18 December 2015
EMA/COMP/658477/2015
Committee for Orphan Medicinal Products

Recommendation for maintenance of orphan designation at the time of marketing authorisation

Ravicti (glycerol phenylbutyrate) for the treatment of urea cycle disorders [carbamoyl phosphate-synthase-1 deficiency, ornithine carbamoyltransferase deficiency, citrullinaemia type 1, argininosuccinic aciduria, hyperargininaemia and ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome)]

During its meeting of 6 to 8 October 2015, the Committee for Orphan Medicinal Products (COMP) reviewed the designations EU/3/10/733, EU/3/10/734, EU/3/10/735, EU/3/10/736, EU/3/10/737 and EU/3/10/738 for Ravicti (glycerol phenybutyrate[1]) as an orphan medicinal product for the treatment of the following urea cycle disorders: carbamoyl phosphate-synthase-1 deficiency, ornithine carbamoyltransferase deficiency, citrullinaemia type 1, argininosuccinic aciduria, hyperargininaemia and ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome). The COMP assessed whether, at the time of marketing authorisation, the medicinal product still met the criteria for orphan designation. The Committee looked at the seriousness and prevalence of the conditions, and the existence of other methods of treatment. As other methods of treatment are authorised in the European Union (EU) for three of the above conditions (carbamoyl phosphate-synthase-1 deficiency, ornithine carbamoyltransferase deficiency, and citrullinaemia type 1), the COMP also considered whether the medicine is of significant benefit to patients with these conditions. The COMP recommended that the orphan designations of the medicine be maintained[2].

Life-threatening or long-term debilitating nature of the condition

The Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of Ravicti for:

‘use as adjunctive therapy for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase

[1] Previously known as glyceryl tri-(4-phenybutyrate).
[2] The maintenance of the orphan designation at time of marketing authorisation would, except in specific situations, give an orphan medicinal product 10 years of market exclusivity in the EU. This means that in the 10 years after its authorisation similar products with a comparable therapeutic indication cannot be placed on the market.

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(ASL), arginase I (ARG) and ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone'.

This falls within the scope of the product's designated orphan indications, which are: carbamoyl phosphate-synthase-1 deficiency, ornithine carbamoyltransferase deficiency, citrullinaemia type 1 (also known as argininosuccinate synthetase deficiency), argininosuccinic aciduria (also known as argininosuccinate lyase deficiency), hyperargininaemia (also known as arginase deficiency) and ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome).

The COMP concluded that there had been no change in the seriousness of the conditions since the orphan designations in 2010. Urea cycle disorders remain long-term debilitating and life-threatening conditions that lead to learning disability and are associated with poor overall survival.

Prevalence of the condition

The sponsor performed a literature search and concluded that there were no major changes in the prevalence of the six urea cycle disorders since the orphan designations in June 2010.

On the basis of the information provided by the sponsor and the knowledge of the COMP, the COMP concluded that the prevalence of the six urea cycle disorders remains below the ceiling for orphan designation, which is 5 people in 10,000. At the time of the review of the orphan designation, the prevalence was estimated to be:

- approximately 0.14 people in 10,000 for carbamoyl phosphate-synthase-1 deficiency. This is equivalent to a total of around 7,000 people in the EU;
- approximately 0.14 people in 10,000 for ornithine carbamoyltransferase deficiency. This is equivalent to a total of around 7,000 people in the EU;
- approximately 0.2 people in 10,000 for citrullinaemia type 1. This is equivalent to a total of around 10,000 people in the EU;
- approximately 0.06 people in 10,000 for argininosuccinic aciduria. This is equivalent to a total of around 3,000 people in the EU;
- approximately 0.03 people in 10,000 for hyperargininaemia. This is equivalent to a total of around 1,500 people in the EU;
- approximately 1.2 people in 10,000 for ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome). This is equivalent to a total of around 61,500 people in the EU.

Existence of other methods of treatment

The COMP noted that, at the time of the review of the orphan designations, no treatments were authorised in the EU for patients affected by argininosuccinic aciduria, hyperargininaemia and ornithine translocase deficiency.

Treatments were authorised in the EU for the treatment of carbamoyl phosphate-synthase-1 deficiency, ornithine carbamoyltransferase deficiency and citrullinaemia type 1 and included Ammonaps (sodium phenylbutyrate) and Pheburane (sodium phenylbutyrate).

Significant benefit of Ravicti

The COMP concluded that the claim of a significant benefit of Ravicti in the treatment of carbamoyl phosphate-synthase-1 deficiency, ornithine carbamoyltransferase deficiency and citrullinaemia type 1 is justified on the basis of data showing that the frequency of hyperammonaemia crises (high blood levels of ammonia) was much lower in patients treated with Ravicti compared with patients treated with other treatments. Furthermore, Ravicti is available as an oral liquid and this is considered to be beneficial especially for children, because it can improve adherence to treatment.

Therefore, although other methods for the treatment of these three urea cycle disorders have been authorised in the EU, the COMP concluded that Ravicti is of significant benefit to patients affected by these conditions.

Conclusions

Based on the data submitted and the scientific discussion within the COMP, the COMP considered that Ravicti still meets the criteria for designation as an orphan medicinal product and that it should remain in the Community Register of Orphan Medicinal Products.

Further information on the current regulatory status of Ravicti can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.