## 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.


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Par Pharmaceutical, Inc. Ex. 1019
Par v. Horizon, IPR of Patent No. 9,561,197
Page 1 of 12

## 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).


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Par Pharmaceutical, Inc. Ex. 1019
Par v. Horizon, IPR of Patent No. 9,561,197
Page 2 of 12

**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


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Par v. Horizon, IPR of Patent No. 9,561,197
Page 3 of 12

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 control at any dose level at either the 24 hour or the 48 hour harvest.


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Par v. Horizon, IPR of Patent No. 9,561,197
Page 4 of 12

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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Par v. Horizon, IPR of Patent No. 9,561,197
Page 5 of 12

phenylacetylglutamine following treatment with oral doses of phenylacetic acid (PA). The amino acid acylation products of sodium benzoate and sodium phenylacetate may substitute for urea nitrogen excretion in all UCD.

The investigational use of PA for the treatment of patients with urea cycle disorders was started in clinical trials performed at Johns Hopkins University, USA, in 1980. Subsequently, the relevant permission was amended to include the investigational use of the combination of sodium benzoate and PA at several dosages. In 1983, a further amendment permitted the use of PB as a substitute for PA. Finally, in 1987, the use of PB only was introduced as a monotherapy replacing the combination therapy.

The Office of Orphan Products Development supported the trial conducted with PB and the US Orphan status designation was granted on 22 November 1993. The results of this trial constitute the basis of the clinical part of the dossier. Although this trial does not comply with the requirements of Good Clinical Practice, it seems that the study population represents a significant proportion of patients with these rare disorders treated in the USA.

**Clinical pharmacology**

Pharmacodynamics – PB is a pro-drug, which is rapidly converted to PA by beta-oxidation in mammalian liver and kidneys. In higher primates, PA is enzymatically conjugated with glutamine in the liver and kidneys to form phenylacetylglutamine (PAG), which is readily excreted in the urine. The glutamine required to excrete the PA will have to be synthesised and the reversible reaction: glutamine $\leftrightarrow$glutamic acid + $NH_4^+$ will proceed to the left and therefore ammonia will be excreted This cannot be demonstrated in animals due to species differences in the metabolic pathway of nitrogen elimination. On a molar basis, PAG is comparable to urea (each containing two nitrogen atoms) and provides an alternative vehicle for waste nitrogen disposal. Thus therapeutic administration of PB has the potential to divert nitrogen away from the blocked or impaired urea cycle and to provide an alternative pathway of excretion.

Experimental support for the hypothesis outlined above is provided by the work of Prof. Brusilow's group at the Johns Hopkins school of Medicine. Brusilow demonstrated in 1991 in a child with carbamyl phosphate synthetase deficiency that administration of PA or PB resulted in the urinary excretion of PAG equivalent to 38-44% of the predicted normal nitrogen excretion. In other children with UCD, administration of PB or PA resulted in a decrease of 25-50% of baseline glutamine. Similar results were found in an adult male patient with ornithine transcarbamylase deficiency, whose plasma ammonium and glutamine levels significantly declined with PB therapy.

Pharmacokinetics – No formal pharmacokinetic studies have been performed with PB. Data from bioequivalence studies, and pilot studies in patients with cancer and haemoglobinopathies are cited.

Studies in cancer patients have been performed where intravenous infusion of PB or PA has been used for anti-tumour activity. After intravenous bolus infusion, PB and PA display non-linear pharmacokinetics with a saturable elimination, which is consistent with an enzymatic process. During treatment with repeated doses of phenylacetate there is evidence of an induction of drug clearance as shown by a significant decrease (27%) in the AUCs obtained at the beginning (days 1-3) compared with those in the end (days 12-14) of therapy, which the authors attribute to enzyme induction. Concentrations over 900 µg/ml were associated with sedation, confusion, nausea and vomiting.

