SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Ammonpas. This scientific discussion has been updated until 1 November 2001. For information on changes after this date please refer to module 8B.

1. Introduction

Ammonaps, sodium phenylbutyrate (PB), is a new active substance. It is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinate synthetase. It is indicated in all patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

The dossier submitted in support of the application comprises data generated by the applicant: all chemical/pharmaceutical data, the two mutagenicity studies for Part III, and for Part IV, the bioequivalence study and a review of the US IND/NDA programme. Additional information was available from published literature.

Urea cycle disorders (UCD) are inherited deficiencies of one of the enzymes involved in the urea cycle, by which ammonium is converted to urea. Ammonium is highly toxic to nerve cells and hyperammonaemia may result in metabolic derangement, leading to anorexia, lethargy, confusion, coma, brain damage, and death.

The most severe forms of UCDs occur early in life (complete enzyme deficiencies). The classic neonatal presentation of all the UCD (with the exception of arginase deficiency) is quite uniform and includes, after a short symptom-free interval of one to five days, poor feeding, vomiting, lethargy, muscular hypotonia, hyperventilation, irritability and convulsions. Without rapid intervention, coma prevails as the condition worsens and leads eventually to deaths. Later onset forms of UCD occur in infancy, at puberty, and in adults subject to physiological stress. In the late onset forms, more subtle symptoms have been described including vomiting, migraine-like headache, changes in the level of consciousness and neurological signs, such as lethargy, somnolence, irritability, agitation, combativeness, disorientation, ataxia and visual impairment. Seizures are a late complication. Finally, delayed physical growth and delay in mental development are common. In female patients with ornithine transcarbamylase deficiency, who are heterozygous, the condition is less severe and they may remain undiagnosed well into adult life.

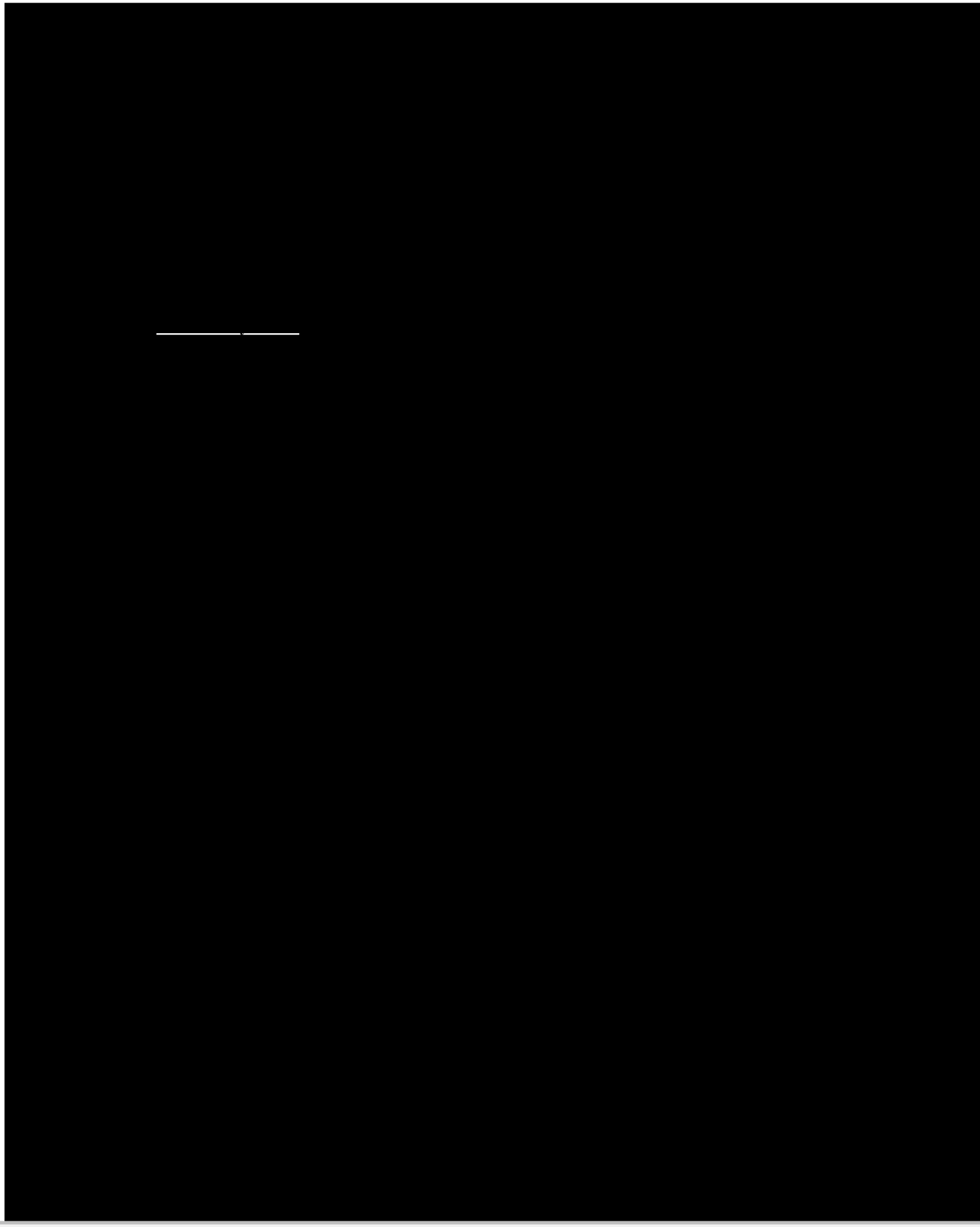
In the absence of systematic screening, the incidence of UCD is difficult to assess and various estimates are found in the literature. On this basis, it is estimated that the overall incidence of all urea cycle disorders has been defined as 1 per 8,200 births.

