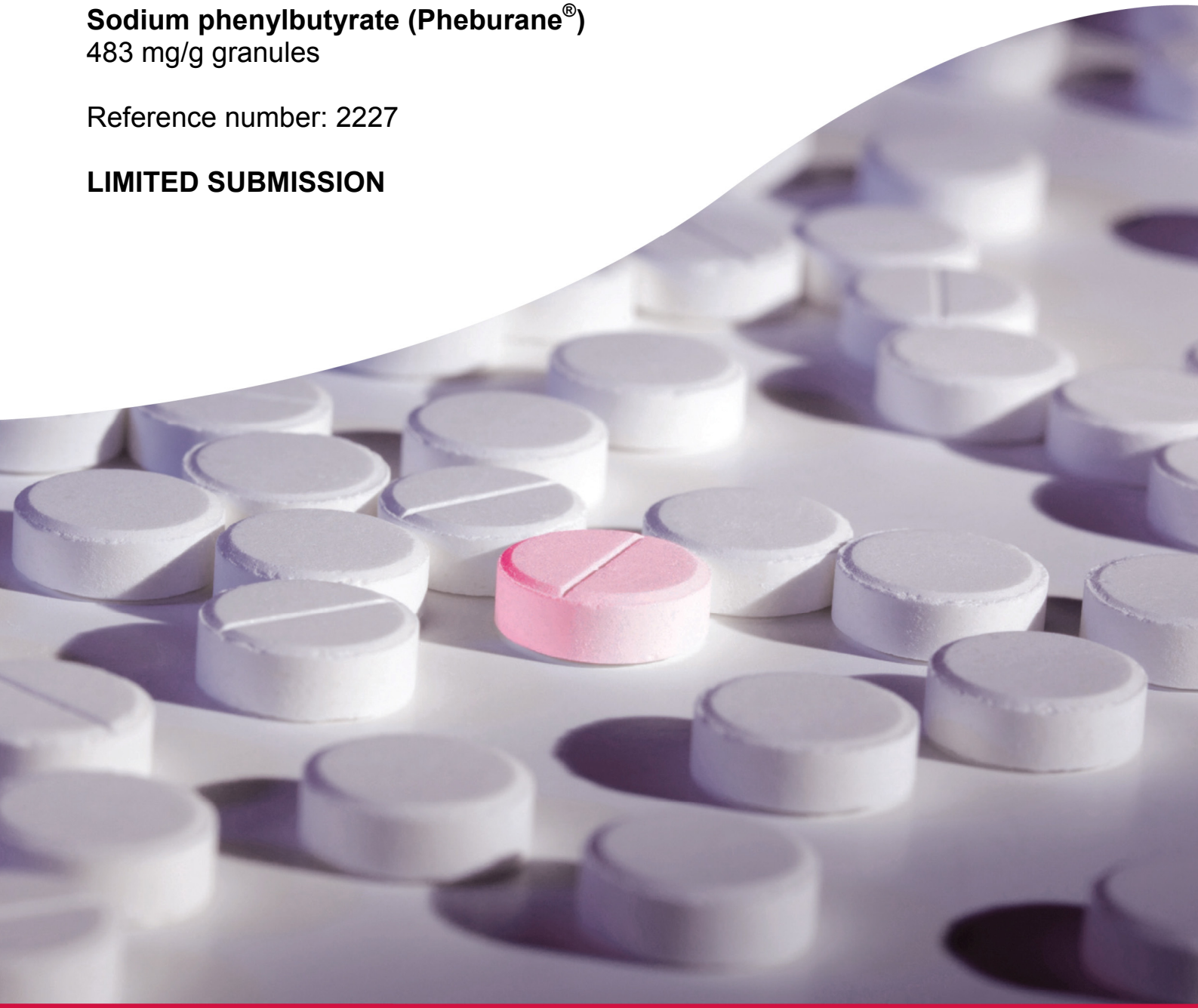
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Sodium phenylbutyrate (Pheburane®)
483 mg/g granules

Reference number: 2227

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Sodium phenylbutyrate (Pheburane®) 483 mg/g granules

This assessment report is based on evidence from a limited submission by Lucane Pharma on 17 July 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Sodium phenylbutyrate (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[2].
Marketing authorisation date	31 July 2013[2]
Comparators	The comparator included in the company submission was sodium phenylbutyrate (Ammonaps®) 940 mg/g granules.
Limited submission details	Sodium phenylbutyrate (Pheburane®) for the above indication met the following criteria for eligibility for a limited submission: • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator(s).

