Annex I

Scientific conclusions

Scientific conclusions

Sickle cell disease (SCD) is a group of autosomal recessive inherited disorders caused by mutations in haemoglobin B, encoding haemoglobin subunit β, resulting in the presence of a mutated form of haemoglobin, haemoglobin S (HbS). The most common type is known as sickle cell anaemia (SCA) that results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells (RBCs). This leads to the RBCs adopting an abnormal sickle-like shape under certain circumstances; with this shape, they are unable to deform as they pass through capillaries, causing blockages. SCD may lead to attacks of pain (SCA with crisis, vaso-occlusive crises (VOCs)) in joints, anaemia, swelling in the hands and feet, bacterial infections, dizziness and stroke. Vaso-occlusion results in recurrent painful episodes and a variety of serious organ system complications that can lead to life-long disabilities and even death. Haemolytic anaemia and vaso-occlusion, being multifactorial pathophysiologic processes, are both a result of the primary molecular event - the formation of polymers of de-oxyhaemoglobin S and RBC sickling.

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

On 14 February 2022, Oxbryta was granted a marketing authorisation in the European Union (EU) as an orphan medicinal product, for the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide (HC, also called hydroxyurea (HU)). The recommended dosage was 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 1500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group indicating a difference of 45.0 (33.4, 56.7; $p < 0.001$). At time of approval, no data in paediatric patients below the age of 12 years was available and the safety and efficacy of Oxbryta in this patient population could therefore not be established. 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 could not be excluded.

In May 2024, the sponsor decided to pause dosing in two ongoing post-authorisation clinical studies due to a potential safety concern. The concern related to an imbalance of deaths observed between voxelotor and placebo in one of the studies (GBT 440-032, also known as C5341021 or HOPE Kids 2), whilst in the other (GBT440-042, also known as C5341026 or RESOLVE), 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 was conducted to determine the reason for the observations.

Study GBT440-032 intended to assess the effect of voxelotor on the transcranial doppler (TCD) ultrasound measurements in SCD participants in children 2 to <15 years of age with SCD and at risk for stroke. In this global study, the majority of study participants were enrolled in sub-Saharan Africa (SSA). Eight (8) deaths were reported in the treatment arm, compared to 2 in the placebo arm (all in SAA). Most of the fatal cases in the voxelotor group were describing incidence of infection, including 5 patients who developed (fatal) malaria or 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 was conducted in Kenya, Nigeria, and Brazil. Concomitant treatment with hydroxyurea/hydroxycarbamide (HU/HC) was allowed. The number of fatal events reported in study participants receiving voxelotor was higher than anticipated. The study had not yet been unblinded at the time, 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 as the cause, or as contributing factor for the death.

At the time the pauses of the studies were notified, overall information was limited and some case narratives from both studies were still not available. However, since concerns due to possible immunosuppressive effects of voxelotor were raised at time of the marketing authorisation (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 target population defined by the authorised indication, these emerging safety data needed to be further reviewed, taking into account all available data, to assess any potential impact on the benefit-risk balance of Oxbryta in its authorised indication.

On 26 July 2024, the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Oxbryta and issue an opinion on whether its marketing authorisation should be maintained, varied, suspended or revoked. In addition, the EC requested the Agency/CHMP to give its opinion, as soon as possible, as to whether temporary measures would be necessary to ensure the safe and effective use of this medicinal product.

On 23 September 2024, the MAH informed the EMA of their intention to cease the marketing of Oxbryta, and to initiate a recall of all batches worldwide. The MAH also informed the Agency that it was discontinuing all ongoing active voxelotor clinical trials and expanded access programs worldwide. The MAH indicated that their decision was based on a review and analysis of the data currently available from ongoing clinical trials and from registry studies, in particular emerging data regarding a safety signal of VOC. On 26 September 2024, considering the newly available data, the CHMP recommended the suspension of the marketing authorisation for Oxbryta (voxelotor) as temporary measure until adoption of a definitive decision in the context of this Article 20 procedure. The Committee also recommended that the marketing and the supply of Oxbryta (voxelotor) be suspended in all concerned EU Member States, as well as the recall of all batches available on the EU market up to the level of pharmacies and hospitals. These temporary measures were communicated with a direct healthcare professional communication (DHPC). The European Commission issued a Decision on the temporary measures on 04 October 2024.

On 16 October 2024, the MAH notified EMA of programming errors in the Real World Evidence (RWE) study GBT440-4R2 (also known as C5341019 or the PROSPECT study). This programming error was then found to affect the previously shared results of both registry-based studies, i.e., study GBT440-4R2 and the other RWE study, GBT440-4R1 (also known as C5341018 or the RETRO study). Corrected results and related analyses became available in March 2025.

Overall summary of the scientific evaluation

The CHMP critically reviewed all available data in relation to the efficacy and safety of Oxbryta to determine whether there is an impact on the benefit-risk balance of Oxbryta in its authorised indication. This included the pivotal study GBT440-031, two post-authorisation studies (GBT440-032 and GBT440-042), two extension studies (GBT440-034 and GBT440-038), as well as two registry-based studies (PROSPECT and RETRO), in the context of all available data submitted by the MAH in writing and during an oral explanation (OE). The CHMP also consulted an ad-hoc expert group (AHEG) and the Pharmacovigilance Risk Assessment Committee (PRAC).

