6 August 2013
EMA/COMP/239416/2013
Committee for Orphan Medicinal Products

# Recommendation for removal of orphan designation at the time of marketing authorisation

## Pheburane (sodium phenylbutyrate) for the treatment of urea cycle disorders (carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency and citrullinaemia type 1)

During its meeting of 12-13 April 2013, the Committee for Orphan Medicinal Products (COMP) reviewed the designations EU/3/12/951, EU/3/12/950 and EU/3/12/949 for Pheburane (sodium phenylbutyrate) as an orphan medicinal product for the treatment of the following urea cycle disorders: carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency and citrullinaemia type 1. 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 condition, and the existence of other satisfactory methods of treatment. As other satisfactory methods of treatment for patients with this condition are authorised in the European Union (EU), the COMP also looked at the significant benefit of the product over existing treatments. As one of the criteria for orphan designation is no longer met (i.e. the significant benefit), the COMP recommended that the orphan designation of the product should not be maintained[1].

The sponsor requested a re-examination of the COMP opinion. After considering the grounds for this request, the COMP re-examined the initial opinion, and confirmed the removal of the orphan designation on 1 July 2013.

### Life-threatening or chronically debilitating nature of the condition

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

'adjunctive therapy in the chronic (long-term) management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase'.

[1] The removal of the orphan designation at time of marketing authorisation means that the product cannot benefit from 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 can be placed on the market.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

This falls within the scope of the product's designated orphan indications, which are: treatment of carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency and citrullinaemia type 1 (also known as argininosuccinate synthetase deficiency).

The COMP concluded that there had been no change in the seriousness of these conditions since the orphan designation in February 2012. The three urea cycle disorders remain conditions that are debilitating in the long term and life threatening because they lead to mental retardation and are associated with poor overall survival.

## Prevalence of the condition

The sponsor performed a literature search and concluded that the prevalence of urea cycle disorders has not changed since the orphan designation in February 2012.

On the basis of the information provided by the sponsor and the knowledge of the COMP, the COMP concluded that the prevalence of the three 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 still estimated to be:

- less than 0.02 people in 10,000 for carbamoyl-phosphate synthase-1 deficiency. This is equivalent to a total of fewer than 1,000 people in the EU;
- less than 0.1 people in 10,000 for ornithine transcarbamylase deficiency. This is equivalent to a total of fewer than 5,000 people in the EU;
- less than 0.24 people in 10,000 for citrullinaemia type 1. This is equivalent to a total of fewer than 12,000 people in the EU.

## Existence of other satisfactory methods of treatment

At the time of the review of the orphan designation, sodium phenylbutyrate was already authorised as Ammonaps in the EU for the treatment of some urea cycle disorders, including carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency and citrullinaemia type 1. This medicine is known to have a bitter taste.

## Significant benefit over existing treatments

The COMP noted that Pheburane is a new, tasteless granule formulation of sodium phenylbutyrate that contains excipients (inactive ingredients) to mask the unpleasant taste of the active substance. Data have been provided that show that Pheburane has improved palatability over Ammonaps and that there are difficulties in administering the latter because of its bitter taste; however, the sponsor has not provided sufficient data to confirm that the improved palatability of Pheburane results in a better outcome for patients with urea cycle disorders, such as improved treatment compliance or enhanced quality of life. As these data are needed to demonstrate that Pheburane is of significant benefit over current treatment, the COMP concluded that the criteria to show a significant benefit of Pheburane in the treatment of urea cycle disorders had not been met.

## Conclusions

Based on the data submitted and the scientific discussion within the COMP, the COMP concluded that Pheburane does not meet one of the criteria for designation as an orphan medicinal product. Therefore, the COMP recommended that the product should be removed from the Community Register of Orphan Medicinal Products.

Further information on the current regulatory status of Pheburane 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.