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included a bioequivalence study, which investigated the use of sodium phenylbutyrate 483 mg/g granules (Pheburane®) versus sodium phenylbutyrate 940 mg/g granules (Ammonaps®) under fasting conditions in healthy adult volunteers (study LUC1001). The company propose that this granule formulation will, however, be almost exclusively prescribed in children[1].

2.1 Evidence of bioequivalence

LUC1001 was a randomised, open-label, two-treatment, two-period, two-sequence, two-way crossover study. The study enrolled 14 healthy adult volunteers (8 males and 6 females); each volunteer received a single dose of either Pheburane® 10.21 g or Ammonaps® 5.32 g (each dose contained 5 g of phenylbutyrate), separated by a one-week washout period and a follow-up visit 24 hours after the last dose of treatment[1,3].

Following administration of Pheburane®, maximum plasma concentrations (C_{max}) ranged between 137 and 318 micrograms/ml of phenylbutyrate over a time period of 0.5–1.25 hours. In volunteers receiving Ammonaps®, C_{max} ranged between 146 and 326 micrograms/ml of phenylbutyrate.

The point estimates (94.12% adjusted confidence interval [CI] range) of the Pheburane®/Ammonaps® mean ratios of C_{max} and AUC_{0-t} were 94.32% (86.95% to 102.31%) and 95.61% (90.34% to 101.19%), respectively. These CIs were within the bioequivalence acceptance range of 80–125%. Therefore, bioequivalence can be demonstrated between Pheburane® and Ammonaps® on rate and extent of absorption of phenylbutyrate[1,3]. Refer to Table 1.

Table 1. Pharmacokinetics of Pheburane® and Ammonaps®

	Pheburane®		Ammonaps®		Statistical analysis (94.12% CI)
Variables	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	
C_{max} (micrograms/ml)	212.453 (46.606)	137.000–318.000	225.150 (49.282)	146.000–326.000	NS (86.95–102.31)
AUC_{0-t} (hours x micrograms/ml)	445.427 (172.434)	234.898–809.492	464.880 (190.356)	265.498–867.064	NS (90.34–101.19)
AUC_{inf} (hours x micrograms/ml)	448.220 (171.880)	235.605–810.507	466.920 (190.356)	267.214–867.744	NS (90.80–101.08)
t_{max} (hours)	0.750±0.228	0.500–1.250	0.500±0.250	0.250–1.250	NS (p = 0.5205)
CI: confidence interval; NS: not significant; SD: standard deviation.					

Both Pheburane® and Ammonaps® were found to be well tolerated in the healthy adult volunteers. One patient in the Ammonaps® arm withdrew from the study due to an adverse event (AE) of vomiting. In both treatment arms, the most commonly reported AE was mild to moderate headache (15 incidences were reported in eight of the volunteers)[1,3].

2.2 Points to note

- In their submission, the company state that continuous compliance with sodium phenylbutyrate is often difficult due to its unpalatable taste[1]. Pheburane® is a new formulation of sodium phenylbutyrate; the granules are coated in order to mask the taste. During the palatability test in the bioequivalence study, Pheburane® was found to be statistically significantly better than Ammonaps® in terms of acceptability, bitterness and saltiness[1,3].
- The bioequivalence study, LUC1001, was conducted in healthy adult volunteers[1,3]; however, this is not representative of the Welsh patient population in which Pheburane® is anticipated to be used[1].
- Bioequivalence was demonstrated in study LUC1001; however, the company highlight that this study was conducted in an ad hoc manner and therefore, a power calculation was not made[1].
- The bioequivalence study, LUC1001, was conducted in healthy adult volunteers under fasting conditions; however, the Summary of Product Characteristics (SPC) states that Pheburane® should be administered with each meal.
- Pheburane® and Ammonaps® contain the equivalent of 2.5 g of sodium per 20 g of sodium phenylbutyrate, which is the maximum recommended daily dose. Therefore, the SPCs advise that sodium phenylbutyrate should be used with caution in patients with congestive heart failure or severe renal insufficiency, and in clinical conditions where there is sodium retention with oedema[2,4].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact evidence presented by the company included a comparison of the annual costs associated with the use of Pheburane® and Ammonaps® for the treatment of urea cycle disorders.

