Common Drug Review
Clinical Review Report

April 2016

Drug	Sodium phenylbutyrate (Pheburane)
Indication	As adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinate synthetase, in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.
Listing request	As per indication
Dosage form(s)	Coated granules for oral intake
NOC date	January 26, 2015
Manufacturer	Médunik Canada

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
ARG	arginase
ASL	argininosuccinate lyase
ASS	argininosuccinate synthetase
CI	confidence interval
CPSI	carbamylphosphate synthetase I
CNS	central nervous system
EMA	European Medicines Agency
FDA	US Food and Drug Administration
HCRR	Health Canada Reviewer's Report
IND	Investigational New Drug
IV	intravenous
NAGS	N-acetylglutamate synthase
NaPA	sodium phenylacetate
NaPB	sodium phenylbutyrate
NDA	New Drug Application
ORNT1	ornithine transporter
OTC	ornithine transcarbamylase
RCT	randomized controlled trial
SD	standard deviation
UCD	urea cycle disorder
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

The urea cycle is responsible for the metabolism of nitrogen produced through the breakdown of protein and other nitrogen-containing molecules; it accomplishes this by converting ammonia to urea, which is excreted from the body. Urea cycle disorders (UCDs) result from genetic mutations that cause defects in any of the five enzymes of the urea cycle: carbamoyl phosphate synthetase I (CPSI), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase (ARG); in the co-factor producer N-acetylglutamate synthase (NAGS); or in the two transporters, ornithine transporter (ORNT1) and citrin. Estimates for the incidence of UCDs range from 1:22,179 to 1:53,717 births. Deficiencies in the urea cycle may result in hyperammonemia due to impaired ammonia metabolism, which can be life-threatening and result in permanent neurological damage if left untreated. Infants with a complete dysfunction in a urea cycle enzyme (other than ARG) often present in the newborn period (neonatal-onset) with hyperammonemic coma with a 50% mortality rate after five years. Patients with partial deficiencies have variable clinical presentations and later onset, but still have a 10% risk of mortality and a significant risk for developmental disabilities. The goals of long-term management of UCDs are to achieve normal development and prevent hyperammonemia, and are achieved through a low-protein diet, essential amino acid supplementation, vitamin and mineral supplementation, pharmacotherapies to increase waste nitrogen excretion, and liver transplantation in selected patients. The only pharmacotherapy licensed for use in Canada for patients with UCDs is Pheburane (sodium phenylbutyrate [NaPB]).

NaPB is a prodrug that is metabolized to sodium phenylacetate (NaPA), which then conjugates to glutamine via acetylation to form phenylacetylglutamine, providing an alternate route of nitrogen elimination. It is indicated as adjunctive therapy in the chronic management of UCDs in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy. NaPB (Pheburane) is available as coated granules to be taken orally with food, with 483 mg of drug per gram of granules. The Health Canada–recommended dose is 450 to 600 mg/kg/day in neonates, infants, and children weighing less than 20 kg. For children, adolescents, and adults weighing more than 20 kg, the recommended dose is 9.9 to 13.0 g/m^2/day. NaPB is also available as an uncoated formulation outside of Canada (Buphenyl in the US; Ammonaps in the European Union [EU]). NaPB is not recommended for the management of acute hyperammonemia.

Indication under review
As adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase, in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.
Listing criteria requested by sponsor
As per indication.

The objective of this systematic review is to examine the beneficial and harmful effects of NaPB for the management of UCDs in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.

Results and Interpretation

Included Studies

One phase 3, open-label, single-arm study conducted in the US and Canada that spanned a time period of 15 years (1981 to 1996) was considered pivotal by Health Canada and was included in this review. This study was conducted as part of the US Food and Drug Administration (FDA) Investigational New Drug (IND) and New Drug Application (NDA) programs, and prospective therapeutic protocols approved by the FDA were designed to prevent hyperammonemia in UCD patients and were modified as new drugs became available. A cohort of NaPB-treated patients was defined for patients enrolled from 1985 to 1994 (Cohort 1), which included 162 patients, 148 of who were evaluable. A second cohort was defined that extended the analysis date and included patients enrolled from 1985 to 1996 (Cohort 2), which included 208 patients, 183 of who were evaluable. Between 1985 and 1987, patients were treated with 250 mg/kg/day NaPB in combination with 250 mg/kg/day sodium benzoate. Beginning in 1987, patients were treated with 450 to 600 mg/kg/day NaPB alone. Patients enrolled in this study had deficiencies in OTC (67%), ASS (21%), and CPSI (12%). A total of 39% patients were rescued from a hyperammonemic episode during the neonatal period (neonatal rescue), 8% of patients were treated from birth (prospectively treated), 16% of patients presented with a hyperammonemic episode after 28 days of age (late-onset), and 37% of patients were females with OTC deficiencies who were enrolled later in life (OTC females). Approximately 55% of patients were younger than 12 years at the time of the last visit to the investigator and 15% of patients had received NaPB for at least five years. The outcomes that were reported included mortality, incidence of hyperammonemic episodes, cognitive development, anthropometric measurements, and plasma levels of ammonia and glutamine.

There were several limitations with the US FDA IND/NDA Study, including the lack of a comparator group, the use of treatment regimens that are no longer used in current clinical practice, the lack of defining outcomes a priori, the lack of standardized data collection methods, and poor reporting. In addition, patients often received treatment before official enrolment into the study. The dosing of NaPB used in earlier treatment protocols was lower than the Health Canada–recommended dose and earlier protocols used sodium benzoate, which is not used in current Canadian clinical practice. Relevant baseline characteristics such as age, compliance with therapy, and length of follow-up were not adequately reported, making it difficult to interpret the results. The NaPB used in this study was not the coated formulation that is being reviewed in this submission.

