EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 February 2013
EMA/212039/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pheburane

International non-proprietary name: **sodium phenylbutyrate**

Procedure No. EMEA/H/C/002500

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

List of abbreviations

ASSD argininosuccinate synthetase deficiency

AL arginosuccinase

ARG arginase

CPSD carbamyl phosphate synthetase deficiency

HA hyperammonaemic

NAGS N-acetylglutamate synthetase

OTCD ornithine transcarbamylase deficiency

PA phenylacetate

PB phenylbutyrate

PAG phenylacetylglutamine

UCD urea cycle disorder(s)

AR assessment report

ASMF active substance master file

CFU colony-forming unit

CRS chemical reference substance

CTD common technical document

EEA European economic area

GMP good manufacturing practice

HDPE high-density polyethylene

HPLC high performance liquid chromatography

IR infrared

Ph. Eur. European Pharmacopoeia

Ppm parts per million

R correlation coefficient

Rpm revolutions per minute

RH relative humidity

RSD relative standard deviation

SmPC summary of product characteristics

TAMC total aerobic microbial count

TYMC total combined yeasts and moulds count

UV ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lucane Pharma submitted on 1 March 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pheburane, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 March 2012.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: "Pheburane 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."

Pheburane was designated as an orphan medicinal product EU/3/12/949, EU/3/12/950, EU/3/12/951 on 09 February 2012 in the following indications: i) Treatment of citrullinaemia type 1, ii) Treatment of ornithine transcarbamylase deficiency and iii) Treatment of carbamoyl-phosphate synthase-1 deficiency.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Pheburane as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Ammonaps instead of non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team was:

Rapporteur: David Lyons

- The application was received by the EMA on 1 March 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 June 2012.
- During the meeting on 16-19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant 20 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 November 2012.
- During the CHMP meeting on 10 - 13 December 2012 the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 January 2013.
- During the meeting on 18-21 February 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pheburane on 21 February 2013.

2. Scientific discussion

2.1. Introduction

Pheburane is a medicinal product that contains sodium phenylbutyrate as active substance. It is intended for oral administration and is available in one pharmaceutical form and strength: granules containing 483 mg/g sodium phenylbutyrate.

Pheburane is a hybrid medicinal product, the reference medicinal product is Ammonaps. Ammonaps has been authorised in the EU since 8 December 1999 and is available in 500 mg tablets and 940mg/g granules.

The therapeutic indication of Pheburane is the same as of Ammonaps. The approved indication is: “Pheburane 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.”

Pheburane 483 mg/g granules is a hybrid medicinal product of Ammonaps 940mg/g granules. Pheburane is presented as a lower strength than Ammonaps 940mg/g granules. This is because Pheburane granules are coated to mask the unpleasant bitter taste of the active substance, and therefore contain less active substance per gram granules. This is explained in the quality section below. Palatability is considered important in view of the target population.

Pheburane was granted an orphan designation on the basis of better palatability; the coated granule formulation reduces/removes the bitter taste associated with the active substance and might have the consequence of improved patient compliance compared to the reference medicinal product Ammonaps. This was considered to be a potential significant benefit over Ammonaps. The COMP reviewed whether the improved palatability will result in improved patient compliance and whether the criteria for orphan designation are fulfilled at the marketing authorisation stage.

The safety and efficacy profile of sodium phenylbutyrate has been demonstrated in several clinical trials, details of which can be found in the EPAR for Ammonaps. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. The applicant submitted a bioequivalence study demonstrating bioequivalence between Pheburane 483 mg/g granules and the Ammonaps 940mg/g granules. Since this application is a hybrid application referring to the reference medicinal product Ammonaps, no new clinical studies regarding pharmacology and efficacy and safety have been conducted.

The main differences between Pheburane and Ammonaps are the dosage form (Pheburane is presented as granules only), pharmaceutical formulation (different excipients), strength (Pheburane is presented as a lower strength), administration device (Pheburane includes one calibrating measuring spoon, whereas Ammonaps granules contain three spoons of different sizes). Since the applicant hasn’t provided data to demonstrate whether administration by gastrostomy or nasogastric tube is possible and if so to indicate whether there are any special measures to be taken, the CHMP recommends the applicant to perform studies to demonstrate that administration by nasogastric tube is feasible, with the view to provide relevant information in the product information.

Pheburane is presented in one pack size. The pack contains one bottle with a dosing spoon. This pack size is consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

Pheburane is presented as white to off-white granules containing 483 mg/g sodium phenylbutyrate as active substance. The composition is described in section 6.1. of the SmPC. The medicinal product is available in HDPE bottles containing 174 g granules (which corresponds to 84 g of sodium phenylbutyrate). Each bottle is packed in an outer carton and is accompanied by a calibrated dosing spoon (graduation of 250 mg) which dispenses up to 3 g of sodium phenylbutyrate.