Pharmacokinetics after oral administration of PB have been studied in healthy volunteers (single dose of 2.5 g, n=2; single dose of 5 g, n= 21), in one patient with ornithine transcarbamylase deficiency and in 8 patients with haemoglobinopathies. PB is rapidly absorbed: measurable plasma levels of PB are detected 15 min after oral administration. Peak concentrations of approximately 1 mmol/l are reached after 1 h. In one study, the elimination half-life was estimated to be 0.8 h. Measurable plasma levels of PA and PAG are detected 30-60 min after oral dosing of PB (the mean peak concentration is 45.3 and 62.8 µg/ml, respectively). The time to peak concentration increases with the dose of PB and is around 3.5 h for both metabolites after a dose of 5 g of PB. The elimination half-life was estimated to be 1.3 and 2.4 hours, respectively for PA and PAG. Recovery of PB and PAG from serial collections of urine has been evaluated in some of the cited studies. It is demonstrated that in most subjects, the kidneys within 24h excrete approximately 80-100% of the drug as the conjugated product, PAG. After oral administration, unchanged drug is not detected in the urine of normal subjects or patients with UCD. It


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Par v. Horizon, IPR of Patent No. 9,561,197
Page 6 of 12

has not been determined if PA is secreted in human milk, therefore Ammonaps is contraindicated during breast-feeding.

For all formulations used in the bioequivalence studies, the total exposure was greater in female than in male subjects, being about 20-25% and 40% higher for PB and PA, respectively. This gender difference has been mentioned in the SPC. This may be due to the lipophilicity of the drug and gender differences in volume of distribution. For PAG the difference was only about 10%. The principal indices of plasma pharmacokinetics of PB, PA and PAG in healthy male and female subjects are tabulated below (Table 1).

**Table 1 - Plasma pharmacokinetics (mean values) in healthy male (m) and female (f) subjects:**

| | $t_{max}$ (h) | $C_{max}$ (µg/ml) | **AUC** (µg·h/ml) | $t_{1/2}$ (h) |
|---|---|---|---|---|
| Phenylbutyrate (PB) | M 1.18<br>F 1.21 | M 192.5<br>F 242.6 | M 480.1<br>F 622.1 | M 0.78<br>F 0.82 |
| Phenylacetate (PA) | M 3.62<br>F 3.73 | M 39.2<br>F 55.1 | M 154.4<br>F 245.8 | M 1.2<br>F 1.26 |
| Phenylacetyl glutamine (PAG) | M 3.25<br>F 3.43 | M 67.4<br>F 66.9 | M 282.7<br>F 297.7 | M 2.12<br>F 2.66 |

*Bioequivalence studies* - In a single dose three-way crossover study, healthy male (n=10) and female (n=11) volunteers received a) PB 500 mg tablets, American Drug Development Inc., b) PB powder, Pharmaceutical services University of Iowa or c) PB 500 mg tablets, Pharmaceutical Services University of Iowa. In all cases the dose was 5 grams. A and B were considered the test and C the reference formulations. Results are tabulated below (Table 2) and indicate that the bioavailability of the powder formulation is less than that of the tablets, but remains within the usual regulatory criterion of ± 20 %.

**Table 2 - Relative bioavailability (mean values) of test tablets (a) and powder (b) compared to reference tablets (c):**

| | $t_{max}$ (h) | $C_{max}$ (µg/ml) | **AUC** (µg·h/ml) | $t_{1/2}$ (h) |
|---|---|---|---|---|
| Phenylbutyrate (PB) | a) 1.4<br>b) 1.0<br>c) 1.2 | a) 218<br>b) 195<br>c) 240 | a) 577<br>b) 494<br>c) 586 | a) 0.77<br>b) 0.76<br>c) 0.85 |
| Phenylacetate (PA) | d) 3.7<br>e) 3.6<br>f) 3.7 | d) 49<br>e) 45<br>f) 54 | d) 211<br>e) 188<br>f) 231 | d) 1.15<br>e) 1.29<br>f) 1.25 |
| Phenylacetyl glutamine (PAG) | g) 3.4<br>h) 3.2<br>i) 3.4 | g) 69<br>h) 63<br>i) 69 | g) 306<br>h) 268<br>i) 301 | g) 2.41<br>h) 2.36<br>i) 2.56 |

All formulations in the bioequivalence study contained approximately the same amount of active substance and relatively minor differences in excipients. No safety problems have been observed from clinical experience with the proposed commercial formulation, as distinct from development formulations.

*Interaction studies* - No studies of drug interactions are included in support of the application. There have been publications reporting that: renal excretion of the PB conjugation product may be affected by concurrent administration of probenecid; hyperammonia may be induced by haloperidol and by valproate; corticosteroid may cause increase in plasma ammmonia levels. More frequent monitoring of plasma ammonia levels is advised in the SPC when using these medications.

There is no formal food interaction study available. The suggestion for administration with food is based on experience gained in clinical practice. In addition, the dose is to be titrated against metabolic states and an important principle would seem to be that the administration with or without is kept constant.

