14 February 2022
EMADOC-1700519818-760652
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Oxbryta, voxelotor (2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde)
Treatment of sickle cell disease
EU/3/16/1769

Sponsor: Global Blood Therapeutics Netherlands B.V

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde
Other name(s)	Oxbryta, 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde,
International Non-Proprietary Name	Voxelotor
Tradename	Oxbryta
Orphan condition	Treatment of sickle cell disease
Sponsor's details:	Global Blood Therapeutics Netherlands B.V. Strawinskylaan 3051 1077 ZX Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	SynteractHCR Deutschland GmbH,
COMP opinion	06 October 2016
EC decision	18 November 2016
EC registration number	EU/3/16/1769
Post-designation procedural history	
Transfer of sponsorship	Transfer from SynteractHCR Deutschland GmbH to Global Blood Therapeutics Netherlands B.V. – EC decision of 11 January 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Paula Boudewina van Hennik / Alexandre Moreau
Applicant	Global Blood Therapeutics Netherlands B.V.
Application submission	23 December 2020
Procedure start	21 January 2021
Procedure number	EMA/H/C/004869/0000
Invented name	Oxbryta
Proposed therapeutic indication	Treatment of haemolytic anaemia associated with sickle cell disease in adults and paediatric patient 12 years and older. Further information on Oxbryta can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Oxbryta
CHMP opinion	16 December 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Enrico Costa
Sponsor's report submission	05 November 2021
COMP discussion	07-09 December 2021

COMP opinion (adoption via written procedure)	17 December 2021

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde was considered justified based on clinical data demonstrating a reduction in haemolysis and sickling of red blood cells;
- the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival;
- the condition was estimated to be affecting approximately 3.2 in 10,000 persons in the European Union, at the time the application was made.
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a significant reduction of haemolysis and sickling of red blood cells in patients with sickle cell disease. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Sickle cell disease (SCD) is characterised by haemolytic anaemia, vaso-occlusion and progressive end-organ damage. SCD is caused by a point mutation in the haemoglobin (Hb) β-chain, converting the glutamic acid residue at position 6 to a valine residue.

The mutation leads to sickle haemoglobin (HbS) following deoxygenation in the microvasculature. HbS polymerization leads to decreased red blood cell (RBC) deformability, morphologic sickling of RBCs, decreased RBC survival, microvascular obstruction and the clinical complications of SCD.

Patients suffer from unpredictable and recurrent episodes of severe pain often leading to significant psychosocial and occupational disability. In addition to painful crises, a systemic vasculopathy leads to chronic and progressive tissue injury across multiple organ systems. Multiple pathophysiologic mechanisms likely contribute to the systemic vasculopathy, including, chronic haemolytic anaemia. The consequences include cognitive dysfunction and stroke, increased susceptibility to infections,

cardiopulmonary complications, renal dysfunction, leg ulcers, priapism in males, and increased mortality.

The approved therapeutic indication "*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*" falls within the scope of the designated orphan condition "*Treatment of sickle cell disease*".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, based on the single pivotal trial (GBT440-031).

Chronically debilitating and/or life-threatening nature

No change in the chronically debilitating and/or life-threatening nature of the condition has been reported since the designation of the orphan medicinal product in 2016. The COMP considered that the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension, leg ulcers and susceptibility to infections, and life-threatening with reduced survival.

Number of people affected or at risk

Based on the sponsor's revised prevalence calculation, the proposed prevalence estimate is 1.116/10,000 in European countries. The sponsor bases their prevalence calculation on an average value derived from incidence data reported from a comprehensive literature review (Table 1).

Prevalence is calculated as Birth prevalence X (patient life expectancy/general population life expectancy) in case of newborn screening data. Patients with SCD face a significantly lower life-expectancy compared to their non-SCD counterparts (Lubeck et al, 2019). Recently, Lubeck et al report a life expectancy of ~54 years in an SCD cohort compared to 76 years in healthy counterparts.

Birth prevalence is calculated as number of diseased newborns / number of newborns screened, where data is available. Where total number screened is not available, total population is used as a denominator for final prevalence. In instances where a total number/estimated number of cases in population have been reported, prevalence was calculated as: (number of cases reported or estimated in general population X 10,000)/population of country that year.