Efficacy

In Cohort 1, 61 patients had been treated with NaPB only with no prior maintenance therapy. Of these patients, four of 16 (25%) neonatal rescue patients died within approximately 15 months. Four of six patients prospectively treated from birth discontinued NaPB treatment within the first 2.5 years of life. Three of 13 late-onset patients ceased treatment after an unknown time. Three of 26 OTC females withdrew from therapy and none died. In Cohort 2, 82 patients had been treated with sodium NaPB only. Of these patients, 18 died during a hyperammonemic episode, with 15 patients in the neonatal rescue group. According to the clinical expert, patients may discontinue a treatment for a number of reasons, including if symptoms are mild, if they cannot tolerate the drug, if they switched to another therapy, or if funding runs out. According to the study, some patients died after their parents' decision to withdraw them from therapy, making the mortality results difficult to interpret. However, historical data suggest that the mortality rate for neonatal rescue patients who did not receive nitrogen-scavenging therapies is much higher than the 25% that was seen in this study.[1]

Of the 148 evaluable patients in Cohort 1, 34 (23%) did not experience any hyperammonemic episodes that required hospitalization during the course of their follow-up (up to nine years) and 114 patients (77%)

experienced at least one episode that required hospitalization. Of the 183 evaluable patients in Cohort 2, 51 (28%) did not experience any hyperammonemic episodes that required hospitalization during the course of their follow-up and 132 patients (72%) experienced at least one episode that required hospitalization. There was no standard definition for hyperammonemia reported in the publications, making it difficult to know how generalizable these results are. As episodes may be triggered by infection and diet, a lack of reporting on the specific trigger and a lack of a standardized diet makes it difficult to interpret the results. However, it appears that hyperammonemic episodes still occur while patients are on therapy.

Results for cognitive development in this study were not well reported because different intelligence quotient (IQ) tests were administered between patients and only some patients were evaluated more than once throughout the study. In addition, children who appeared to be developing normally were tested less frequently than children with evidence of developmental delay. Results suggest that the majority of patients who were evaluated had cognitive impairment, with the neonatal rescue patients demonstrating the greatest impairment in cognitive performance. This is in line with previous observational studies that found that children with neonatal-onset disease had a higher likelihood of having an intellectual disability, but children with late-onset disease also demonstrated neurocognitive and behavioural impairment.[2]

At study entry, patients had lower height and weight than average, with neonatal rescue patients having the largest deviation from normal. Height and weight-for-age z scores remained relatively stable over time throughout the study, but values were not reported for either cohort. The clinical expert noted that some patients would have normal growth curves while others may not, and that this variation is attributed to diet. Without height and weight information for individual patients, or data on the range of heights and weights, it is difficult to determine the precise variation in growth across the population.

Plasma ammonia levels were monitored for 85 patients during stable periods (i.e., not hyperammonemic episodes). Based on 281 measurements, 45 patients (53%) had at least one measurement exceeding the upper limit of normal (ULN) and 6% of measurements were greater than two times the ULN. Plasma glutamine levels were presented for subgroups according to diagnosis, onset, and age. The normal range was 337 to 673 µmol/L. Mean glutamine levels were lower in the young patient groups — the neonatal-rescue and prospectively treated from birth groups (677 ± 343 µmol/L) and late-onset OTC males younger than 18 years (700 ± 331 µmol/L) — than for the patient groups older than 18 years (> 1,000 µmol/L). As neither the timing nor method of sample collection was reported, it is difficult to draw any conclusions based on the plasma ammonia and glutamine levels reported for patients during stable periods.

The NaPB formulation used in the US FDA IND/NDA Study was the unmasked formulation (Buphenyl), while the NaPB formulation of interest in this review is the taste-masked formulation. The manufacturer conducted a pharmacokinetic study to demonstrate bioequivalence of the two formulations, and found that the two formulations were bioequivalent with respect to the rate and extent of absorption of phenylbutyrate.

Harms

A total of 102 patients (56%) reported at least one adverse event. As safety data were obtained from investigator case reports, data sources were dependent on spontaneous reporting. Instruments such as questionnaires or diaries were lacking. Due to the condition of many UCD patients, capture of adverse events would have been limited. A total of 13 patients (7%) withdrew from the study due to poor compliance or upon a parent's request, which was often related to poor tolerance or acceptance of the

drug by the child. Adverse events leading to discontinuation included nausea, vomiting, headache, unpleasant taste, behavioural changes, and unsteadiness and/or dizziness.

A total of 248 adverse events were reported in 102 patients. Of the 248 adverse events, 90 (36%) were related to the central nervous system (CNS) and included hyperactivity, speech disorder, seizures, and mental retardation. Although it is unclear whether these CNS-related adverse events were due to disease progression rather than the drug, high plasma levels of phenylacetate, the major metabolite of NaPB, have been reported to be associated with reversible neurological adverse events in cancer patients receiving intravenous infusions of phenylacetate.[3] However, phenylacetate levels remain relatively low after NaPB administration.

Amenorrhea was reported in 23% of menstruating women, although it is unclear whether contraceptive use may have contributed to this number. Decreased appetite was reported in 4% of patients. Body odour was reported in 3% of patients. Bad taste and taste aversion was reported in 3% of patients. The clinical expert noted that this number is much lower than expected, as unmasked NaPB is known to have a salty and bitter taste, leading to aversive reactions in the majority of patients.[4] Patient input highlighted the burden of administration and tolerability associated with uncoated NaPB due to the taste profile, which may lead to non-compliance. In a French program that granted UCD patients (N = 25) who could not tolerate the taste-unmasked formulation of NaPB (Ammonaps) access to the taste-masked formulation (Pheburane), patients rated the "acceptability" of Pheburane as higher than Ammonaps.[5]