2.2.2. Active substance

Sodium phenylbutyrate is a white or yellowish-white, hygroscopic powder, freely soluble in water and in methanol, and practically insoluble in methylene chloride. The drug substance has an unpleasant taste. The chemical name is sodium 4-phenylbutanoate.

Sodium phenylbutyrate has a non-chiral molecular structure. Evidence has been provided that the polymorph form of the active substance is the same as in the reference medicinal product Ammonaps. The molecular structure of sodium phenylbutyrate was elucidated using ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, elemental analysis and mass spectroscopy.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure within the current Marketing Authorisation Application. There is a monograph of sodium phenylbutyrate in the European Pharmacopoeia, but no Ph.Eur. certificate of suitability been issued for the active substance.

Manufacture

Sodium phenylbutyrate is supplied by one active substance manufacturer, it is synthesised by a two-step process using well defined starting materials and reagents. Adequate specifications and control methods have been presented for the intermediate products, starting materials and reagents. Process validation was conducted on three production-scale batches. Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it considered satisfactory.

Specification

The active substance specification includes tests for appearance, solubility, identity (IR, test for sodium), pH (Ph.Eur.), assay (titration), impurities (HPLC, GC), residual solvents (GC), water content (KF) and heavy metals (Ph.Eur.). The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph n° 04/2008:2183. Additional specifications have been set for residual solvents to control the contents of solvents used in the final stage of synthesis (methanol and acetone) in accordance with the ICH guideline of residual solvents (ICH Q3C). This additional method has been adequately validated.

Batch analysis data have been provided on three commercial batches produced with the proposed synthetic route. The results are within the specifications and demonstrate that the active ingredient can be manufactured reproducibly.

Stability

Three production scale batches of the active substance, packed in a package equivalent to the intended commercial package, were put on long term (25°C/60% RH) stability studies for up to twelve months, and accelerated (40°C/75% RH) stability studies for up six months, according to the ICH conditions. The following parameters were tested: appearance identity, pH, water content, impurities and assay. The analytical methods and specifications for stability are the same as for release testing, except for the water content for which a higher limit was accepted at stability because the drug substance is hygroscopic. It was demonstrated that the water content has no impact on the purity of the active substance under the proposed shelf life limit. Results on stress conditions have been provided on at least one batch. The stress conditions investigated were: alkali (1M NaOH at 80°C for 24 hours), acid (1M HCl at 80 °C for 24 hours), oxidation (20% H2O2 for 24 hours), heat (dry heat at 100 °C for 12 hours) and light (exposure to a near-UV lamp for 24 hours). The stress study confirm that the HPLC method used is stability indicating and appropriate for the routine analysis and the long term stability studies of sodium phenylbutyrate.
In general, the stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable and the stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The objective of the pharmaceutical development was to develop a formulation that is bioequivalent to the existing product, Ammonaps 940 mg/g granules, and with the unpleasant taste of the active substance masked. The taste is considered an important finished product characteristic in view of the target population, which includes infants and children. The product also has to allow the dosage to be adjusted in accordance with the needs of the patient. It was decided that these objectives could best be met by a granule presentation in which neutral cores are coated with an inner layer containing the active substance and an outer layer which masks the taste. Several types of neutral cores were investigated and sucrose spheres were selected as they formed granules with satisfactory taste and stability which dissolved more rapidly than those made using microcrystalline cellulose. Also the size of the sugar spheres was carefully selected.

The development of the active substance coating solution aimed at finding a solution with good spraying characteristics. Then, the masking layer coating solution was developed. Two coating solutions for the outer masking layer were investigated, and the solution which gave better masking of the taste was selected for further development. The ratio of active substance to sugar spheres was subsequently optimised and the process parameters were also adjusted in order to maximise the efficiency of the spraying process.

The in-vitro dissolution of two batches of Pheburane granules was compared with that of a batch of Ammonaps granules. Whereas the dissolution of the uncoated Ammonaps granules was very rapid, the Pheburane batches dissolve more slowly at all pH values. The observed delay in the dissolution is linked to the fact that Pheburane granules are coated and likely explains why the Pheburane formulation is found to be more palatable to patients. Nevertheless the Pheburane dissolution profile is considered adequate and a bioequivalence study confirmed bioequivalence between Pheburane granules and Ammonaps granules, see clinical part below. The palatability of the final formulation was tested in healthy adults, the study demonstrated that the coated granules were found to be significantly better than the reference medicinal product with respect to acceptability, bitterness and saltiness immediately after dosing. For more information see the clinical part below.

