Glycerol phenylbutyrate (Ravicti®) for the treatment of urea-cycle disorders

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 12 September 2017

Zorginstituut Nederland has carried out an assessment of the medicinal product glycerol phenylbutyrate (Ravicti®), whereby they came to the following conclusion.

In a letter dated 14 August 2017 (CIBG-17-04956) the Minister of WVS asked *Zorginstituut Nederland* to carry out a marginal assessment of whether glycerol phenylbutyrate (Ravicti®), a fluid for oral use, can be included in the Medicine Reimbursement System (GVS). The Zorginstituut has completed its assessment.

The manufacturer asked for placement in cluster 0A16AXAO V, which includes Ammonaps® and Pheburane®, medicines with sodium phenylbutyrate as active substance. This fulfils the criterion for marginal assessment that at least two products must be included in the cluster. The said products both contain sodium phenylbutyrate, a structural analogue of glycerol phenylbutyrate.

Glycerol phenylbutyrate (Ravicti®) is available as a liquid for oral use. Each ml of liquid contains 1.1 g glycerol phenylbutyrate.

Glycerol phenylbutyrate is registered for the adjunctive chronic treatment of adults and children aged ≥ 2 months with urea-cycle disorders (UCD)* who cannot be treated with dietary protein restriction alone and/or amino acid supplements.

Glycerol phenylbutyrate must be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, protein-free calorie supplements).
The recommended daily dose of Ravicti® is between 4.5 ml/m^2 and 11.2 ml/m^2 [5.3 g/m^2 – 12.4 g/m^2].

Outcome of assessment
Based on the interchangeability criteria, glycerol phenylbutyrate (Ravicti®) can be regarded as being interchangeable with sodium phenylbutyrate. Ammonaps® and Pheburane®, both of which have sodium phenylbutyrate as active ingredient, are already included in GVS cluster 0A16AXAO V.

The World Health Organisation (WHO) has not established a DDD for glycerol phenylbutyrate. The DDD for sodium phenylbutyrate has been established and is 20.0 g/dag. Based on the conversion factor indicated in the SmPC for the DDD of sodium phenylbutyrate, the standard dose of glycerol phenylbutyrate is 18.92 g/dag (which is the equivalent of 17.2 ml/dag Ravicti® 1.1 g/ml).

* Glycerol phenylbutyrate is registered for urea-cycle disorders (UCD) including deficiencies in carbamoyl phosphate synthase I (CPS), ornithine carbamoyl transferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase-deficient hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome

Advice
Based on the above, glycerol phenylbutyrate (Ravicti®) can be placed on List 1A in cluster 0A16AXAO V with a standard dose of 18.92 g/day, which is the equivalent of 17.2 ml/day Ravicti® 1.1 g/ml.

For further information, please contact: JBoer@zinl.nl; warcg@zinl.nl

The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.