Conclusions

One phase 3, open-label, single-arm study conducted in the US and Canada that spanned a time period of 15 years (1981 to 1996) was considered pivotal by Health Canada and was included in this review. The US FDA IND/NDA Study enrolled patients with a diagnosis of CPSI, OTC, or ASS deficiencies and treated patients with 250 mg/kg/day NaPB and 250 mg/kg/day sodium benzoate between 1985 and 1987, and with 450 to 600 mg/kg/day NaPB after 1987. A total of 148 evaluable patients were enrolled between 1985 and 1994, and 183 patients between 1985 and 1996. Results were difficult to interpret due to the lack of a control or comparator group; the lack of a rigorous study design; the lack of methods and objectives defined a priori; the use of treatment regimens and doses that are no longer used in current Canadian practice; and poor reporting of relevant data, including compliance with therapy, length of follow-up, and age of patients. When the results of this trial are compared with historical data in patients who received no maintenance therapy for UCDs from other studies, treatment with NaPB maintenance therapy reduced the mortality rate in neonatal rescue patients, although the mortality in late-onset patients was similar. Results also suggested that the majority of patients on maintenance therapy treatment still experience hyperammonemic episodes despite lowered ammonia levels, and that almost all patients evaluated had evidence of cognitive impairment that worsened over time.

CNS-related adverse events were reported, although it was unclear whether these were due to disease progression or phenylacetate, the active component of NaPB. Few patients reported experiencing taste aversion, which is unexpected, given the bitter and salty taste profile of uncoated NaPB. The NaPB formulation used in the US FDA IND/NDA Study was the uncoated formulation, while the NaPB formulation of interest in this review is the taste-masked formulation. The manufacturer conducted a pharmacokinetic study to demonstrate bioequivalence of the two formulations. In a study of a subgroup of patients who could not tolerate uncoated NaPB (Ammonaps) and who were granted access to coated NaPB (Pheburane), patients rated the acceptability of Pheburane as higher than Ammonaps.

1. INTRODUCTION

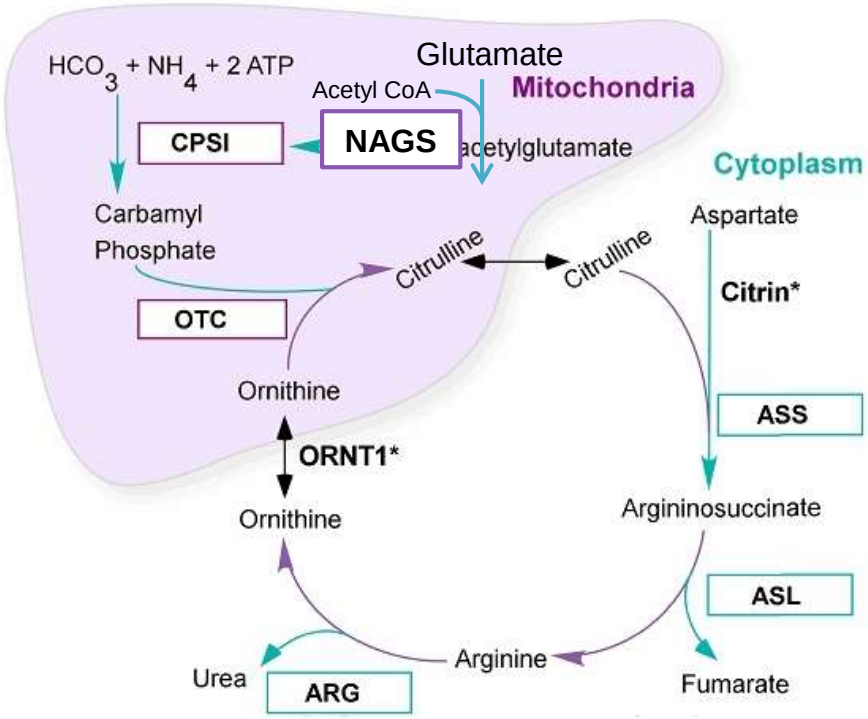
1.1 Disease Prevalence and Incidence

The urea cycle is responsible for the metabolism of nitrogen produced through the breakdown of protein and other nitrogen-containing molecules; it accomplishes this by converting ammonia to urea, which is excreted from the body (Figure 1).[6,7] The urea cycle is also responsible for the endogenous production of arginine, ornithine, and citrulline. Urea cycle disorders (UCDs) result from genetic mutations that cause defects in any of the five enzymes of the urea cycle: carbamoyl phosphate synthetase I (CPSI), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase (ARG); in the co-factor producer N-acetylglutamate synthetase (NAGS); or in the two transporters, ornithine transporter (ORNT1) and citrin. Deficiencies of CPSI, ASS, ASL, ARG, NAGS, ORNT1, and citrin are inherited in an autosomal recessive manner, while OTC deficiencies are inherited in an X-linked manner. The incidence of UCDs is difficult to determine due to the rarity of the condition and undiagnosed cases, but estimates ranging from 1 in 22,179 to 1 in 53, 717 births have been reported.[8] Most recent estimates of prevalence are around 1 in 35,000 births, or about 11 cases per year in Canada.[9] The incidence of OTC deficiencies is higher than other UCDs and affects males and females differently due to its X-linked inheritance, with affected males being more likely to present neonatally with severe hyperammonemia, and female carriers presenting with a later onset.[2,10]

Deficiencies in the urea cycle may result in excessive ammonia levels due to impaired metabolism, which can be life-threatening and result in permanent neurological damage if left untreated. Data from non-human primates given ammonium acetate show neurological toxicity at ammonia levels above 190 µmol/L, which correspond with human experience showing toxicity between 100 and 200 µmol/L.[11-13] Persistently higher ammonia levels in chronically managed patients are associated with higher rates of neurological impairment and at any time, ammonia levels above 150 µmol/L may require urgent ammonia-lowering therapy.[8,14,15] Infants with a complete dysfunction in a urea cycle enzyme (other than ARG) often present in the newborn period (neonatal-onset) with hyperammonemic coma with a 50% mortality rate after five years.[16] Survivors often experience severe developmental delay and recurrent hyperammonemic episodes.[14] Patients with partial deficiencies have variable clinical presentations and later onset, but still have a 10% risk of mortality and a significant risk for developmental disabilities.[2,16] The frequency, severity, and duration of hyperammonemia correlates with brain damage and developmental disabilities, highlighting the importance of prompt diagnosis and treatment.[2]