The formulation differences between Pheburane and the reference medicinal product Ammonaps are considered significant. Whereas Ammonaps is presented as granules containing 940 mg sodium phenylbutyrate per gram granules, Pheburane granules contain 483 mg sodium phenylbutyrate per gram granules. Pheburane is presented as a lower strength than Ammonaps 940mg/g granules due to the coating technology that is used to mask the unpleasant bitter taste of the active substance. The excipients used in Pheburane are different from the excipients used in the reference medicinal product Ammonaps. All excipients used in Pheburane granules comply with the current specifications of the European Pharmacopoeia and are commonly used excipients for this pharmaceutical form. The excipients are: sugar spheres (core of granules), hypromellose (film-coating agent), ethylcellulose (film-coating agent for taste masking), macrogol (plasticiser) and povidone (binder). The difference in excipients is not considered to affect the clinical performance of the medicinal product and all excipients are considered safe. Pheburane contains sucrose, which triggers a special warning statement in section 2 of the SmPC. This excipient is not present in the reference medicinal product Ammonaps.

Adventitious agents

No excipients derived from animal or human origin have been used

Manufacture of the product

Pheburane granules are manufactured by a standard manufacturing process, the main manufacturing steps are: i) preparation of the two coating solutions, ii) coating of the sugar pellets with the active substance solution, iii) coating of the active beads with the ethyl cellulose solution to mask the taste of the active substance and iv) blending and filling. The process has been optimised during the course of development. The manufacturing process has been validated and it was demonstrated to be capable of reproducibly producing a finished product of the intended quality. Adequate in-process controls are in place for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for appearance, identification (HPLC, IR), dissolution (Ph.Eur.), water content (KF), tapped density, residual ethanol (GC), uniformity of mass of delivered dose (Ph.Eur.), assay and related substances (HPLC) and microbiological purity (Ph.Eur.). The non-compendial analytical methods have adequately been validated. Batch analysis results on three industrial batches confirm consistency and uniformity of manufacture and indicate that the process is capable of consistently producing a finished product that meets the predefined specifications and that the manufacturing process is under control.

Stability of the product

Stability data have been provided for at least three production scale sub-batches The stability batches have been manufactured according to the manufacturing process proposed for marketing and the samples were packed in the container proposed for the market (HDPE bottles with a desiccant in the cap). Up to twelve months stability data have been provided under long term conditions (25ºC/60%RH) and intermediate conditions (30ºC/65%RH) for one batch, and up to nine months for two additional batches, according to ICH conditions. Six months stability data under accelerated conditions (40ºC/75%RH) was provided for four batches. Samples were tested for appearance, identification, assay, related substances, dissolution, uniformity of delivered dose, water content and microbiological purity. The analytical procedures used were stability indicating.

The stability results provided reveal no trends in relation to appearance, loss on drying, assay, content of related substances, uniformity of delivered dose, or microbiological purity.

In view of the hygroscopic nature of the drug substance, in-use stability studies have been conducted on two batches over a period of 45 days. No significant changes were noted for any of the parameters monitored: appearance, assay, related substances, water content, delivery test, microbial purity and dissolution.

The stability studies also include a test to confirm that the integrity of the ethylcellulose layer (responsible for taste masking) remains unaffected during the proposed shelf life of the granules. Results of the coating integrity test have been provided for four batches stored under long-term conditions for up to 12 months. In view that no results have been presented for samples stored under either accelerated or intermediate conditions, the CHMP considers the appropriate storage condition to be 'Do not store above 25 ºC'.

The proposed container closure system (a 250 ml HDPE bottle with an integral desiccant in a child-resistant cap) is adequately described and is considered appropriate for granules which contain a hygroscopic drug substance. Based on available stability data, the proposed shelf-life and in use shelf life as stated in section 6.3 of the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Pheburane granules are coated to mask the taste of the active substance and as a result, Pheburane (483mg/g granules) is presented in a lower strength than the reference medicinal product Ammonaps (940mg/g granules). Pheburane contains different excipients than Ammonaps, in particular the presence of sucrose is noted and this has been reflected in the SmPC.

