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.

2. Chemical, pharmaceutical and biological aspects

Composition

Ammonaps is presented as tablets and granules containing sodium phenylbutyrate. Two standard and simple pharmaceutical formulations of sodium phenylbutyrate were produced with commonly used excipients. The tablets (500 mg) contain approximately 74% active substance and the granules provide 940 mg sodium phenylbutyrate/g granules.

In order to dose accurately and especially for smaller amounts required for infants, three measuring spoons have been introduced for the granules, giving doses of 0.95 g, 2.9 g and 8.6 g. The overall uniformity of doses obtained from the three measuring spoons is acceptable and the individual weights are within the Ph. Eur. limit of 10% for single-dose powders.

The proposed container for both granules and tablets is a high density polyethylene (HDPE) bottle with a desiccant unit, closed with a polypropylene caps (child resistant). The materials have been adequately tested for conformance to USP requirements.

Active substance

Pharmaceutical data on the active substance have been presented in an EDMF (European Drug Master File). Sodium phenylbutyrate is off-white to slightly yellow powder, which is soluble in water. A four-step synthetic process with acceptable in-process controls manufactures it. Process validation data show the synthesis to be under control. Satisfactory specifications were provided for the starting material, solvents, reagents and intermediates. The manufacturer of the active substance has adequately validated the analytical methods used. The manufacturer of the finished product to re-test the active substance uses the same methods; full re-validation is to be carried out on these methods and results provided.

Sodium phenylbutyrate has a simple structure and presents no polymorphic forms. The pathway of synthesis has confirmed the evidence of its chemical structure, by elemental analysis, ^{1}H-NMR and IR spectroscopy.

The specification includes tests for appearance, bulk density, water content, identifcation by IR and HPLC, heavy metals, pH, assay and impurities. Three main related substances are specified: α-tetralone, 3-benzoylpropionic acids and 4-cyclohexylbutyric acids. Further impurities (e.g. isomer 2-phenylbutyric acid) can be detected by a GC or HPLC assay method but have not been found in the active substance. While the limits for impurities have been toxicologically accepted, it is suggested that in view of the high doses to be given (> 2 g/day), limits should be reviewed and tightened when further batch data are available. Residual solvents are also specified at a suitable limit in agreement with CPMP/ICH guidance.

Analytical results from three batches show compliance with the specification and indicate suitable uniformity.

The active substance (3 batches) was tested for up to 12 months under real-time (25°C/60%RH) and accelerated condition (40°C/75%RH). It was also tested in solvent and solution, under the influence of pH and oxidative conditions. The shelf-life specification includes appearance, assay, impurities, pH and water. Increases in water content were observed but are not linked to the increases in 3-benzoylpropionic acid also seen in stability batches and are not detrimental to the stability of sodium phenylbutyrate. A 12-month retest period can be approved.

Other ingredients

Satisfactory information has been provided on the excipients. All excipients will be released against relevant Ph.Eur. Monographs. For those excipients derived from tallow (i.e. magnesium and calcium stearate), a TSE declaration was provided in accordance with the EU requirements (Commission Decision 97/534/EC).

Product development and finished product

No detailed pre-formulation studies were performed. The tablets and granules are manufactured using simple formulations based on commonly used excipients, standard pharmaceutical equipment and processes. The function of the excipients is stated.

Forced degradation studies have been conducted under extreme temperature and acidic conditions. They indicate a rise in 3-benzoylpropionic acid level, as well as some degradants not detectable by HPLC, but these extreme conditions do not reflect the product as marketed. Results of up to 0.006% w/w were found from batches tested for 3-benzoylpropionic acids.

Batches manufactured at different sites have been used in clinical trials and bioequivalence studies. Results of a three-way crossover study in healthy volunteers receiving 5 grams doses of tablets or granules indicate that the bioavailability of the granule formulation is less than that of the tablets, but remains within the usual criterion of ± 20%. This will be further discussed in Part IV.

The manufacturing processes for both granules and tablets consist of multi-stage blending, compaction, granulation, and compression as the final step for tablets. The processes are satisfactorily described.

Mixing times, equipment conditions and in-process controls are described for both formulations accordingly (weight, thickness, hardness, friability for the tablets, fill volume for the granules and bulk and tapped density testing for both tablet and the granules) and their parameters are specified within acceptable limits. Results from clinical (7 and 5 batches for granules and tablets, respectively) and production (2 batches for granules and tablets) batches indicate acceptable batch-to-batch consistency.

A revised finished product specification (for both the site of manufacture and the site of batch release) has been provided in compliance with EU requirements. Control tests on the finished product use adequately validated methods and include requirements for appearance, identification of active substance, assay and impurities determination, bulk density testing for granules, and average weight, uniformity of weight, disintegration and dissolution for the tablets. The microbiological quality is controlled in accordance with Ph. Eur., but is proposed as a non-routine method.