*Special patient groups* - The pharmacokinetics of PB have been studied in male patients with hepatic cirrhosis (oral administration, 20 g/day in three doses). Plasma levels of PB followed the peak and


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Par v. Horizon, IPR of Patent No. 9,561,197
Page 7 of 12

trough pattern familiar from healthy subjects and UCD patients. The conversion of PA to PAG was relatively slower in these patients with impaired hepatic function as evidenced by progressive accumulation of PA in the plasma of 3 out of the 6 patients studied; this pattern is not found in subjects with normal liver function. In addition, PB and PA were detected in urine. This suggests that in patients with cirrhosis the capacity of the metabolic pathway of PA is reduced.

The pharmacokinetics of PB have not been studied in patients with renal impairment.

Appropriate information concerning these high risk groups is contained in the SPC.

*Dosage* - No formal dose finding study has been performed. The proposed daily dosage was derived on the basis that one mole of PB will be metabolised to one mole of PAG, and from the estimated nitrogen to be excreted on a restricted intake. Excretion of 0.09 g/kg/d of PAG nitrogen would require a dose of 0.6 g/kg/d of PB. It is likely that the efficiency of excretion varies between patients and individual titration is recommended on the basis of therapeutic monitoring. Based on this reasoning, the following regimen is proposed:

- 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.

**Clinical efficacy**

The most important efficacy data are derived from the Phase III clinical trial, based on the US-IND/NDA program. In this study, patients with UCDs [deficiency of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinate synthetase (ASS)] were enrolled in an open, non-comparative multicentre study. The first patient was enrolled in 1985 and the cut-off for data analysis was February 1996. The IND program consisted of two cohorts of data, as outlined below.

Study population - The first treatment program (1985-1994) consists of 162 patients, of which 148 were evaluable (87 with prior therapy and 61 without prior therapy). The following UCDs had been diagnosed: OTC 99 patients, ASS 31 patients and CPS 18 patients. The distribution of the evaluable patients and classification of the population according to time of diagnosis is presented in Table 3. Of this population, 55% of patients were less than twelve years old at the time of the last visit to the investigator and 15% had received PB therapy for five years or more.

**Table 3 - Treatment population by time of onset and enzyme deficiency (1985-1994):**

| DIAGNOSIS/ONSET | OTC | CPS | ASS | Total |
|---|---|---|---|---|
| Neonatal rescue | 19 | 12 | 27 | 58 (39%) |
| Prospectively treated | 4 | 4 | 4 | 12 (8%) |
| Late onset | 21 | 2 | 0 | 23 (16%) |
| OTC females | 55 | 0 | 0 | 55 (37%) |
| Total = 148 | 99 | 18 | 31 | |

Notes: rescue = neonates rescued from hyperammonaemic encephalopathy (HE); prospective = neonates known to be at risk of UCD and treated immediately after birth; late-onset = patients presenting with HE after 28 days of age; OTC females = mutation at the OTC locus of one of their X-chromosomes.

Further information supplied in support of this application relates to a cohort of 208 patients, of which 183 were evaluable (cut-off date: February 1996). The patient population comprised 95 (52%) females and 88 (48%) males. The following UCDs had been diagnosed: OTC 122 patients, ASS 39 patients and CPS 22 patients. The distribution of the evaluable patients and classification of the population according to time of diagnosis was as follows:

- rescue : 72 (39%)
- prospective: 14 (8%)
- late-onset: 29 (16%)
- OTC females: 68 (37%)


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Par v. Horizon, IPR of Patent No. 9,561,197
Page 8 of 12

Efficacy results:

The efficacy criteria evaluated were: survival, incidence of hyperammonaemic episodes, cognitive development, growth, plasma ammonia and glutamine levels. The development of a coherent overview is hindered by the heterogeneity of the UCDs patients, with different age of onset and the possible effect of the presence or absence of prior treatment.

*Patient survival* - If the meaning of no prior therapy is taken as indicating stabilisation at birth and maintenance on PB, the results of the first treatment program indicate that 4 of 16 rescue patients died in approximately 15 months. Four of 6 prospectively diagnosed patients and treated at birth ceased treatment within the first two and a half years of life. Three of 13 late onset patients ceased treatment after an unknown time. Patients classified as OTC females have a better outlook than others; there were no deaths in a total of 26 patients and only 3 withdrawals from therapy.

At the time of the last reporting, 82 patients had been treated with PB only, whereas 101 of the patients had already been treated according to previous protocols. Overall survival rate was approximately 80%. Eighteen patients (15 in the rescue group) died during an hyperammonaemic episode, sometimes after the decision to discontinue the therapy had been taken by the parents.