In the pivotal study of the initial marketing authorisation, i.e., study GBT440-031, no detrimental effects on incidence of death or VOCs/SCA with crisis were observed. On the contrary, a slight favourable trend in the rates of VOC was observed following prolonged treatment. However, studies GBT440-032 and GBT440-042 showed an imbalance in the incidence of death (study GBT440-032), a higher-than-expected number of deaths (open-label uncontrolled follow-up period of study GBT440-042), and an imbalance in VOCs (study GBT440-032) and rate of SCD-related SCA with crisis (both studies).

In study GBT440-032, the incidence of SCA with crisis was 59.2% in the voxelotor arm vs 37.9% in the placebo arm. Although absolute VOC incidence remained low, the annualised rate of VOCs showed an imbalance with 1.098 and 0.580 events/year in the voxelotor and placebo arms, respectively. Eight deaths were reported in the voxelotor treatment group, compared to two deaths in the placebo group.

In study GBT440-042, the incidence of SCA with crisis was 44.4% in participants receiving voxelotor vs 25.6% in the placebo arm during the 12-week randomised treatment period. However, no VOC incidence was evaluated. A total of 11 deaths were reported in patients treated with voxelotor, of which one occurred during the placebo-controlled, blinded period, eight occurred during the open-label extension period, and two occurred after the study was paused. No deaths were reported in the placebo group.

The CHMP considered the multiple potential factors that could have contributed to the increased rates of death and VOC/SCA with crisis observed in the voxelotor arms of studies GBT440-032 and GBT440-042, but not observed in study GBT440-031. These factors included concomitant infections, concomitant HU use, treatment adherence, geography, young age, haemoglobin response, and impact of immunosuppression associated with SCD. The possible role of hampered release of oxygen in tissues from stabilised HbS on susceptibility to VOC, infections and overall immunity was also considered. The increased number of deaths on voxelotor compared to what was seen in study GBT440-031 could potentially be explained by a suboptimal patient care received during (an) acute event(s) (e.g., VOC, sepsis, or malaria). Nevertheless, no single causal factor could be identified as responsible for the observed differences between the voxelotor arm and the placebo arm in the two post-authorisation studies GBT440-032 and GBT440-042, or between these studies and study GBT440-031. In this respect, it must be noted that these two post-authorisation studies concerned randomised controlled trials, which would correct the influence of any external factors (such as suboptimal patient care) as they would apply equally to both arms.

Moreover, clear immunosuppressive effects of voxelotor were observed in rat and monkey studies, at the time of the marketing authorisation. Collectively, the clinical data show that voxelotor might possibly increase susceptibility to (severe) adverse events in certain group of patients. However, possible mechanisms that make a subpopulation more susceptible to these adverse events are unknown. Therefore, it is not possible to identify a specific patient population at increased risk in order to exclude such patients from treatment with voxelotor.

Overall, the safety data presented is of concern. Given that the causes of the increase in deaths and VOCs/SCA with crisis are unknown and the at-risk populations cannot be identified, it is clear that risk factors cannot be mitigated. Therefore, the CHMP considers that the identified risks of death and VOC/SCA with crisis are of relevance to Oxbryta in its authorised indication in the EU.

Several potential measures to minimise the risks of VOC and death in patients with SCD have been considered. These included increased clinical monitoring, restrictions to the indication, communication about the risks identified and a controlled access programme integrated with a registry to enforce the restricted use and enable the collection of evidence to characterise VOC and death in the EU population.

Following the advice of the AHEG, the MAH proposed to increase the frequency of monitoring for improvement in haemolytic anaemia (laboratory results and clinical status) to, at least every 4 weeks for the first 3 months after treatment initiation, followed by 3-monthly monitoring (following the frequency of routine monitoring in study GBT440-031 and its subsequent open-label extension study). However, as also highlighted by the AHEG, close routine clinical monitoring is already standard practice for this patient population. VOC is the most common and characteristic clinical manifestation of SCD, which is monitored as part of routine clinical practice i.e. reviewing VOC history since last visit, assessing patterns of increased severity or frequency and evaluating the occurrence of chronic pain vs. acute VOCs. Therefore, in the view of CHMP, and as advised by PRAC, more frequent clinical assessment is considered unlikely to be effective for prior detection and prevention of infections or VOCs.

The MAH also proposed restricting the indication to less vulnerable patients or in the absence of alternative treatment options (i.e. restricting only to adults receiving concomitant hydroxycarbamide (HC), or as monotherapy for whom HC is inappropriate or at high risk of blood transfusion complications, and recommending against the use in patients with active leg ulcers). The MAH further proposed to communicate about the risks identified through the addition of warnings and precautions in the product information and the introduction of a patient card, later replaced by the introduction of a controlled access programme aimed at supporting the use in this restricted patient population. This programme would include a Healthcare Professional (HCP) guide to increase awareness of risks, while also supporting therapeutic decisions and counselling on the risks; a HCP checklist to document appropriateness of the prescription; a risk awareness dialogue form to document discussions between prescribers and patients, along with recommended actions should they arise; and a patient diary to capture VOC events for discussion during healthcare visits. The dissemination of a DHPC was also proposed in order to ensure awareness of HCP regarding the new risks and associated measures.