UCDs are diagnosed using a combination of clinical parameters, laboratory parameters, family history, and genetic testing.[14] Because hyperammonemia is the hallmark for most UCDs and may cause permanent damage, blood ammonia levels should be taken to evaluate a patient with suspected UCD in an emergency setting if there is an unexplained change in consciousness, unusual neurological illness, liver failure, or suspected intoxication.[14] If hyperammonemia is confirmed, plasma amino acids, blood or plasma acylcarnitines, urinary organic acids, and orotic acids should be determined along with basic laboratory investigations in order to differentiate between hyperammonemia due to inborn errors from other conditions.[14] The specific UCD can be determined using laboratory parameters based on argininosuccinate, citrulline, arginine, ornithine, and orotic acid levels.[14] For confirmation of diagnosis, genetic testing or enzymatic assays using liver biopsy samples should be performed.[14] According to the Urea Cycle Disorders Consortium, an elevated plasma ammonia level of ≥ 150 µmol/L in neonates or > 100 µmol/L in children and adults is a strong indication for the presence of a UCD.[17]

FIGURE 1: THE UREA CYCLE



ARG = arginase; ASL = argininosuccinate lyase; ASS = argininosuccinate synthetase; ATP = adenosine triphosphate; CoA = coenzyme A; CPSI = carbamoyl phosphate synthetase I; NAGS = N-acetylglutamate synthetase; NH_4 = ammonia; ORNT1 = ornithine transporter; OTC = ornithine transcarbamylase.
* Transporters.
Source: Mew AN, Lanpher BC, Gropman A, Chapman KA, Simpson KL, Summar ML. Figure 1. The urea cycle. From: Urea cycle disorders overview. 2015 Apr 9 [cited 2015 Dec 18]. In: GeneReviews at GeneTests Medical Genetics Information Resource [database on the Internet]. Seattle (WA): University of Washington; © 1993-2018 University of Washington. Available from: www.ncbi.nlm.nih.gov/books/NBK1217/

1.2 Standards of Therapy

European guidelines for the diagnosis and management of UCDs were developed over the span of three years using a Delphi process.[14] The majority of recommendations were based on low levels of evidence, due to the rarity of UCDs. The following is a summary based on the recommendations provided in this guideline.

When a patient presents with hyperammonemia, ammonia detoxification and measures to reverse catabolism must not be delayed unless a decision for withdrawal of treatment and palliative care is made.[14] Prognosis is considered very poor if the hyperammonemic coma lasts more than three days, if the intracranial pressure increases, or if ammonia peaks at > 1,000 µmol/L.[14] If ammonia levels exceed 500 µmol/L in neonates and children, dialysis should be performed.[14] In adults with acute decompensations, dialysis should be started if ammonia levels exceed 200 µmol/L, due to adults' susceptibility for developing intracranial hypertension and cerebral edema with hyperammonemia. The method of choice for ammonia detoxification is hemodialysis, but this may not be effective in infants due to technical and hemodynamic complications, and so continuous veno-venous hemofiltration may be used.[14]

Drug therapies used for the treatment of acute decompensations include the nitrogen scavengers sodium benzoate and sodium phenylacetate (Ammonul, EU), which provides an alternate route of nitrogen elimination. In Canada, Ammonul is available through the Special Access Programme (SAP). Ondansetron may also be administered to prevent vomiting in the patient. Protein intake should be minimized temporarily, but feeding needs to commence to meet metabolic demands. Following improvement of hyperammonemia (< 100 µmol/L), reintroduction of protein and essential amino acids should not be delayed beyond 24 to 48 hours, increasing daily to the required amount.[14]

As there is no cure for UCDs, the goals of long-term management of UCDs are to achieve normal development and prevent hyperammonemia; this is achieved through a low-protein diet, pharmacotherapies to increase waste nitrogen excretion, and liver transplantation in selected patients.[14] A low-protein diet helps minimize the nitrogen load on the urea cycle, and the amount of protein tolerated by each patient must be determined individually. If natural protein tolerance is too low to achieve normal growth and metabolic stability, essential amino acid supplementation is required. Diet therapy alone is insufficient, in the majority of cases, and nitrogen scavengers are usually necessary.[18,19] Nitrogen scavengers used as an adjunct to diet for the management of UCDs include sodium benzoate and sodium phenylbutyrate (NaPB). In Europe, sodium benzoate is the preferred drug, while in the US, NaPB is recommended as chronic maintenance therapy.[14,17] More recently, glycerol phenylbutyrate has also been available as a nitrogen-scavenging therapy.[20,21] All patients should be monitored for plasma arginine and given arginine and citrulline supplementation due to impaired synthesis in the urea cycle.[14] Liver transplantation is a curative option for patients with UCDs, but it cannot reverse neurologic sequelae. Liver transplantation should be performed in patients without irreversible neurological damage who are in a stable metabolic condition, generally between three and 12 months of age.[14]

Patients with UCDs require lifelong monitoring, including anthropometric data, biochemical tests, dietary and drug review, history of intercurrent illness, and use of the emergency regimen. Visit intervals should be individualized on the basis of age, growth, severity, metabolic stability, and compliance with diet and drug therapy. Young and severely affected patients may need monitoring every three months, while annual reviews may be enough for older or less severe patients.[14]

1.3 Drug

NaPB is a prodrug that is metabolized to sodium phenylacetate (NaPA), which then conjugates to glutamine via acetylation to form phenylacetylglutamine, a compound that is excreted by the kidneys. This provides an alternative nitrogen elimination pathway. NaPB (Pheburane) is available as coated granules to be taken orally, with 483 mg of drug per gram of granules. The Health Canada–recommended dose is 450 to 600 mg/kg/day in neonates, infants, and children weighing less than 20 kg. For children, adolescents, and adults weighing more than 20 kg, the recommended dose is 9.9 to 13.0 g/m^2/day. NaPB is also available as an uncoated formulation outside of Canada (Buphenyl in the US; Ammonaps in the European Union [EU]).