*Hyperammonaemic episodes* - Data on HA episodes were initially presented as adverse events. However, because they clearly relate to the underlying disease and because therapy with PB is designed to prevent their occurrence, a reduction in frequency might be taken as evidence of efficacy of PB; the HA data has therefore been reviewed in that light.

Of the 148 evaluable patients, 34 (23%) did not experience any HA episodes requiring hospitalisation during the course of their follow-up (up to 9 years) and 114 experienced at least one episode. An overview of the occurrence of HA episodes based on 118 patients is given in Table 4.

**Table 4 - The occurrence of hyperammonaemia - events/patients - (frequency per patient):**

| | Neonatal Rescue | Neonatal prospective Rx | Late onset | OTC female |
|---|---|---|---|---|
| No antecedent treatment | 5/11 (0.45) | 3/2 (1.5) | 4/10 (0.4) | 7/23 (0.30) |
| Antecedent treatment | 6/31 (0.1) | 0/5 | 3/8 (0.38) | 6/28 (0.2) |

Patients having received antecedent treatment seem to do better. It is likely that patients in the PB only group (no antecedent treatment) would have been recruited later than those having received antecedent treatment. Considering the small number of patients, a conclusion could not be drawn.

In the last up-to date report, this number had increased to 51 out of the 183 evaluable patients (28%). Among the group of patients (n=115) treated for more than one year, the annual incidence (expressed as average per patient) of hyperammonaemic episodes was 1.1 in the rescue group, 1.9 in the prospective group, 0.6 in the late-onset group and 0.8 in the OTC-females group. Seventy-eight out of these 115 patients (68%) had one or less than one hyperammonaemic episode per year.

*Cognitive development* - Cognitive performance was evaluated using IQ measuring scales when possible. As different scales were used for different patients, results were converted into a functional scoring system: average (score 4), average/borderline (score 4/3), mentally retarded (score 2), severely retarded (score 1). The most severely affected patients (non-verbal and/or non-responsive) were also placed in the last category. Results indicate that even for the best group, i.e. OTC females, only 6/25 patients had a normal mental capacity; the IQs of the OTC-females were distributed in all categories. The patients in the rescue group showed the greatest impairment in cognitive performance. In the prospective group, none of the patients exceeded the score of low average/borderline, but none was in the severely retarded category either. Data on mental status of OTC patients on antecedent treatment and on PB are shown, no evident difference between treatments emerges.

The significance of the results in cognitive development is difficult to estimate because only some of the patients were evaluated repeatedly, the reliability of estimates during the first months of life is unknown and different types of tests were sometimes used to assess the same patient. However, this population is vulnerable to episodes of hyperammonaemic encephalopathy, each of which may result in neurological damage. Historical data suggest that untreated patients with UCDs are on a trajectory of cognitive decline.


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Par Pharmaceutical, Inc. Ex. 1019
Par v. Horizon, IPR of Patent No. 9,561,197
Page 9 of 12

*Growth* - Both height and weight of these patients were lower than average upon entry into the study. Rescue patients showed the largest deviations from normal. Height and weight-for-age z scores remained relatively stable over time, demonstrating that PB does not alter the expected growth trajectory.

Plasma ammonium and glutamine levels - Plasma ammonium values (excluding those obtained during hospitalisation for an hyperammonaemic episode) of 85 patients during periods of stable disease (281 measurements) have been reported. A total of 45 patients (53%) had at least one measurement exceeding the upper limit of normal and 6% of the values were more than two times higher than the upper limit for normal. Plasma glutamine concentration has been shown to correlate with plasma ammonium concentration and should be maintained at levels less than 1000 µmol/l. Higher levels indicate that dietary or drug therapy requires modification. Glutamine levels (mean ± SD in µmol/l, normal range, 337-673) during treatment with PB according to the type of enzyme deficiency were the following:

- rescue and prospective group <18 y (n=77) 677 ± 343
- late-onset OTC males <18 y (n=17) 700 ± 331
- late-onset OTC and CPS >18 y (n=8) 1001 ± 426
- OTC females > 18 y (n=19) 1004 ± 298
- OTC females <18 y (n=47) 1074 ± 369

- Discussion on clinical efficacy

No controlled trials have been done to test the effect of alternative medication (e.g. sodium benzoate, sodium phenylacetate). The superiority, if any, of phenylbutyrate over phenylacetate remains a matter for conjecture. A study against placebo is not feasible for ethical reasons.