At the time of the CHMP opinion, there were no unresolved quality issues.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature and the SmPC of the reference product Ammonaps. The overview justifies why there is no need to generate additional non-clinical

pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

The non-clinical pharmacology overview summarises the primary pharmacodynamics, and general (secondary) pharmacodynamics. No own conducted studies were submitted in this application; the overview refers to the published literature on sodium phenylbutyrate (NaPB) and the reference product Ammonaps. The mechanism of action of NaPB is through provision of an alternate pathway to excrete waste nitrogen, by the phenylacetylglutamine conjugate. NaPB is rapidly metabolised by beta-oxidation to phenylacetate (PA), which is conjugated with phenylacetyl-CoA, which in turn combines with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is then excreted by the kidneys, thus providing an alternate mechanism of nitrogen excretion to the urea cycle. The mechanism is well characterised and supports the indication for management of urea cycle disorder(s) (UCDs). The lack of newly generated pharmacodynamic data is acceptable given the extensive clinical experience with the reference product, Ammonaps.

According to the literature data the therapeutic potential of NaPB has also been studied in a number of disease models. As recently reviewed by Iannitti and Palmieri, studies indicate a potential for NaPB in treatment of a range of conditions including cancer, neurodegenerative disorders and ischaemic injury. The submitted data does not address potential adverse effects due to secondary pharmacodynamic activity and it does not discuss safety pharmacology or pharmacodynamic drug interactions. These are not considered as matters of concern due to the available body of evidence of clinical efficacy and safety of the reference product.

2.3.3. Pharmacokinetics

Submitted pharmacokinetic absorption data are limited, but is compensated by the available clinical data. The clinical PK studies reported in literature suggest that NaPB is readily absorbed under fasting conditions with maximal plasma concentration after 2 hours. In addition a 1:1 blood ratio of NaPB in brain, eyes, heart, kidney and liver is reported. The submitted data suggests decreased brain distribution in mature animals. NaPB is quickly metabolised, as PA is measurable in plasma within one hour. A recent study has shown that new metabolites of PB, which do not carry nitrogen, may be formed following interference of carbohydrate and lipids. Among the newly identified metabolites, several were not detected in humans or were found at a very low level. The extrapolations of the findings to humans are limited therefore this finding doesn't raise any concerns. Excretion is mostly predominantly as phenylactylglutamine, with 80-100% excreted in urine by 24 hours. This process forms the basis of its mechanism of action in treating UCDs and is well characterised.

2.3.4. Toxicology

The non-clinical toxicology overview includes literature reports from single- and repeated-dose studies, genotoxicity studies, and a teratogenicity study.

The single-dose study was undertaken to investigate genotoxicity and was inadequately designed to determine an LD_{50} for NaPB. Although lethality was seen at the lowest dose (1586 mg/kg), this is a supra-therapeutic dose and based on extensive clinical use, acute toxicity of PA is not considered to be a concern. In a non-GLP 28 day repeated-dose study, subcutaneous administration of 550 mg/kg/day

PA did not produce any clear adverse effects or histological abnormalities in vital organs. A study of juvenile animals suggests PA causes impairment of brain development in the immature rodent. Limited insight can be gained from the repeated-dose studies as oral administration was not studied, no toxicokinetic exposure data are reported, and no long term toxicity studies are reported. However, these deficiencies are acceptable considering the clinical experience with the reference product for this hybrid application.

Bacterial reverse mutation assays and an *in vivo* micronucleus test did not show any evidence of genotoxic potential. This is supported by a recent literature report where NAPB was found to promote DNA repair and survival in normal human fibroblasts. No carcinogenicity studies were undertaken. This is considered acceptable since NaPB is a histone deacetylase inhibitor and has shown anticancer activity, and is unlikely to have significant carcinogenic potential.

The limited reproductive toxicity studies suggest PA may affect fertility and post natal development. The findings of these studies are adequately reflected in the SmPC section 4.6.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pheburane manufactured by LUCANE PHARMA is considered unlikely to result in any significant increase in the combined sales volumes for all sodium 4-phenylbutyrate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased. The CHMP concluded that Pheburane is not expected to pose an additional risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical part of the MAA dossier is based on literature review data and reference to the non-clinical safety and efficacy of the reference product. No own conducted studies have been submitted. The pharmacology and toxicology data are limited, but considering the evidence of clinical efficacy and safety of the reference product, this is acceptable.

2.3.7. Conclusion on the non-clinical aspects

A summary of the literature overview on non-clinical data for sodium phenylbutyrate was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for granules containing sodium 4-phenylbutyrate. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for this MA application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 in its current version is of particular relevance.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Not applicable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study:

Study 109551: An open label two period, crossover study to determine the bioequivalence of two formulations of a single dose of sodium phenylbutyrate granules and to compare the taste of these two formulations in healthy volunteers.

