# NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Committee for Medicinal Products for Human Use (CHMP) made by the European Commission (EC):

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| Product(s) Name(s) | Oxbryta |
| Active substance(s) | Voxelotor |
| Pharmaceutical form(s) | All |
| Strength(s) | All |
| Route(s) of Administration | All |
| Marketing Authorisation Holder(s) | Pfizer Europe MA EEIG |

**Background**

Voxelotor is a Haemoglobin S (HbS) polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to Red Blood Cells (RBCs). By increasing the affinity of haemoglobin (Hb) for oxygen, voxelotor demonstrates dose- dependent inhibition of HbS polymerization. Voxelotor inhibits RBC sickling andimproves RBC deformability.

On 14 February 2022, Oxbryta was granted a marketing authorisation by the European Commission. Oxbryta is currently authorised in the EU, as an orphan medicinal product, 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. The recommended dosage is 1500 mg taken orally once daily. The efficacy was demonstrated on Hb response rate (defined as a Hb increase of > 1 g/dL (0.62 mmol/L) from baseline to Week 24). The response rate for voxelotor 1 500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$).

At time of marketing authorisation, voxelotor was shown to decrease the humoral immune response to antigens in both rats and monkeys. Further, exposure-dependent decrease in white blood cells (WBC) within the normal range was observed in clinical studies, whereas no evident increase in infection rates was observed during the pivotal study in the 1500 mg group. The effects observed in animals were reflected under warnings and precautions in the product information, together with a statement that the clinical relevance in already immunocompromised patients or in patients treated with immunosuppressive drugs cannot be excluded.

**Issues to be considered**

In May 2024, the sponsor decided to pause dosing in two ongoing global clinical studies due to a potential safety concern observed in said studies. The concern related to an imbalance of deaths between voxelotor and placebo in one of the studies (GBT 440-032, also known as C5341021), whilst in the other (GBT440- 042, also known as C5341026) the total number of deaths was higher than anticipated. Dosing was also paused for participants of those two

studies who enrolled in the open label extension (GBT440-038, also known as C5341023) while an evaluation is conducted to determine the reason for the observations.

Study GBT440-032 intended to assess the effect of voxelotor on the transcranial doppler ultrasound measurements in SCD participants in children 2 to <15 years of age with sickle cell disease and at risk for stroke. It is a global study, in which the majority of study participants were enrolled in sub-Saharan Africa. In this study, 8 deaths were reported in the treatment arm, compared to 2 in the placebo arm (all in Sub-Saharan Africa). Most of fatal cases in the voxelotor group describe incidence of infection, including 3/8 patients who developed (fatal) malaria and 2/8 patients with sepsis.

Study GBT440-042 intended to assess the effect of voxelotor and standard of care (SOC) compared to placebo and SOC on leg ulcer healing in participants ≥ 12 years of age with SCD. It is conducted in Kenya, Nigeria, and Brazil. Concomitant treatment with hydroxyurea/hydroxycarbamide (HU/HC) was allowed. A higher number of fatal events than anticipated in study participants receiving voxelotor was observed. The study has not yet been unblinded, but most of these deaths (8/9 fatal cases) occurred in patients who entered the open-label part of this study. In 4 cases, malaria was identified either the cause or contributing factor.

The investigator and sponsor considered that none of the fatal cases were related to voxelotor in these studies.

A couple of case narratives from study GBT440-032 are still not available, nor those from study GBT440-042, and overall information provided to date is limited. However, given the fact that concerns due to possible immunosuppressive effects of voxelotor were raised at time of the MA (with immunosuppressive effects observed in animal studies and decrease in WBC in clinical studies), and the study population in those studies partially overlap with the intended population based on the authorised indication, the findings from these emerging safety data need to be further reviewed, taking into account all available data, to determine whether there is an impact on the benefit-risk balance of Oxbryta in the authorised indication.

In view of the above, the EC initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency/CHMP to assess the above concerns and their impact on the benefit-risk balance of the centrally authorised medicinal product Oxbryta (voxelotor).

The EC requests the Agency/CHMP to give its opinion by March 2025 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked. The CHMP may consider seeking advice from the PRAC if relevant.

In addition, the EC requests the Agency to give its opinion, as soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product.

Signed Date
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General