Published data indicate that treatment with PA and/or PB resulted in less HA episodes than did treatment with sodium benzoate alone. From historical data on female heterozygous patients with undiagnosed OTC deficiency, 11 of 61 patients (18%) had experienced episodes of encephalopathy and 9 had died during or subsequent to those episodes. For symptomatic OTC deficiency females having had at least one HA episode, 29 of 32 patients survived at least five years. The comparison suggests an effect of PB on mortality, albeit details of treatment duration are not sufficient to allow a direct comparison.

A number of patients with various UCDs have received orthotopic liver transplant to provide enzyme replacement therapy. A review of the results from a US survey on 16 UCD patients transplanted between 1986 and 1996 (10 OTC, 3 CPS and 3 ASS) indicates a survival rate of 88% (14 patients were alive) in a follow-up period of approximately 1-6 years. Liver transplantation may offer a better outcome; however, insufficient time has elapsed for the adverse effects of immunosuppression to emerge. The possibility of liver transplantation has been mentioned in the SPC.

**Clinical safety**

Safety exposure data has been acquired from the case reports prepared by the investigators participating in the clinical study. The data presented below have been taken from the last-up-to date individual data listings covering 183 patients.

*Deaths* - One patient died from metabolic acidosis and cerebral oedema following accidental overdose of sodium benzoate and PA after mis prescription of an intravenous rescue regimen.

Withdrawal from studies due to adverse events - The reasons for withdrawal from PB therapy often do not relate to adverse events but to the difficulties of follow up and to alternative therapies such as liver transplantation. Fifteen patients (8%) had a liver transplant. Thirteen other patients withdrew from the study because of poor compliance or upon parent's request, which was often related to poor tolerance or poor acceptance of the drug by the child. The adverse events leading to discontinuation seem to be nausea, vomiting, headache, unpleasant taste, behavioural changes, and unsteadiness/dizziness.

*Serious adverse events and adverse events* - Given the dependence of the PB protocols on spontaneous reporting, the lack of a questionnaire or diary and the mental retardation of many of the patients, assessment of AEs is bound to be incomplete, and the frequency of adverse events must be regarded as an approximation. Among 183 patients, 102 patients (56%) reported at least one adverse event; a total of 248 events were reported. Among these 248 events, 90 were related to central nervous system


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Par v. Horizon, IPR of Patent No. 9,561,197
Page 10 of 12

(36%), such as hyperactivity, speech disorder, seizures, and mental retardation; but many of these are likely to be due to the neurological condition of the patients associated with UCDs.

The other most frequent adverse events were reported as follows: amenorrhoea and irregular menstrual cycles (23 % of menstruating female patients), decreased appetite (4 % of all patients), body odour probably caused by the metabolite, phenylacetate (3 %) and bad taste or taste aversion (3 %).

Cases of the following were reported in 2 % or fewer patients:

- gastrointestinal: abdominal pain, gastritis, nausea/vomiting, constipation, rectal bleeding, peptic ulcer disease, pancreatitis
- haematological: aplastic anaemia and ecchymoses
- cardiovascular: arrhythmia and oedema
- renal: renal tubular acidosis
- psychiatric: depression
- skin: rash.
- miscellaneous: headache, syncope and weight gain.

*Laboratory abnomalities* - It is difficult to discriminate between changes associated with PB and those due to UCD. They were reported as follows:

- metabolic: acidosis (14 %), alkalosis (7 %), hyperchloremia (7 %), hypophosphatemia (6 %), hyperuricemia (2 %), hyperphosphatemia (2 %), hypernatremia (1 %) and hypokalemia (1 %)
- nutritional: hypoalbuminemia (11 %) and decreased total protein (3 %)
- hepatic: increased alkaline phosphatase (6 %), increased liver transaminases (4 %) and hyperbilirubinemia (1 %)
- haematological: anaemia (9 %), leucopenia (4 %), leucocytosis (4 %), thrombocytopenia (3 %) and thrombocytosis (1 %)

*Reversible neurotoxicity* - In the Phase I pharmacokinetic studies conducted in cancer patients and in children with lysinuric protein intolerance where PA has been administered intravenously, symptoms of neurotoxicity have been observed. These manifestations were predominantly somnolence and dizziness. They were rapidly reversible and clearly related to plasma concentrations of PA higher than 3.5 mmol/l. As expected for such a small and lipophilic molecule, PA readily penetrates into the CNS.