Indication under review
As adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamyl phosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase, in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.
Listing criteria requested by sponsor
As per indication.

The objective of this systematic review is to examine the beneficial and harmful effects of NaPB as adjunctive therapy for the management of UCDs in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.

TABLE 1: KEY CHARACTERISTICS OF NITROGEN-SCAVENGING THERAPIES FOR UREA CYCLE DISORDERS

	Sodium Phenylbutyrate	Glycerol Phenylbutyrate	Sodium Phenylacetate and Sodium Benzoate
Mechanism of Action	Prodrug metabolized to phenylacetate, which conjugates with glutamine to form phenylacetylglutamine to be excreted by the kidneys, providing another route of nitrogen elimination.	Metabolized to release phenylbutyrate, which is then oxidized to phenylacetate, which conjugates with glutamine to form phenylacetylglutamine to be excreted by the kidneys, providing another route of nitrogen elimination.	Phenylacetate conjugates with glutamine to form phenylacetylglutamine, which is excreted by the kidneys. Benzoate conjugates with glycine to form hippuric acid, which is excreted by the kidneys. This provides other routes of nitrogen elimination.
Indication	As adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinate synthetase, in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.	For the chronic management of adult and pediatric patients aged 2 years or older with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.	As adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.
Route of Administration	Oral (nasogastric or gastrostomy tube for patients unable to take product orally).	Oral (nasogastric or gastrostomy tube for patients unable to take product orally).	IV
Dosage Form[a]	**Pheburane**: Coated granules with 483 mg NaPB per gram of granules **Buphenyl (US) and Ammonaps (EU):** Powder with 940 mg NaPB per gram of powder or Tablet with 500 mg NaPB per tablet	**Ravicti (US):** Liquid (1.1 g/mL)	**Ammonul (EU):** Concentrated infusion solution (5 g/50 mL) to be diluted with 10% dextrose injection at ≥ 25 mL/kg before administration

	Sodium Phenylbutyrate	Glycerol Phenylbutyrate	Sodium Phenylacetate and Sodium Benzoate
Recommended Dose	**Patients < 20 kg:** 450 to 600 mg/kg/day **Patients > 20 kg:** 9.9 to 13.0 g/m^2/day Granules or powder should be divided into equal amounts and given with each meal or feeding.	**NaPB-naive patients:** 4.5 to 11.2 mL/m^2/day (5.0 to 12.4 g/m^2/day) **Switching from NaPB:** Total daily dose of NaPB (g) × 0.86 = daily dose in mL Maximum total daily dose is 17.5 mL (19 g). Liquid should be divided into 3 equal doses per day.	**Patients < 20 kg:** 250 mg NaPA and 250 mg sodium benzoate per kg **Patients > 20 kg:** 5.5 g/m^2 NaPA and 5.5 g/m^2 sodium benzoate Infuse as loading dose over 90 to 120 min, followed by maintenance infusion of same dose administered over 24 h until plasma ammonia levels are normalized or patient can tolerate oral nutrition and medication.
Serious Side Effects/Safety Issues	Decreased appetite, body odour, taste aversion, amenorrhea (females). High levels of phenylacetate may result in neurotoxicity (somnolence, fatigue, light-headedness).	High levels of phenylacetate may result in neurotoxicity (somnolence, fatigue, light-headedness).	Hyperventilation, metabolic acidosis, hypokalemia. High levels of phenylacetate may result in neurotoxicity (somnolence, fatigue, light-headedness).
Other	Not recommended for management of acute hyperammonemia.	Not recommended for management of acute hyperammonemia. Contraindicated in patients younger than 2 months.	Not recommended for the chronic management of urea cycle disorders.

EU = European Union; IV = intravenous; NaPA = sodium phenylacetate; NaPB = sodium phenylbutyrate.
[a] Pheburane is the only drug commercially available in Canada; all other drugs are available outside of Canada, as specified.
Source: Health Canada product monograph for Pheburane,[22] Drug information for Buphenyl,[23,24] Ammonaps,[25,26] Ravicti,[20,21] and Ammonul.[27]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of NaPB for the treatment of UCDs.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients of all ages with urea cycle disorders Subgroups: Time of presentation (neonatal-onset or late-onset), organic acid metabolic disorder (yes or no), urea cycle deficiency
Intervention	Sodium phenylbutyrate
Comparators	• Sodium benzoate • Sodium benzoate and sodium phenylacetate • Glycerol phenylbutyrate • Liver transplant • Diet • Placebo
Outcomes	**Key Efficacy Outcomes** • Mortality (all-cause, disease-related) • Hyperammonemic episodes • Cognitive development (e.g., IQ test scores, developmental delays) • Anthropometric measurements (e.g., weight, height, head circumference) • Plasma ammonia and glutamine levels • Health-related quality of life with a validated scale (caregiver and/or patient) **Other Efficacy Outcomes** • Hospitalization • Patient adherence and/or satisfaction • Caregiver burden **Harms Outcomes** AEs, SAEs, WDAEs, menstrual disturbances (females), neurotoxicity, decreased appetite, body odour, taste aversion, hypokalemia
Study Design	Published and unpublished phase 3 RCTs

AE = adverse events; IQ = intelligence quotient; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Pheburane (Sodium Phenylbutyrate) and urea cycle disorder.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 17, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on March 16, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Devices Regulatory Approvals, Advisories and Warnings, Drug Class Review, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in Appendix 3.