Using a survey carried out in 2009, the company reported 165 patients being managed for urea cycle disorders in England and Scotland[1,5]. Based on population statistics, the company estimate that approximately nine patients in Wales would receive sodium phenylbutyrate for the treatment of urea cycle disorders; they estimate that approximately five patients would receive the granule formulation[1].

According to the company submission, the cost of Pheburane® is anticipated to be £3.94 per gram of sodium phenylbutyrate; this is the same price as Ammonaps® tablets[1]. The cost of Ammonaps® granules is £3.23 per gram of sodium phenylbutyrate[6]. Therefore, the annual cost of treating five patients with Ammonaps® granules, at an average dose (determined by the company) of 4.7 g per day, would be £27,750. If all five patients were to receive Pheburane® then this would lead to an increased expenditure of £6,045[1]. The annual costs calculated in Table 2 are derived from dose ranges. Based on these figures, AWTTC estimates that if all five patients were to receive Pheburane® then this would lead to an increased expenditure of £5,830–£7,775.

3.2 AWTTC critique of the budget impact analysis

- In their submission, the company have utilised patient numbers for England and Scotland from a survey carried out in 2009[5]; Welsh figures have been estimated using population statistics, and may therefore be subject to uncertainty. In 2012, an updated study was published in which 175 patients were reported to be managed for urea cycle disorders in England and Scotland[7].
- The company estimate that approximately five out of a total of nine patients in Wales would be eligible for treatment with Pheburane®[1]; however, the company have not provided evidence to support this number.
- The company anticipate that all patients already receiving the granule formulation of sodium phenylbutyrate would switch to Pheburane®[1]. However, this could be an overestimation in cost as all patients may not switch treatments.
- Pheburane® can be stored below 25°C whereas Ammonaps® requires refrigeration (although the patient may store the finished product for a single period of three months at a temperature not above 25°C, after which the product must be discarded)[4]. The applicant company do not appear to have taken these costs into consideration in their budget impact analysis.

3.3 Comparative unit costs

Table 2. Example comparative annual acquisition costs

Medicine	Example regimen*	Cost per patient per year†
Pheburane®	450–600 mg/kg/day	£6,471–£8,629
Ammonaps®	450–600 mg/kg/day	£5,305–£7,074

* Dosing is based on a child weighing 10 kg
† Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of December 2013[6].
This table does not imply therapeutic equivalence of medicines or the stated doses.
Refer to the SPCs for full dosing details[2,4].

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, sodium phenylbutyrate (Pheburane®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that sodium phenylbutyrate (Pheburane®) may be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 24 July 2013
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Lucane Pharma. Form C: Limited appraisal submission. Sodium phenylbutyrate (Pheburane®). 2013.
2 Lucane Pharma. Pheburane®. Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002500/WC500147373.pdf. Accessed Aug 2013.
3 Guffon N, Kibleur Y, Copalu W et al. Developing a new formulation of sodium phenylbutyrate. *Arch Dis Child* 2012; 97 (12): 1081-5.
4 Swedish Orphan Biovitrum Ltd. Ammonaps® 940 mg/g granules. Summary of Product Characteristics. 2013. Available at: http://www.medicines.org.uk/emc/medicine/21411/SPC/AMMONAPS+940+mg+g+granules/. Accessed Aug 2013.
5 Adam S, Champion H, Daly A et al. Dietary management of urea cycle disorders: UK practice. *J Inherit Metab Dis* 2010; 30.
6 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2013. Available at: http://www.mims.co.uk/. Accessed Dec 2013.
7 Adam S, Champion H, Daly A et al. Dietary management of urea cycle disorders: UK practice. *J Hum Nutr Diet* 2012; 25 (4): 398-404.