29 July 2024
EMA/CHMP/348130/2024

CHMP List of questions

To be addressed by the marketing authorisation holder(s) for Oxbryta

Procedure under Article 20 of Regulation (EC) No 726/2004

Oxbryta EMEA/H/A-20/1538/C/004869/0014

Marketing authorisation holder(s): Pfizer Europe MA EEIG

INN/active substance: voxelotor

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The marketing authorisation holder (MAH) is requested to address the following questions:

Ongoing clinical trials

1. The MAH is requested to report all available safety data, emphasising serious adverse events and deaths from studies GBT440-032 and GBT440-042 (including the open-label extension study GBT440-038). Where data would be consistent with a detrimental effect of voxelotor, unblinded data should be provided. This should include, but not be limited to:

    a. A complete and detailed analysis of all safety data from these trials and their management (including an accurate timeline of voxelotor intake, other treatments and the adverse events), particularly complete and detailed analyses of all deaths (irrespective of cause of death) and concomitant infections.

    b. An assessment of potential risk factors for adverse outcomes in the overall population and in particular during treatment with voxelotor. The analysis should consider baseline criteria as well as (laboratory) values under treatment such as haemoglobin (Hb) and white blood cell (WBC) counts.

    c. A comparison of rates of severe/serious adverse events in voxelotor arm versus placebo arm and external sources.

    d. Rates of severe malaria and other infections, as well as other concomitant diseases, including a discussion on the possible impact of voxelotor use on their development/progression and vice versa the impact of these underlying infections/diseases on the efficacy/safety of voxelotor.

    e. Contribution of non-compliance to voxelotor in relation to the fatal cases observed.

    f. Contribution of non-compliance to concomitant therapy needed for treatment of co-morbidities in relation to the fatal cases observed.

    g. The role of any abrupt treatment interruptions in the fatal cases.

    h. Contribution of discontinuation of exchange transfusion/red blood cells (RBC) transfusions in sickle cell disease (SCD) patients who are receiving this for stroke prophylaxis.

    i. A discussion regarding the possible link between a large change (increase or decrease) in Hb levels at the time of death and the fatal cases reported. Please also consider Hb (including HbF% and HbS%), WBC, lactate dehydrogenase (LDH), bilirubin and C-reactive protein (CRP) levels along with blood culture tests, as individual and aggregated data in these fatal cases.

    j. Interim data from all ongoing trials including data of the data safety monitoring board (DSMB) and detailed minutes of the DSMB meetings.

2. The MAH should provide a comparison and critical discussion of the safety profile observed in GBT440-032 and GBT440-042, including the open-label extension GBT440-038, to the safety profile observed in the studies that supported the initial marketing authorisation (MA). This should include, but not be limited to:

    a. A comprehensive analysis of the number of SCD related events (e.g., vaso-occlusive crisis (VOC), severe haemolytic anaemia, acute chest syndrome (ACS), and other) before and

after treatment with voxelotor for all patients enrolled within the voxelotor trials, including those who experienced fatal events.

b. The infection rates and all laboratory data relevant to the immunity (e.g. WBC counts, neutrophils, lymphocytes, other WBC components).

c. A possible rebound effect due to any abrupt interruptions of the voxelotor treatment.

d. Characteristics/risk factors present that may predict the different results in the studies supporting the MA and in studies GBT440-032 and GBT440-042 including the open label extension.

e. Risk minimisation measures implemented within these studies, medical care provided, impact of concomitant medications (hydroxyurea, RBC transfusions, prophylaxis used for malaria and any other treatments). The discussion should consider any mechanistic aspects.

Good clinical practice

3. The MAH should share information on already requested/ongoing inspections inside/outside the EU, all good clinical practice (GCP) inspection reports (translated to English as appropriate) available for trials GBT440-032 and GBT440-042 (including the open-label extension study GBT440-038) and trials not already assessed with voxelotor and include responses to any findings. Also sponsor/contract research organisation (CRO) audit reports and responses to any findings in the context of these trials should be provided. Evaluations on the suitability of participating sites should also be included.

Safety data post-marketing

4. The MAH should provide and review all safety data obtained from post marketing reporting and public literature. In particular:

   a. All fatal cases reported post marketing.

   b. All cases of infection reported post marketing.

   c. Any emerging safety data since the data lock of the latest periodic safety update report (PSUR).

   d. Any reported cases of supranatural Hb increase (overshooting) during voxelotor use.

   e. Any information relevant to potential suboptimal medicine prescription by healthcare professionals (HCP) (e.g. initial prescription of a lower dose to minimise the safety risks or risk of overshooting).

   The conclusive summary in answer to this question should focus on characteristics/risk factors that may predict the events observed in studies GBT440-032 and GBT440-042, including the open-label extension GBT440-038.

5. The MAH should explain why the fatal cases occurring in the ongoing clinical trials were not included in the current PSUR single assessment (PSUSA) procedure as late-breaking information.

Non-clinical data

6. A summary of up to date non-clinical data should be provided, with of a focus on data related to changes in the immune system or haemoglobin level, together with a discussion as to whether those could have increased the susceptibility or severity of infections in voxelotor users.

Other (regulatory) authorities

7. The MAH should share any relevant information provided to other regulators, and detail of any completed or ongoing regulatory action related to voxelotor, related to the emerging safety issues or benefit-risk concerns with voxelotor, and the reasons for said actions.

Exposure-response

8. The MAH should report on observed efficacy in GBT440-032, GBT440-042 and the open-label extension study GBT440-038 and explore a potential relation between efficacy and occurrence of (serious/severe) adverse events. It should be evaluated if any such relation is completely explained by exposure. An analysis of continuous variables is preferred over a comparison of subgroups (bins).

Mechanism

9. The MAH should discuss the possible mechanisms explaining the fatal cases observed.

Benefit-Risk balance

10. Based on the above, the MAH should provide an updated assessment of the benefit-risk balance of Oxbryta in its authorised indication, and provide proposals for any measures (including changes to the product information) which could be implemented to improve the benefit-risk balance of Oxbryta.