3. RESULTS

3.1 Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 2). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 2: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

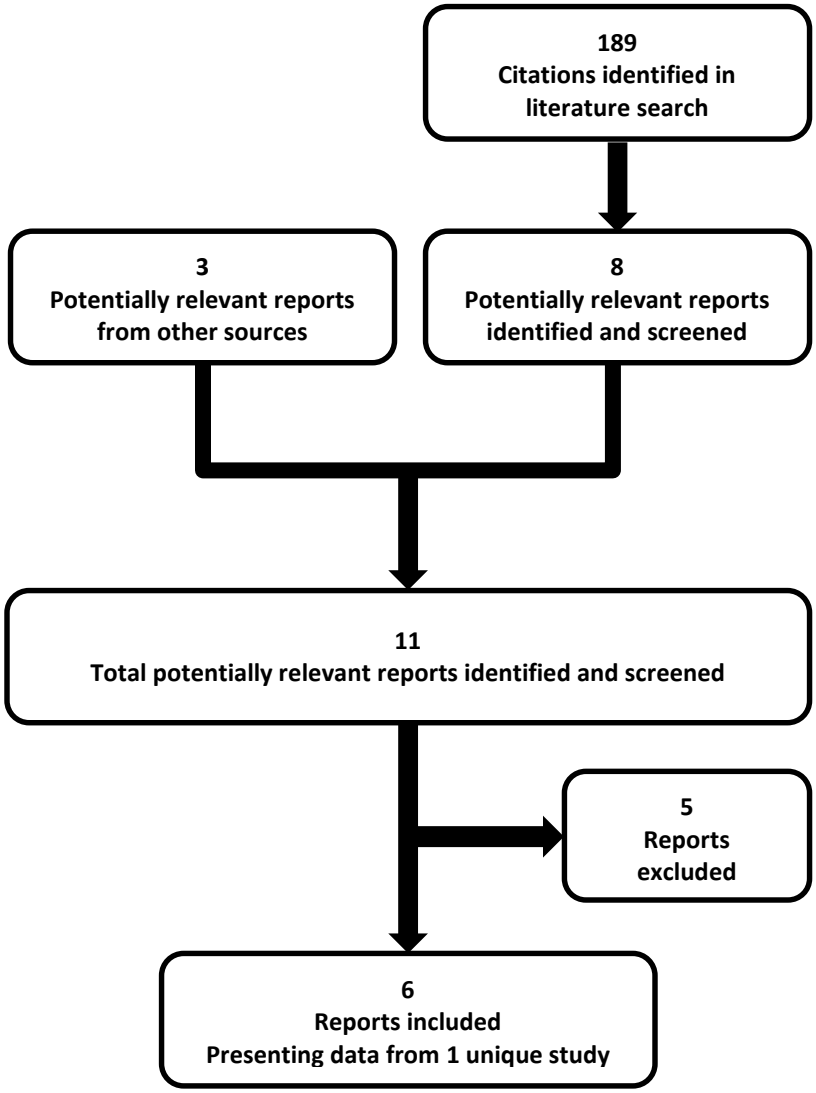


TABLE 3: DETAILS OF INCLUDED STUDY

		US FDA IND/NDA Study
DESIGNS & POPULATIONS	**Study Design**	Phase 3, open-label, single-arm
	Locations	United States, Canada
	Enrolled (N)	Cohort 1 (1985 to 1991): 162 Cohort 2 (1985 to 1996): 208
	Evaluable (N)	Cohort 1 (1985 to 1994): 148 Cohort 2 (1985 to 1996): 183
	Inclusion Criteria	Diagnosis of UCD (deficiency of CPSI, OTC, or ASS)
	Exclusion Criteria	Not reported
DRUGS	**Intervention**[a]	Protocol II (1985): 250 mg/kg/day NaPB in tablet of granule form + 250 mg/kg/day sodium benzoate Protocol III (1987): 450 to 600 mg/kg/day NaPB in tablet or granule form
	Comparator(s)	None
DURATION	**Duration**	All treatment protocols: 15 years (1981 to 1996) NaPB protocol: 11 years (1985 to 1996)
OUTCOMES	**End Points**[b]	• Survival • Incidence of hyperammonemic episodes • Cognitive development • Growth • Plasma levels of ammonia and glutamine
NOTES	**Publications**	Maestri et al. 1991[28] Maestri et al. 1995[29] Maestri et al. 1996[30]

ASS = argininosuccinate synthetase; CDR = CADTH Common Drug Review; CPSI = carbamoyl phosphate synthetase I; EMA = European Medicines Agency; FDA = Food and Drug Administration; HCRR = Health Canada Reviewer's Report; IND/NDA = Investigational New Drug and New Drug Application programs; NaPB = sodium phenylbutyrate; OTC = ornithine transcarbamylase; UCD = urea cycle disorder.
Note: Three additional reports were included (HCRR,[31] EMA scientific discussion,[32] CDR submission[33]).
Source: HCRR,[31] EMA scientific discussion,[32] CDR submission.[33]
[a] The NaPB used in the US FDA IND/NDA Study was the uncoated formulation, which differs from the coated formulation that is being reviewed in this submission.
[b] Outcomes were not defined a priori.