2.4.2. Pharmacokinetics

Methods

Study design

Study 109551 was an open label, two period, single dose, crossover study in healthy volunteers to determine the bioequivalence of two formulations of sodium phenylbutyrate granules 5 grams; and to compare the taste of the two formulations. Treatments were administered in fasting state (at least 10 hours) as Ammonaps uncoated granules 5.32 grams and Pheburane coated granules 10.21 grams.

The study was conducted at the Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, University of the Free State, Bloemfontein, South Africa.

The study consisted in two treatment periods separated by a wash-out period of seven calendar days.

A full blood count, clinical chemistry, HIV and Hepatitis B & C tests, as well as serum pregnancy test were performed at screening. A full blood count and clinical chemistry investigations were performed at the post study evaluation.

On admission to the clinic subjects selected their own beds, which determined their randomisation number for the study. Subjects' numbers were allocated in this way. Subjects received the medication labelled with their number, according to the randomisation schedule.

Venous blood samples for the determination of phenylbutyrate concentrations were taken at the following time points:

Table 1. Pharmacokinetic Blood Sampling Schedule

Day	*Sampling time (hours)*	*Clock time* (hh:mm)*	*Blood (9 mL)*
1	*Pre-dose*	*07:15*	*B 0*
	0.25	*07:45*	*B 1*
	0.5	*08:00*	*B 2*
	0.75	*08:15*	*B 3*

	1	*08:30*	*B 4*
	1.25	*08:45*	*B 5*
	1.5	*09:00*	*B 6*
	2	*09:30*	*B 7*
	2.5	*10:00*	*B 8*
	3	*10:30*	*B 9*
	3.5	*11:00*	*B 10*
	4	*11:30*	*B 11*
	6	*13:30*	*B 12*
	8	*15:30*	*B 13*
	12	*19:30*	*B 14*
	16	*23:30*	*B 15*

** Actual clock times varied between subjects, in relation to actual dosing times.*

To ensure compliance, the IMP was administered by the principal investigator and designee. A mouth check was performed to ensure that the subjects had swallowed the medication.

Test and reference products

After an overnight fast of at least 10 hours, subjects received an oral dose of 5 g sodium phenylbutyrate of either the test or reference product according to the randomisation schedule. Subjects received each product once. Subjects received 5.32 g uncoated granules of the reference product or 10.21 g of the coated granules of the test product with 240 mL water.

Reference Product (A)

Generic name: Sodium phenylbutyrate

Trade name: Ammonaps

Marketing Authorisation Holder: Swedish Orphan International AB Country of origin: Sweden

Dosage form: Uncoated granules: 5.32 grams containing 5 g of sodium phenylbutyrate

Dose: 5 g of sodium phenylbutyrate under fasting conditions

Mode/route of administration: Oral

Batch number: 3321.021A

Expiry date/Retest date: February 2012

Assayed product content: Not available

Test Product(B)

Generic name: Sodium phenylbutyrate

Trade name: Pheburane

Manufacturer: Lucane Pharma

Country of origin: France

Dosage form: Coated granules: 10.21 grams containing 5 g of sodium phenylbutyrate

Dose: 5 g of sodium phenylbutyrate under fasting conditions

Route of administration: Oral

Batch number: 4602502V2

Expiry date/Retest date: November 2011

Assayed product content: 100%

Population(s) studied

Sample size

A first cohort of fourteen healthy, Caucasian, non-smoking male and female subjects was entered into the first stage of the study and assigned to treatment sequence according to the randomisation schedule.

Based on the results of the first cohort, the option of adding additional subjects was not exercised as bioequivalence was demonstrated in the analysis of data obtained from thirteen subjects of the first cohort.

Main inclusion criteria

Subjects who met the following criteria were considered eligible to participate in the study:

Healthy male and female subjects 18 to < 56 years of age.

Body Mass Index between 18.5 and 30 kg/m2.

Body mass not less than 50 kg.

Findings within the range of clinical acceptability in medical history and physical examination, and laboratory results within the laboratory reference ranges for the relevant laboratory tests.

Normal 12-lead electrocardiogram (ECG) and vital signs, or abnormalities.

Females should be sterile or using a reliable method of contraception.

Main exclusion criteria

Any significant medical condition, use of any medication in the previous two weeks, substance abuse.

Analytical methods

Quantitative analyses of phenylbutyrate (assayed as phenylbutyric acid) in the plasma samples and in suitable quality controls were performed by the PAREXEL Bioanalytical Services Division using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Pharmacokinetic variables

The rate and extent of absorption of phenylbutyrate from the reference and test products as on the following variables were compared for each subject and product using the actual sampling intervals (relative to medication administration):

Primary Variables:

- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration versus time data pairs [AUC_t], where t is the time of the last quantifiable concentration.