*Pregnancy and lactation* - Regarding the use of PB during pregnancy, concerns have been raised in view of its effect on rapidly dividing cells and of the results of animal toxicity studies. PB should not be used during pregnancy and breast-feeding because pre- and postnatal exposure studies in rat pups have shown that PA produces CNS lesions. Appropriate information has been given in the SPC.

- Discussion on clinical safety

Long-term data on the safety of PB in the treatment of UCD are sparse. Since patients were not monitored under controlled conditions and were not provided a diary for recording adverse events, the documentation of the events was not consistent. Many events could be a consequence of the diseases; the often-profound mental retardation of the patients and the difficulty of separating possible side effects of treatments from those of the underlying diseases make evaluation difficult.

## 5. Overall conclusions and benefit/risk assessment

*Quality* - The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. However, the impurity limits and the dissolution specification will be reviewed in the light of the data from future production batches of the active substance and finished products. The shelf-life content limits for both finished products will also be reviewed in the light of further stability results.

*Preclinical pharmacology and toxicology* - Toxicological evaluation is particularly difficult to interpret because of differences between humans and animals. Available data indicate that sodium phenylbutyrate acts as a pro-drug, and the mechanism of action of the active metabolite, phenylacetate, is dependent on the biochemical mechanisms used to metabolise and excrete nitrogen.


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Par Pharmaceutical, Inc. Ex. 1019
Par v. Horizon, IPR of Patent No. 9,561,197
Page 11 of 12

Since these differ significantly between mammalian species, a suitable animal model is difficult to achieve.

In a review of the available data, no overt toxicity was noted. 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. Carcinogenicity and fertility studies have not been conducted. The available data indicate that PB is foetotoxic, affecting mainly the brain. Appropriate information has been included in the SPC and pregnancy is contra-indicated.

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.

*Efficacy* - Clinical data from the US IND program, supported by data from the published literature, have been used to demonstrate that sodium phenylbutyrate is a safe and effective treatment for the chronic treatment of UCD. No controlled trials have been done to test the effect of alternative medication. A study against placebo is not feasible for ethical reasons. However, the data presented suggest a treatment effect of PB but its merits relative to other pharmacological intervention are undecided.

*Safety* - Long-term safety exposure data of PB in the treatment of UCD are sparse, but in view of the rarity of the diseases, the often-profound mental retardation of the patients and the difficulty of separating possible side effects of treatments from those of the underlying diseases, the safety profile was accepted as being sufficient to allow authorisation. Monitoring of laboratory parameters, plasma ammonium and glutamine levels are recommended in the SPC.

**Benefit/risk assessment**

Taking into account the fact that UCDs is a rare disease, with limited treatment options, and potentially devastating consequences, the CPMP considered that, despite the limited data available with respect to pre-clinical and clinical sections of the dossier, PB offers an acceptable adjunctive therapy in the chronic management of the UCDs.

Overall, progressive improvement in the prevention of hyperammonaemic episodes has been achieved in the successive therapeutic protocols that have resulted in the use of PB. At present, the overall survival rate is approximately 80% for a disease, which in its neonatal presentation was almost always fatal within the first year of life. Clinical results indicate that early diagnosis and immediate initiation of therapy are important in minimising developmental disabilities. The experience to date is suggestive that stabilisation of cognitive performance can be obtained by preventing episodes of hyperammonaemic encephalopathy.

For optimal results, PB should be combined as adjunctive therapy with dietary management and amino acid supplementation. Nutritional management is essential in these patients and their diet needs to be custom-designed by their physician.

Regarding the use of PB during pregnancy and lactation, concerns have been raised in view of the results of animal toxicity studies. PB is contra-indicated during pregnancy and breast-feeding because exposure studies in rat pups have shown that PA produces CNS lesions.

In view of its high sodium content, PB should be used with caution in patients with a risk of developing oedema. Similarly patients with impaired hepatic function are in a higher risk of toxicity, since the neurotoxic product PA may accumulate.

In conclusion, based on the available data on quality, safety and efficacy, and despite the deficiencies in the documentation provided and considering the favourable benefit/risk ratio for this medicinal product intended for a fatal and very rare disease, the CPMP recommended a Marketing Authorisation should be granted for this medicinal product under exceptional circumstances in accordance with Article 13 (2) of Council Regulation (EEC) No 2309/93, as amended, and Part 4 G of the annex to Council Directive 75/318/EEC.


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Par Pharmaceutical, Inc. Ex. 1019
Par v. Horizon, IPR of Patent No. 9,561,197
Page 12 of 12