3.2 Included Studies

3.2.1 Description of Studies

One phase 3, open-label, single-arm study conducted in the US and Canada that spanned a time period of 15 years (1981 to 1996) was considered pivotal by Health Canada and was included in this review. This study was conducted as part of the US FDA Investigational New Drug and New Drug Application (IND/NDA) programs and used the uncoated formulation of NaPB (Buphenyl) and not the coated formulation (Pheburane) that is being reviewed in this submission. This study was not conducted by the manufacturer of Pheburane; therefore, access to data was limited, as a full Clinical Study Report was not available and data were available only through published studies, the Health Canada Reviewer's Report (HCRR) for Pheburane, and the European Medicines Agency (EMA) Scientific Discussion for Ammonaps.[28-32] In the US FDA IND/NDA Study, prospective therapeutic protocols

approved by the FDA were designed to prevent hyperammonemia in enrolled patients and were modified as new drugs became available. NaPB (Buphenyl) was introduced as a treatment regimen in 1985, and the cut-off for data analysis was February 1996.

A cohort of NaPB-treated patients was defined for patients enrolled from 1985 to 1994 (Cohort 1), which included 162 patients, 148 of whom were evaluable. A second cohort was defined that extended the analysis date and included patients enrolled from 1985 to 1996 (Cohort 2), which included 208 patients, 183 of whom were evaluable. Of the 183 evaluable patients, 82 were treated with NaPB only, while 101 patients had already been treated according to previous protocols (sodium benzoate and/or NaPA) before receiving NaPB.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients were initially enrolled in this study through various means, and participation was voluntary or based on parental consent. Some patients were selected prior to birth based on the diagnosis of a previously affected sibling with neonatal onset based on parental consent.[28,29] For these patients, a diagnosis of the specific UCD was determined prior to birth via prenatal DNA analysis or amniocentesis and enzyme analysis of cultured cells, or determined after birth. Other patients, particularly females with OTC deficiencies (heterozygous), were enrolled in the study later in life (younger than 18 years) after referral to the appropriate study centre.

b) Baseline Characteristics

According to the HCRR and EMA reports, 55% of patients were younger than 12 years at the time of the last visit to the investigator. The gender distribution was reported for Cohort 2, and there were approximately equal numbers of females and males in the study. Patients enrolled in this study had deficiencies in OTC (67%), ASS (21%), and CPSI (12%).The study population was divided into four categories based on the diagnosis and onset of disease: patients who were rescued from hyperammonemic encephalopathy during the neonatal period (neonatal-rescue, 39%); patients at risk of a UCD who were treated from birth (prospectively treated, 8%); patients presenting with hyperammonemic episode after 28 days of age (late-onset, 16%); and female patients with OTC deficiencies (OTC females, 37%). More than half the patients had received maintenance therapy other than NaPB.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

	US FDA IND/NDA Study	
Characteristic	**Cohort 1 (1985 to 1994) N = 148**	**Cohort 2 (1985 to 1996) N = 183**
Age	NR	NR
Gender, n (%)		
Female	NR	95 (52)
Male	NR	88 (48)
UCD, n (%)		
OTC	99 (67)	122 (67)
ASS	31 (21)	39 (21)
CPSI	18 (12)	22 (12)

Characteristic	US FDA IND/NDA Study	
	Cohort 1 (1985 to 1994) N = 148	Cohort 2 (1985 to 1996) N = 183
Diagnosis and onset, n (%)		
Neonatal-rescue	58 (39)	72 (39)
Prospectively treated from birth	12 (8)	14 (8)
Late-onset (aged > 28 days)	23 (16)	29 (16)
OTC females	55 (37)	68 (37)
Prior UCD maintenance therapy,[a] n (%)		
Yes	87 (59)	101 (55)
No	61 (41)	82 (45)
No prior UCD maintenance therapy,[b] n (%)		
Neonatal-rescue	16 (11)	NR
Prospectively treated from birth	6 (41)	NR
Late-onset (aged > 28 days)	13 (9)	NR
OTC females	26 (18)	NR

ASS = argininosuccinate synthetase; CPSI = carbamoyl phosphate synthetase I; EMA = European Medicines Agency; FDA = Food and Drug Administration; HCRR = Health Canada Reviewer's Report; IND/NDA = Investigational New Drug and New Drug Application programs; NaPB = sodium phenylbutyrate; NR = not reported; OTC = ornithine transcarbamylase; UCD = urea cycle disorder.
[a] Prior UCD maintenance therapy taken during the study through earlier protocols.
[b] No other UCD maintenance therapy taken during the study other than NaPB.
Source: HCRR,[31] EMA scientific discussion.[32]

TABLE 5: TREATMENT POPULATION BY TIME OF ONSET AND ENZYME DEFICIENCY (COHORT 1)

Diagnosis and Onset	OTC	CPSI	ASS	Total
Neonatal-rescue	19	12	27	58
Prospectively treated from birth	4	4	4	12
Late-onset (aged > 28 days)	21	2	0	23
OTC females	55	0	0	55
Total	99	18	31	148

ASS = argininosuccinate synthetase; CPSI = carbamoyl phosphate synthetase I; EMA = European Medicines Agency; FDA = Food and Drug Administration; HCRR = Health Canada Reviewer's Report; IND/NDA = Investigational New Drug and New Drug Application programs; OTC = ornithine transcarbamylase; UCD = urea cycle disorder.
Source: HCRR,[31] EMA scientific discussion.[32]

3.2.3 Interventions

During the 15-year period of the study, treatment protocols were modified based on the availability of investigational new drugs. The formulation of NaPB that was used in this study was the uncoated formulation (Buphenyl).

a) Protocol I

In the first protocol, patients received 250 mg/kg/day sodium benzoate administered orally as maintenance therapy (protocol I) prior to 1984.

b) Protocol II

The second protocol added 250 mg/kg/day NaPA (protocol IIa) in 1984 or 250 mg/kg/day NaPB (protocol IIb) in 1985 as oral maintenance therapies, to be taken in combination with 250 mg/kg/day sodium benzoate. NaPB was administered as tablets or granules.

c) Protocol III

The dosing regimen for NaPA and NaPB was modified in 1987 to 450 to 600 mg/kg/day (protocol III), during which sodium benzoate was no longer administered.