However, since the mechanisms underlying the increased risk of VOCs/SCA with crisis and death observed in studies GBT440-032 and GBT440-042 are unknown, no specific risk factors or patient subgroups at no risk could be identified. The CHMP shares the view of the AHEG regarding the need for therapeutic options for patients with SCD. However, while SCD is recognised as a disease with a high unmet medical need, it is important to note that the authorised indication for voxelotor specifically targets the treatment of haemolytic anaemia resulting from SCD, rather than the disease itself.

The PRAC also advised that, in the absence of an evidence-based strategy to mitigate the risks of VOC and death, and without identification of the risk factors contributing to these adverse outcomes, the risks associated with voxelotor cannot be adequately mitigated. As a consequence, no population within the authorised indication for Oxbryta in the EU at no risk of VOC and death could be identified. Moreover, extensive information is already provided to these patients as part of their ongoing care, and the proposed additional communication tools are not expected to improve the management or otherwise effectively minimise the risks. Likewise, regarding the proposed controlled access programme to support the use of Oxbryta in a restricted patient population, it should be recalled that it has not been possible to identify a population in which the risk of VOC and death is absent. Therefore, the proposed restricted indication does not differentiate or narrow the population by risk factors. Instead, it focuses on the use of voxelotor as mono or combination therapy with HU, which is not considered to be based on existing robust data given that HU use did not show a consistent effect on deaths and VOCs/SCA with crisis events. In patients with complications from blood transfusions, Oxbyta is neither a life-saving therapy nor has it been evaluated for its impact on Quality of Life. Even under a narrowly defined indication, there are no available measures to mitigate the risks associated with VOCs or SCA with crises, including the potential for fatal outcomes. In addition, the counselling provided in the context of the controlled access programme is not considered to meaningfully contribute to the management of these risks, in view of the extensive information already received by

patients treated with Oxbryta. In consequence, while a controlled access programme might in the future yield further insights regarding the occurrence of these events, it would not at time of implementation protect patients exposed to Oxbryta against the risk of VOC and death. Therefore the CHMP, in line with the PRAC, concludes that the measures considered would not adequately minimise the risk, in any of the subsets of the authorised indication.

In conclusion, considering the seriousness of the identified risks in the context of the benefits of Oxbryta, the CHMP is of the view that the benefit-risk balance of Oxbryta is not favourable in all subsets of the authorised indication.

While it is understood from the MAH that a double-blinded randomised controlled trial to further characterise the risk of VOC may be performed in the USA and Europe, the outcome of such trial remains entirely hypothetical; and this proposal in any event has no bearing on the conclusion based on the data available at present. The same applies to possible alternative study designs considered by the MAH, namely a registry capturing all voxelotor-exposed patients within a controlled access programme, using a matched control design, or a pragmatic randomised controlled trial with a real-world data control arm.

The CHMP, having considered the matter, recommends the suspension of the marketing authorisation for Oxbryta. The CHMP considers that, for the suspension to be lifted, additional robust evidence is needed to define a clinically relevant patient population in which the benefit-risk balance of voxelotor is favourable.

This conclusion is without prejudice to the potential need for other updates to the terms of the marketing authorisation in view of the new data assessed in this procedure (e.g. regarding observed ADRs and gradual dosing reduction strategy when discontinuing treatment, as discussed in section 2.2.5) if the suspension of the marketing authorisation would be lifted.

CHMP opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Oxbryta (voxelotor).
- The CHMP reviewed the data from studies GBT440-032 and GBT440-042, in the context of all available data submitted by the MAH in writing and during an oral explanation, as well as the views expressed by a group of independent experts and patient representatives at an ad hoc meeting (AHEG) and the outcome of a consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).
- The CHMP noted the established efficacy of voxelotor to treat haemolytic anaemia.
- The CHMP noted an increased number of vaso-occlusive crises (VOCs)/sickle cell anaemia (SCA) with crisis and deaths with voxelotor compared to placebo in the randomised controlled studies GBT440-032 and GBT440-042.
- The CHMP noted that the underlying mechanisms that could explain the increased numbers of VOCs/SCA with crisis and deaths following treatment with voxelotor in studies GBT440-032 and GBT440-042 are not established. Therefore, the CHMP considered these important new safety concerns relevant to the authorised use of Oxbryta in the EU.
- In the absence of specific risk factors, the CHMP could not identify any measures that could effectively minimise these risks, nor any subset of patients within the authorised indication in which the benefits of Oxbryta would outweigh the identified risks.

The Committee, as a consequence, considers that the benefit-risk balance of Oxbryta is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisation for Oxbryta.

In order for the suspension to be lifted, the MAH shall submit robust evidence that defines a clinically relevant patient population in which the benefit-risk balance of the treatment is favourable.