Secondary Variables:

- Area under the plasma concentration versus time data pairs, with extrapolation to infinity [AUC_{inf}]
- Residual area [(AUC_{inf}] – AUC_t) / AUC_{inf}].
- Time to maximum observed plasma concentration (T_{max}).
- Terminal elimination rate constant λz).
- Apparent terminal half-life ($t_{½}$.z).
- Number of points used to estimate the terminal rate constant (λz).

Safety variables

Safety variables were abnormalities in laboratory variables and/or adverse events recorded using MedDRA terminology.

Palatability

Taste variables (acceptability, bitterness, saltiness and sweetness) were evaluated using visual analogue scales (VAS) immediately after administration of the product, 30 minutes after and 2 hours after. On a 100 mm scale 0 indicated totally acceptable/not bitter – salty - sweet and 100 indicated totally unacceptable/very bitter – salty – sweet. Descriptive statistics were tabulated per product. The reference and test products were compared using an analysis of variance with sequence, product, period and product*period effects on untransformed data. Point estimates and 95% confidence intervals for the "test - reference" mean differences of these variables at each time point were calculated and tabulated.

Statistical methods

The decision rule of bioequivalence (all subjects) was based on characteristics C_{max} and $AUC_{t,}$ AUCinf and $t_{½.z}$ on log-transformed data of phenylbutyrate, using ANOVA with sequence, subject, treatment and period effects. The respective 94.12% (adjustment of alpha-level due to multiple testing) confidence intervals were calculated and compared to the regulatory interval [0.8-1.25]. For T_{max} a non-parametric Wilcoxon signed rank test was used and the calculated p-value reported.

Results

Subject disposal

Fourteen subjects (8 males and 6 females) were considered eligible and entered into the study. One female subject (Subject 7) was withdrawn from the study during Treatment period I (Ammonaps) due to an adverse event (vomiting). Thirteen subjects completed both treatment periods. Subjects' mean age was 27.8 years (s.d. 11.6) and mean body mass index was 23.9 kg/m2 (s.d. 3.4).