Table 1: Summary of Incidence and Prevalence of SCD by Country

Country	Years of Screen	Number of patients screened	Number of SCD patients reported	Population prevalence reported	Population in last year of calculation	Birth prevalence reported/calculated (x/10,000)	Life expectancy in general population	Life expectancy in SCD	Final prevalence	Reference
Germany (Berlin + Brandenburg)	2015-2016	29079	7	NA	3574830	2.41	81.88	54.00	1.588	Lobitz et al, 2019
Germany (Hamburg)	2013-2014	16697	3	NA	81,450,370	1.80	81.88	54.00	1.185	Grosse et al, 2016
Germany (Heidelberg)	2012-2013	37838	3	NA	1746342	0.79	81.88	54.00	0.523	Kunz et al, 2016
Germany (registries)	2015-2019	NA	439	2000	83,517,045	NA	81.88	54.00	0.239	Kunz et al, 2019
Spain (Madrid)	2003-2018	1048222	187	NA	6,497,124	1.78	83.99	54.00	1.147	Garcia-Morin et al, 2019
Spain	2016	400,000	48	NA	46,634,140	1.20	83.99	54.00	0.772	Daniel et al, 2018 (ref Cela et al 2017)
France	2006-2016	NA	NA	26100	64667596	NA	83.13	54.00	3.125	Leleu et al, 2020
France	2016	NA	431	NA	64,667,596	5.45	83.13	54.00	3.538	Daniel et al, 2018
Netherlands	2016	NA	NA	30	16,981,295	NA	82.78	54.00	0.004	Daniel et al, 2018
Malta	2017	4,730	0	NA	437,933	0.00	83.06	54.00	0.000	Daniel et al, 2018
Italy	2019	NA	NA	1275	60,550,075	NA	84.01	54.00	0.153	National Register of Thalassemia and Hemoglobinopathies
Median	0.772									
Average	1.116									

Considering that there is a degree of uncertainty over the actual prevalence of SCD in the EU due to the fact that 1) the prevalence numbers are heterogenous due to factors like differential immigration between countries in Europe, and 2) the fact that the number of patients with sickle cell disease is steadily increasing in the EU due to migration (*Hickman et al 1999, Gulbis et al 2006, Modell et al 2007, Roberts et al 2007, Colombatti et al 2016*), it is considered that the previously accepted prevalence estimate from COMP of "less than 2 per 10,000 persons" is still applicable. The sponsors proposed prevalence estimate is 1.116/10,000 is in line with this value.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

At present there are three medicinal products authorized for patients with SCD in the European Union/EEA, two of which contain the active substance hydroxycarbamide (hydroxyurea [HU]):

- Siklos (hydroxycarbamide) is centrally approved in the EU for the prevention of recurrent painful VOCs including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome.

- Xromi (hydroxycarbamide) is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age.
- Adakveo (crizanlizumab) is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in SCD patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/ hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

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. Vaso-occlusive phenomena and haemolysis are clinical hallmarks of sickle cell disease (SCD), but vaso-occlusive disease (VOD) is commonly associated with haemolysis and SCD patients with haemolytic anaemia can also suffer from VOD. Therefore, it is considered that there is a certain degree of overlap between the target populations of Oxbryta and currently authorized products. However, the voxelotor-eligible population is still deemed to be broader, as administration of Oxbryta is not linked per se to vaso-occlusive events. Approximately half the individuals with homozygous HbS disease do not experience vaso-occlusive crises (VOCs) and may therefore not be eligible for treatments for the prevention of VOC. But haemolytic anaemia is universally present among these patients. The severity of haemolytic anaemia in SCD is known to be correlated with chronic complications like renal impairment, leg ulcers, stroke, pulmonary hypertension and early mortality.

Furthermore, despite several currently available, the disease is in many patients not sufficiently controlled and there is still an unmet medical need for new treatments. The only potentially curative treatment currently available for SCD is bone marrow transplantation. This treatment is primarily limited to children and adolescents, with use of a matched sibling donor and a myeloablative conditioning regimen, which is associated with considerable risks. Frequent blood transfusions are often required, but these are associated with iron accumulation and several other risks.

The COMP concluded that there is no approved treatment that qualifies as a satisfactory treatment for the purpose of the examination of the significant benefit vis-à-vis Oxbryta, as the authorised treatment options do not cover the entire patient population for which Oxbryta is intended.

Significant benefit

The target population of Oxbryta includes patients for whom no other satisfactory methods are available (see above). No justification for significant benefit is therefore expected.

4. COMP position adopted on 17 December 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of sickle cell disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, stroke, chronic kidney disease, pulmonary hypertension, susceptibility to infections and skin ulcers and life-threatening with reduced survival;

- at present no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Oxbryta.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Oxbryta, 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde, voxelotor for treatment of sickle cell disease (EU/3/16/1769) is not removed from the Community Register of Orphan Medicinal Products.