blood and RBCs are observed between 6 and 18 hours after oral administration. The PK are linear over the dose range of 100 mg to 2,800 mg. Steady-state after repeated administration is reached within 8 days and exposures of voxelotor plasma and whole blood (Table 3) are consistent with accumulation predicted based on single dose data in patients with SCD.

Table 3: Pharmacokinetics parameters of voxelotor in plasma and whole blood (Subjects with SCD)

PK parameter	**Voxelotor 1,500 mg Geometric mean (%CV)**
Plasma PK	
$AUC_{0\text{-}24h}$ (microgram·hr/mL)	278 (28.4)
C_{max} (microgram/mL)	14 (24.5)
Half-life (hours)	38.7 (30.2)
Whole Blood PK	
$AUC_{0\text{-}24h}$ (microgram·hr/mL)	3830 (33.5)
C_{max} (microgram/mL)	180 (31)

Effect of food

In healthy subjects, administration of a single 900 mg dose of Oxbryta with a high-fat meal resulted in a 45% and 42% increase in whole blood C_{max} and AUC, respectively, compared to fasted conditions.

In clinical studies, subjects with SCD took voxelotor without instructions with respect to food intake and had plasma and whole blood voxelotor exposures similar to subjects with SCD who took voxelotor after an overnight fast. The difference is less than 20% for any of the parameters and not considered to be clinically significant. Therefore, voxelotor can be taken with or without food.

Distribution

Voxelotor is absorbed into plasma and is then distributed predominantly into RBCs due to its preferential binding to Hb. Voxelotor apparent volume of distribution of the central compartment and peripheral compartment in patients with SCD are 333 L and 72.3 L in plasma, respectively. Protein binding is 99.8% *in vitro*. The blood-to-plasma ratio is approximately 15:1 in patients with SCD.

The pharmacokinetics of voxelotor in healthy subjects is different from patients with SCD due to the differences in blood-to-plasma partitioning (ratio 32:1). The volume of distribution in healthy subjects is approximately 754 L.

Biotransformation

In vitro and *in vivo* studies indicate that voxelotor is extensively metabolized through Phase I (oxidation and reduction), Phase II (glucuronidation) and combinations of Phase I and II metabolism. Oxidation of voxelotor is mediated primarily by CYP3A4, with minor contribution from CYP2C19, CYP2B6, and CYP2C9. Sulfatation of voxelotor is mediated primarily by SULT1B1 and SULT1C4 and direct glucuronidation of voxelotor is mediated by UGT1A1 and UGT1A9. The major plasma metabolite results from O-dealkylation-sulfation and represents 16.8% of voxelotor-related material in plasma. Five further metabolites accounted for a total of 23% of voxelotor-related material in plasma, with individual contributions up to 9%. All other metabolites were less than 5%.

Elimination

The major route of elimination of voxelotor is by metabolism with subsequent excretion of metabolites into urine and faeces. The excretion of unchanged voxelotor is minimal (< 1% of dose in urine). The geometric mean (%CV) terminal elimination half-life of voxelotor in patients with SCD is 38.7 hours (30.2%) with concentrations in plasma, and whole blood declining in parallel. The apparent oral clearance of voxelotor was estimated as 6.1 L/h in plasma in patients with SCD.

Special populations

Patients with renal impairment

There was no clinically significant effect of renal function on the excretion of voxelotor in subjects without SCD and patients with SCD. Following a single 900 mg dose of voxelotor, whole blood exposures in subjects with severe renal impairment

(eGFR < 30 mL/min/1.73 m^2) were 25% lower compared to healthy controls. The unbound plasma concentrations were comparable. In patients with SCD, a trend for higher voxelotor exposure was observed with lower Cystatin C levels. Higher levels of Cystatin C typically observed with renal impairment were not associated with higher voxelotor exposure.

Voxelotor has not been evaluated in patients with ESRD requiring dialysis.

Patients with hepatic impairment

In plasma, the C_{max} was 1.2-fold higher in subjects with mild hepatic impairment (Child Pugh A), 1.5-fold higher in subjects with moderate hepatic impairment (Child Pugh B) and 1.4-fold higher in subjects with severe hepatic impairment (Child Pugh C), and the AUC_{inf} was 1.1-fold higher in subjects with mild hepatic impairment, 1.2-fold higher in subjects with moderate hepatic impairment and 1.9-fold higher in subjects with severe hepatic impairment. In whole blood, increase in exposure was similar to that in plasma. No dose adjustment is warranted in subjects with mild to moderate hepatic impairment, but it is recommended to reduce the daily dose of voxelotor to 1,000 mg in subjects with severe hepatic impairment (see section 4.2). The plasma and whole blood C_{max} values in patients with severe hepatic impairment after dose adjustment are expected to be similar to those in patients with normal hepatic function treated at the recommended dose of 1,500 mg daily. The plasma and whole blood AUC are expected to be ~25% higher in subjects with severe hepatic impairment after dose adjustment compared to those in patients with normal hepatic function treated at the recommended dose of 1,500 mg daily.