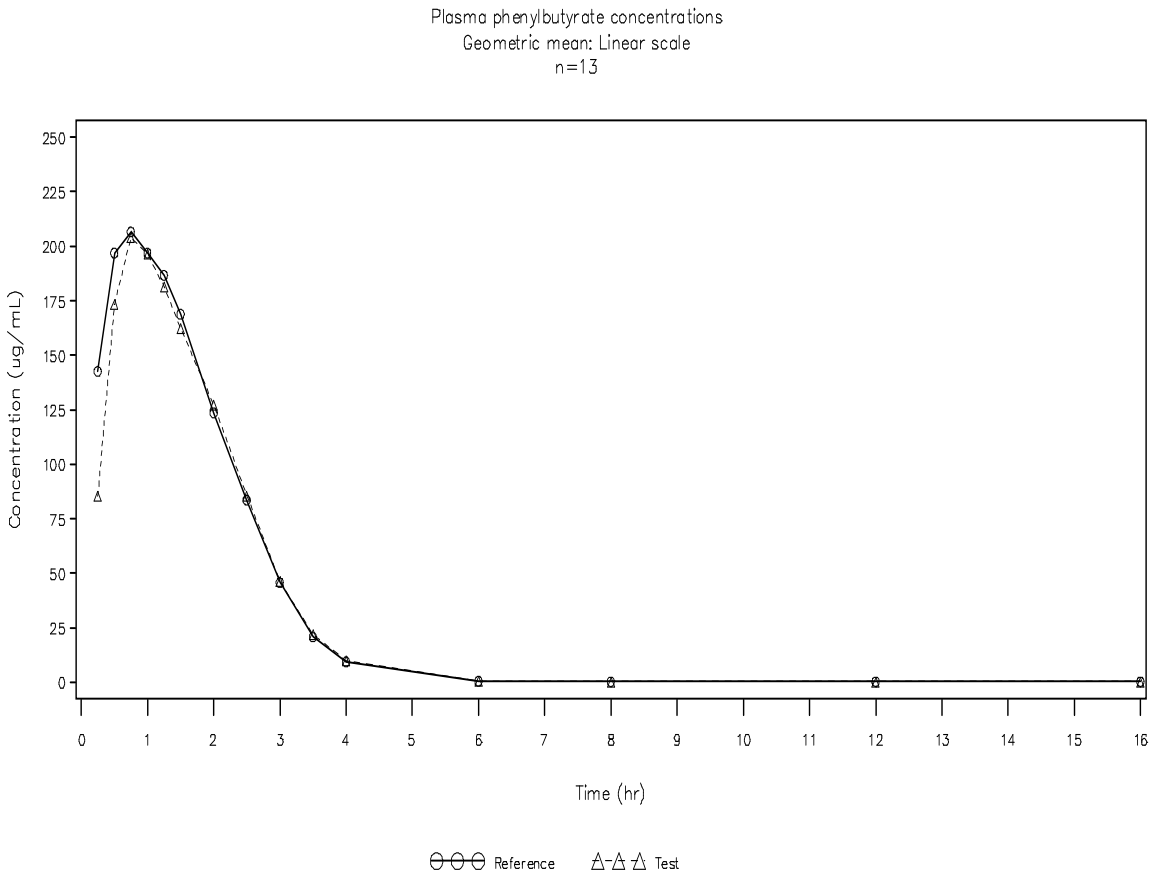
Pharmacokinetics

Following single-dose administration of the test and reference products, maximum plasma concentrations of 1140 and 1200 µmol/L of phenylbutyrate (Table 2) were reached at a median time of approximately 0.75 hours and 0.5 hours post-dose, respectively.

Table 2. Pharmacokinetics of sodium phenylbutyrate granules (2 different products) in healthy volunteers

	Ammonaps (Reference product)		**Pheburane** (Test product)	
Variable	**Geometric mean *(SD)***	**Range**	**Geometric mean *(SD)***	**Range**
C_{max} *(µg/mL)*	225.150 *(49.282)*	146.000 – 326.000	212.453 *(46.606)*	137.000 – 318.000
AUC_t *(h·µg/mL)*	464.880 *(190.356)*	265.498 - 867.064	445.427 *(172.434)*	234.898 - 809.492
AUC_{inf} *(h·µg/mL)*	466.920 *(190.356)*	267.214 - 867.744	448.220 *(171.880)*	235.605 - 810.507
t_{max} *(h)*	0.500	0.250 – 1.250	0.750	0.500 – 1.250

The point estimates of the "test/reference" mean ratios [94.12%CI] of Cmax, AUC0-t and AUC0-∞ for phenylbutyrate were 94.32% [86.95;102.31], 95.61% [90.34;101.19] and 95.80% [90.8;101.08], respectively. The analysis of variance on Cmax, AUCt and AUCinf after logarithmic transformations did not show any significant differences between the two products, neither any period or sequence effect. Confidence intervals of geometric means for Cmax and AUCt were within the required range for not rejecting bioequivalence. The Tmax difference was not significant (Wilcoxon singed rank test, p-value = 0.5205). The plasma/time concentration curves for reference and test product are shown below.



Palatability

The outcome of the taste testing immediately after dosing is shown in Table 3. The differences at 0.5 hours post-dose were much less marked and at 2 hours post-dose were negligible. The confidence intervals indicate a statistically significant difference between the products with regard to acceptability, bitterness and saltiness. The assessment of the acceptability immediately after dosing was worse during the Treatment period 1 than Treatment period 2, irrespectively of the product administered.

Table 3. LS mean taste scores immediately after dosing

	Ammonaps	Pheburane	Difference	95% CI
Acceptability	55.14	20.89	-34.25	-56.79, -11.71
Bitter	59.62	11.69	-47.93	-62.20, -33.65
Salty	43.01	12.13	-30.88	-49.26,-12.50
Sweet	11.01	11.56	0.54	-10.04,11.13

Safety data

Safety and tolerability

No serious adverse events were reported during the study, and none of the adverse events was of severe intensity. No adverse events related to laboratory variables were reported.

Twenty-eight treatment emergent adverse events were reported by 12 of the 14 subjects. Of these, 6 were assessed as not related or unlikely related to treatment, and 22 adverse events to be probably related or related.

Adverse events

Headache (15 incidences reported by 8 subjects) and ageusia (5 incidences reported by 5 subjects) were the predominant adverse events reported. One subject vomited and was subsequently withdrawn from the study. The intensity of the adverse events was rated as "mild" or "moderate". The summary of the drug-related adverse events is presented in the table below:

Table 4. Summary of Drug-related Adverse Events

Adverse event	Ammonaps	Pheburane
Headache	8	7
Ageusia	5	-
Vomiting	1	-
Body weakness	1	-

Conclusions

Based on the presented bioequivalence study Pheburane is considered bioequivalent with Ammonaps.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

Bioequivalence

The own generated clinical data consists of one bioequivalence study that is considered pivotal for the MA application. Study 109551 aimed to establish the bioequivalence of two formulations of sodium phenylbutyrate, Pheburane, the test treatment, and Ammonaps, the reference product. Due to the limited previous experience and/or published data on the PK of phenylbutyrate the study was planned to be run in two stages, the second stage to be run in case the results obtained in the first stage would have not allowed a firm conclusion on the bioequivalence. That is, a power calculation was not made; an initial cohort of subjects was studied with the provision that should bioequivalence not be demonstrated a further cohort could be added based on the experience from the first cohort. Given the circumstances at the time the study was planned the CHMP considers this as an appropriate approach. In fact, the first cohort of fourteen subjects was sufficient to establish bioequivalence.