The dissolution medium, previously simulated intestinal fluid, has been changed to water. The dissolution specification has been tightened to 80% in 45 minutes but this should be reviewed again in the light of further data. Dissolution results using both media show slightly greater dissolution in water, but dissolution is essentially complete in both media at the same time. The disintegration limit is set slightly higher than usual (at 20 min); this is acceptable as the results do not impact adversely on dissolution.

A commitment is given by the applicant to submit certificates of analysis for the first three production batches, tested to the EU specifications. Limits for impurities will be reviewed when further batch data are available.

On the basis of the inspection carried out at Pharmaceutics International Inc on 13-15 May 1998, the inspection report confirmed that the operations are in general compliance with the principles and guidelines of GMP (see the Annex II).

Stability studies have been carried out at 25ºC/60%RH up to 24 and 36 months on batches of granules and tablets made by Pharmaceutics International, and at 40ºC/75%RH for 6 months. Shelf-life content limits of 93-107% have been accepted for the finished products on the basis of the variability in results, though no degradation appears to occur. The limits should be reviewed again when further stability data are available. The analytical methods used are those for routine finished product testing or similar, validated methods. No change of appearance was observed. Content and impurity levels remain within the proposed limits as specified. Satisfactory stability data for the full shelf-life have been provided and based on the resulting data, a 2-year shelf life is acceptable for both granules and tablets when stored below 30ºC.

- Discussion on chemical, pharmaceutical and biological aspects

Ammonaps granules and tablets are conventionally formulated and manufactured using standard pharmaceutical technology. A suitable specification has been submitted for the active substance. The limits for impurities have been toxicologically accepted (see Part III). A single specification for each

finished product formulation is also proposed, with revised specification for dissolution parameters and impurity limits. In line with the requirements for the active substance, the impurity limits should be reviewed when further data are available.

Overall, the chemical-pharmaceutical dossier is generally acceptable. The company was however requested to provided, within the agreed timeframe, additional data, which have not been satisfactorily resolved; these are defined in the follow-up measures as listed in the company's undertaking letter (see section II.3 of this report).

3. Toxico-pharmacological aspects

Pharmacodynamics

Pharmacodynamic effects relating to the proposed indications are as outlined in section 4 (Clinical pharmacology/Pharmacodynamics).

General pharmacodynamics - A number of studies seem to indicate the ability of PB to inhibit tumour growth in vitro, and that phenylacetate and probably phenylbutyrate have neuroinhibitory and neurotoxic potential under the in vitro and ex-vivo conditions studied.

Two rat models of human phenylketonuria were developed, one involved exposure to PA injected s.c. twice daily from day 2-28 of life. In the other, pregnant rats were exposed to PA during gestation. Reduced brain weight, abnormalities in learning, and in neurotransmitter uptake are consistently noted. It was argued that high concentrations are unlikely during therapeutic use of PB because of poor transfer across the adult blood-brain barrier. The implications of these findings with respect to human foetal brain are unknown (see also below - Reproductive and development toxicity studies)

Pharmacokinetics

Studies in the juvenile rat, where subcutaneous administration was used, and in the adult cat, where intravenous administration was used, have been performed. Even though pharmacokinetic data after oral administration are not available, it can be expected that being an organic acid, PB will be rapidly and extensively absorbed after oral administration. It is converted to its active metabolite, PA by beta-oxidation. In single subcutaneous dose studies from birth to maturity in rats, PA penetrated tissues rapidly and extensively, with tissue levels usually equivalent to those in blood. Like other organic acids, PA is actively excreted in urine by tubular secretion as the amino acid conjugate.

Toxicology

Single dose toxicity - No single dose toxicity studies have been carried out. However, sufficient information is available from the animal pharmacology above. The doses of PA given in these studies were low. Taken together, the results of the studies suggest that single doses of PA by both the intravenous and subcutaneous routes are well tolerated.

Repeated-dose toxicity - There are no repeated dose studies available. However, information available from the animal pharmacology above makes a convincing case that parenteral administration of phenylacetate causes impairment of brain development in the immature rodent. Because phenylacetate can cross into human CNS, the observations in rodents should be considered a potential hazard for the therapeutic use of PB.

Carcinogenicity - Carcinogenicity studies have not been performed. These deficiencies are not considered to be an impediment to the granting of a Marketing Authorisation in view of ICH-S1A: guideline on the need for carcinogenicity studies of pharmaceuticals.

Genotoxicity and mutagenicity - A bacterial reverse mutation assay (Ames test, plate incorporation method) was conducted with PB at concentrations in the range of 52-5000 µg/plate, using five strains of Salmonella Typhimurium, in the presence and absence of rat liver microsomal enzymes (S9). No cytotoxicity or revertant colonies were observed at the top dose. A bone marrow micronucleus test was also conducted using rats of both sexes (5 animals/sex/group; PB 878-1568-2800 mg/kg single oral gavage). Deaths occurred in top dose (7/10, at 2800 mg/kg) and mid-dose (2/10, at 1568 mg/kg) groups. The frequency of micronucleated cells was not significantly different from the negative

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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