The treatment strategies used are to reduce dietary protein intake, and to provide an alternative vehicle to urea for the excretion of nitrogen waste. Currently none of the possible treatments for hyperammonaemia are approved in Europe. Enzyme replacement therapy through liver transplantation provides an additional treatment option. In most patients this procedure has markedly improved their metabolic abnormalities and permitted a normal protein intake, however, transplantation for UCD is a relatively recent treatment option and its long-term benefits are as yet unknown.

Sodium phenylbutyrate is a prodrug and is rapidly metabolised to phenylacetate. It promotes the synthesis of phenylacetylglutamine, which then serves as a substitute vehicle for waste nitrogen excretion. The recommended dose is:

- 450 - 600 mg/kg/day in neonates, infants and children weighing less than 20 kg
- 9.9 - 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults.

The safety and efficacy of doses in excess of 20 g/day has not been established.



Attention should be drawn to the fact that the Ames test did not comply with the ICH-requirements (i.e. two recommended strains of E. coli were not included to pick-up A-T and G-C base pair mutations) and there are no pharmacokinetic data in either rat or man to validate the in vivo study in terms of reaching adequate plasma levels. Despite these deficiencies, the results of both studies did not give raise to any evidence of mutagenic potential.

Reproductive and development toxicity studies - Studies on administration to pregnant rodents indicate that CNS damage may occur in animals exposed in utero. However, as drug administration did not commence until day 9 of gestation, after the main period of organogenesis, these studies are not optimal for the assessment of teratogenic potential. In female pregnant rats, spontaneous abortions occurred, birth weight of the offspring was significantly lower than in controls, weight gain of the pups over the lactation period was reduced, and brain weight at sacrifice was low. It also seems likely that spermatogenesis and therefore fertility would be affected in the male rat.

Impurities - In the active substance, α-tetralone, 3-benzoylpropionic acid and 4-cyclohexylbutyric acid are the potential impurities identified. According to the ICH requirements, the threshold for toxicological qualification of impurities is 0.05% (w/w) and of degradation products is 0.1%, when the total daily intake exceeds 2 g, as in the case of Ammonaps. The limits for cyclohexylbutyric acid and for other impurities in the active substance and in the release specification for the tablets and granules are higher than the threshold (at 0.1%), but the limits have been found to be toxicologically acceptable. No adverse events would be expected as a result of these impurities, but the applicant is required to submit further data from manufacturing batches and these data will be reviewed (see also Part II).

- Summary and conclusion on preclinical pharmacology and toxicology:

There are no formal toxicity studies; no overt toxicity was noted in a review of the data available. A bacterial reverse mutation and a rat bone marrow micronucleus test have been carried out with sodium phenylbutyrate and did not give rise to any evidence of mutagenic potential. The available data indicate that PB is fetotoxic, affecting mainly the brain; effects on reproduction and organogenesis have not been conventionally investigated. This has been dealt with in the SPC, where pregnancy is contra-indicated and an explanation is given in the appropriate section of the document.

The deficiencies of the pre-clinical section of the dossier should be viewed in the light of the CPMP recommendation for an approval under exceptional circumstances. As required for an authorisation under exceptional circumstances, appropriate information is provided in the product information to draw the attention of the medical practitioner to the fact that the currently available data concerning the medicinal product in question is inadequate in certain specified respects. The conditions for which this medicinal product would be indicated would fall within the scope of the Proposed European Parliament and Council Regulation (EC) on Orphan Medicinal Products.

4. Clinical aspects

Ammonaps, sodium phenylbutyrate (PB), is a new active substance with the proposed therapeutic indication "adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamyl phosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase". Urea Cycle Disorders (UCD) are inherited deficiencies of one of the enzymes involved in the urea cycle, by which ammonium is converted to urea. Excess dietary protein and the nitrogenous substances produced by endogenous protein turnover are normally metabolised to yield energy and the by-product ammonium, which is excreted in the urine as urea. Each pass through this cycle results in the elimination of one molecule of urea, which contains two atoms of waste nitrogen. Due to deficiencies of the urea cycle, the conversion of ammonium ion to urea is impaired to varying degrees, and consequently its excretion is reduced. Ammonium is highly toxic to nerve cells and hyperammonaemia can damage the central nervous system leading to cerebral oedema and death.

The elimination of nitrogen from the human body by a moiety other than urea was first proposed in 1914, when Lewis described the stoichiometric relationship between the decrease in urine nitrogen as urea and the appearance of hippurate nitrogen in a normal subject given sodium benzoate. Subsequently, Sherwin in 1919 demonstrated the quantitative elimination of nitrogen in humans via

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