With and estimated elimination half-life for phenylbutyrate of 0.8 hours (Ammonaps SmPC), the 7 day-wash-out period is regarded as adequate.

The inclusion/exclusion criteria are found acceptable and the population included is representative for the targeted patient population. The pharmacokinetic variables and the sampling schedule were found adequate.

No major protocol deviations, that could have affected the trial outcome, are noted.

Administration methods

One of the formulation differences between Pheburane and Ammonaps granules is the presence of a coating meant to mask the bitter taste of the active substance. The only clinical experience with the new formulation has been obtained in fourteen adults included in the bioequivalence study. The study treatments were administered orally with water. This is adequately reflected in section 4.2 of the SmPC.

As for the originator it is envisaged that the medicine can be sprinkled on to a spoonful of semi-solid foods and administered as such. This is considered acceptable by the CHMP since both Pheburane and the reference product have the same formulation: granules.

No data has been submitted on whether Pheburane can be administered through nasogastric tubes. This information is properly reflected in the SmPC section 4.2. The CHMP recommends the applicant to perform studies to demonstrate that administration by nasogastric tube is feasible. .

Palatability

The applicant has evaluated palatability using a simple visual analogue scale (VAS) and Pheburane scores markedly better in the criteria of general acceptability, bitterness and saltiness. For sweetness there is no difference and none would be expected (the outer coating is cellulose and should be nearly tasteless) the lack of a difference between the formulations for sweetness can be taken as a control indicating that the VAS does discriminate where there is a difference. Moreover, the difference in the number of subjects reporting ageusia in the test (0) and reference (5) treatment arms confirms the positive findings from the VAS scoring. There are no data indicating that the improved palatability will lead to improved compliance but the presumption is not unreasonable.

Safety

The only additional clinical data generated by the applicant is based on a single exposure to a five gram dose of Pheburane in fourteen healthy volunteers. No firm conclusion can be drawn on such small body of data.

The two principal qualitative formulation differences between Pheburane and Ammonaps are the presence of a sucrose core and additional excipients; hypromellose, ethycellulose, macrogol, and povidone, in Pheburane which are absent from Ammonaps.

Sucrose is present as 403 mg/483 mg of active substance (83%) which based on treatment at the top of the recommended dosage range translates to an additional sucrose load of approximately 10 g/day for those under 20 kg and 20 g/day for an ‘average’ 70 kg man, and adds 40 Kcal and 80 Kcal, respectively, to daily calorie intake which is not deemed clinically important. There is an appropriate sucrose warning in the proposed SmPC.

The additional excipients in the Pheburane formulation are well known and are generally considered inert from a clinical point of view and are not expected to pose any additional risk.

Based on the submitted data no new safety issues have been identified.

2.4.6. Conclusions on clinical aspects

A summary of the literature overview on clinical data of sodium phenylbutyrate use in urea cycle disorders and a bioequivalence study to the reference product Ammonaps was submitted by the applicant and accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Based on the presented bioequivalence study Pheburane is considered bioequivalent with Ammonaps.

Based on the submitted data no new safety issues have been identified beyond the ones highlighted in Ammonaps' SmPC.

The CHMP recommends the applicant to perform studies to demonstrate that administration by nasogastric tube is feasible, with the view to provide relevant information in the product information.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP did not require the applicant to submit a risk management plan because the reference medicinal product Ammonaps does not have a risk management plan.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

Periodic safety update reports should be submitted for Pheburane in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. The next data lock point is 31/12/2015.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a hybrid version of Ammonaps 940 mg/g granules. Pheburane is intended for the treatment of chronic management of urea cycle disorders.

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."

No nonclinical studies have been provided for this application and the submitted non-clinical overview based on literature data was considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis for this MA application with a cross-over design conducted under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pheburane met the protocol-defined criteria for bioequivalence when compared with Ammonaps. The point estimates and their 90% confidence intervals for the parameters AUC0-t,, $AUC0_{inf}$, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A positive benefit/risk ratio can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pheburane in the following indication:

"Pheburane 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."

is favourable and therefore recommends the granting of the marketing authorisation, subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic safety update reports**

The marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

Not applicable.