Effect of gender, race, and body weight

No clinically significant differences in the pharmacokinetics of voxelotor were observed based on gender, race, and body weight (28 to 135 kg).

Effect of age

No clinically significant differences in the pharmacokinetics of voxelotor were observed based on age (12 to 59 years).

Effect of haematocrit

The blood-to-plasma partitioning of voxelotor increases with increasing haematocrit. As haematocrit increased from 30.5% in SCD patients (median at 1,500 mg daily) to the maximum haematocrit measured at 1,500 mg daily (35.1%), the blood-to-plasma partitioning increased from 14.8 to 16.4 (11% increase).

Patients with HbSC genotype

Voxelotor steady state whole blood AUC and C_{max} were 50% and 45% higher in HbSC genotype patients (n=11) compared to HbSS genotype (n=220) patients and voxelotor steady state plasma AUC and C_{max} were 23% and 15% higher in HbSC genotype patients compared to HbSS genotype patients.

In vitro drug interactions

CYP enzymes: *In vitro*, voxelotor is an inhibitor and inducer of CYP2B6 and an inhibitor of CYP2C8, CYP2C9, CYP2C19 and CYP3A4. The clinical relevance is currently unknown (see section 4.5).

UGT enzymes: In vitro data indicate that voxelotor is not an inhibitor of UGT1A1, UGT1A9 and UGT2B7 at maximal systemic concentration. Due to solubility issues, no concentrations up to maximal intestinal concentrations could be investigated for UGT1A1. No inhibition was observed towards UGT1A1 up to 100 micromol (the highest concentration investigated).

Transporter-mediated interactions: Voxelotor is not an inhibitor of P-gp, BCRP, OATP1B3, OCT2, OAT1, MATE2-K, or BSEP. Voxelotor act as an inhibitor of OATP1B1, OAT3 and MATE1 transporters (see section 4.5). Voxelotor is not a substrate of P-gp, BCRP, OATP1A2, OATP1B1, OATP1B3, or BSEP.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Repeated dose toxicity

The major findings associated with repeat-dose administration of voxelotor was compensatory erythropoiesis, manifested as increased red blood cell mass (↑ RBC, HCT, Hb, RET) correlated microscopically with hypercellular bone marrow and splenic red pulp and increased splenic weight in rats, mice and cynomolgus monkeys. In monkeys, early stages of this effect were seen at dose levels comparable with clinical exposure (exposure multiple of ~0.6 based on the plasma C_{max} values). Voxelotor also caused GI intolerance attributed to local irritation. Other findings attributed to voxelotor include induction of CYP enzymes in the liver of mice and rats, altered T cell-dependent antigen response in rodents and monkeys and prolongation of corrected QT (QTc) intervals in monkeys. Following the immunization with keyhole limpet hemocyanin (KLH), voxelotor caused the significantly reduced IgG (rats, monkeys) and IgM (monkeys) titres, a delayed peak in the antibody response (monkeys) and the changes in the relative lymphocyte distribution (rats). These effects were seen at the exposure multiple of the anticipated clinical exposure ~0.6 in monkeys and ~4.0 in rats based on plasma C_{max} value. Treatment with voxelotor at the exposure multiple ~2.5 of the anticipated clinical exposure led to the QT and QTc intervals prolongation in monkeys.

Reproduction and development

Treatment of rats with voxelotor at exposure multiple ~4 of the anticipated clinical exposure caused a reduced sperm motility and an increased percentage of abnormal sperm, as well as an increased testicular and prostate weight and reduced seminal

vesicles weight. These effects did not, however, affect the reproductive performance. Voxelotor was not teratogenic in rats and rabbits at exposure levels causing maternal toxicity (exposure multiple based on blood AUC of 2.8 in rats and 0.3 in rabbits). Voxelotor is excreted in milk of lactating rats. Milk exposure was up to 0.4-fold plasma exposure of the dams, leading to subsequent plasma exposure in pups. In the pre- and postnatal developmental toxicity study, adverse effects on the progeny, manifested as reduced pup viability index and persistently lower pup weight, were seen at the predicted exposure multiple of ~2.6 of the anticipated human exposure.

Environmental risk assessment

Environmental risk assessment studies have shown that voxelotor is not bioaccumulative and toxic to the environment; however, it has the potential to be persistent in sediments (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)

Croscarmellose sodium (E468)

Sodium laurilsulfate (E487)

Silica, colloidal anhydrous (E551)

Magnesium stearate (E470b)

Tablet film-coating

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Polyethylene glycol (E1521)

Talc (E553b)

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a polypropylene child-resistant cap and an aluminium induction seal. The bottle also contains a silica gel desiccant canister and polyester coil.

Pack-size of 90 film-coated tablets.

6.6 Special precautions for disposal

This medicinal product may persist in the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/07/2022

10 DATE OF REVISION OF THE TEXT

25/06/2024