All treatment protocols included natural protein and calories for all patients, and essential amino acids for patients with a CPSI or OTC deficiency. Arginine freebase was administered to all patients.

All patients received hemodialysis or hemofiltration during episodes of hyperammonemia.

3.2.4 Outcomes

No primary or secondary outcomes were defined in the US FDA IND/NDA study and, as such, there were no standard data collection frameworks defined a priori to evaluate outcomes of interest. Efficacy outcomes evaluated included survival, incidence of hyperammonemic episodes, cognitive development, growth, and plasma levels of ammonia and glutamine.

No definition of hyperammonemia was reported.

Cognitive development was evaluated using intelligence quotient (IQ) measuring scales when possible. As different scales were used for different patients, results were converted into a functional scoring system: average (4), average/borderline (4/3), mentally retarded (2), and severely retarded (1). The most severely affected patients (non-verbal and/or non-responsive) were placed in the severely retarded category.

3.2.5 Statistical Analysis

No statistical analyses were planned and results are presented descriptively.

a) Analysis Populations

No analysis sets were defined. Only results from evaluable patients were presented. The definition of "evaluable" was not reported.

3.3 Patient Disposition

A total of 162 patients were enrolled in Cohort 1, with 148 patients who were evaluable and included in the efficacy and safety sets. In Cohort 2, 208 patients were enrolled, of whom 183 were evaluable.

TABLE 6: PATIENT DISPOSITION

	Cohort 1 (1985 to 1994)	Cohort 2 (1985 to 1996)
Enrolled, N	162	208
Evaluable, N (%)	148 (100)	183 (100)
Discontinued from therapy	NR	28 (15)
Liver transplant	NR	15 (8)
Poor compliance or parent's request	NR	13 (7)
Safety, N	-	183 (100)

Source: HCRR = Health Canada Reviewer's Report,[31] European Medicines Agency scientific discussion.[32]

3.4 Exposure to Study Treatments

According to the summary in the HCRR, 15% of patients had received NaPB for at least five years.

Compliance with treatment was not well documented.

3.5 Critical Appraisal

3.5.1 Internal Validity

The US FDA IND/NDA Study was an open-label, single-arm trial with no control or comparator group. The lack of a comparator group makes it difficult to quantify the comparative efficacy and safety of NaPB to other regimens for the maintenance therapy of patients with UCDs.

The study reported data for evaluable patients only. There was no definition of "evaluable" reported, which further limits the interpretation of the reported data.

Relevant baseline characteristics of enrolled patients were not adequately reported, including comorbidities and age. In addition, relevant parameters such as diet and compliance with therapy were not reported on during the trial. As diet and protein intake plays an important role in the manifestation of hyperammonemic episodes, this information would have been pertinent. Appropriate compliance would be necessary for NaPB to exert its effect, and compliance may be problematic due to the bitter taste of the formulation that was used in the study. Without data on compliance with treatment, it is difficult to determine how compliance would have affected efficacy of the treatment.

The outcomes of this trial were not well reported and the length of follow-up time (mean, median, range) for patients was also not reported, making it difficult to interpret the results. In addition, outcomes were not defined a priori and no standard data collection framework was employed. For the mortality results in certain subgroups, it was reported that patients discontinued treatment, but it was unclear whether they died later. For cognitive development and anthropometric measurements, no specific values were presented for baseline and post-baseline measurements and results were only presented descriptively, making the interpretation of results difficult. However, it was reported that cognitive outcomes were difficult to estimate because different tests were used and not all patients were evaluated.

It was not reported under which conditions plasma ammonia and glutamine levels were taken. According to the expert consulted for this review, both ammonia and glutamine levels fluctuate during the day, depending on time of day and whether it is under fasting conditions. Due to the lack of reporting, it is unclear what the results for plasma ammonia and glutamine levels indicate.

Due to the urgent intensive care required to treat hyperammonemic episodes, some patients received treatment before official enrolment into the study protocol. Few inclusion and exclusion criteria were reported and it appeared that all patients with a diagnosis of CPSI, OTC, or ASS deficiencies were included. The treatment protocols for acute hyperammonemia included intravenous infusions of high-dose sodium benzoate and NaPA, which may have influenced survival outcomes.

3.5.2 External Validity

The NaPB formulation used in the US FDA IND/NDA Study was the taste-unmasked formulation (Buphenyl), which is not the same formulation as the taste-masked formulation (Pheburane) being reviewed. However, the active component of the granules is NaPB in both formulations. In this study,

some patients would have received the tablet version of NaPB, which is not available in the taste-masked version.

Patients who were recruited prior to 1987 may have been treated with other maintenance therapies (sodium benzoate with or without NaPA) prior to receiving NaPB.

No definition of hyperammonemia was reported in the study. This is concerning, as the threshold at which a physician may define a hyperammonemic episode may differ between physicians. The clinical expert consulted for this review noted that community physicians outside of academic centres may have a lower threshold of ammonia level at which they would consider a patient to be experiencing a hyperammonemic episode.

Although the exact numbers were not specified, the majority of patients were from US centres, as this study was conducted as part of the FDA IND/NDA programs and the main academic centre was based out of the Johns Hopkins Hospital. In addition, the study was conducted during the 1980s and 1990s, during which different treatment regimens were used for patients with UCDs. This would limit generalizability of study findings to current Canadian clinical practice.

The US FDA IND/NDA Study spanned a 15-year time frame, but the length of follow-up of patients was not well reported. However, it is likely that this long time frame would have followed patients for many years, providing information on their long-term outcomes. In addition, this long time frame provided information on 183 UCD patients, which is a large sample, given how rare these disorders are in the general population.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2).

3.6.1 Mortality

a) Cohort 1 (1985 to 1994)

For Cohort 1, mortality results were presented for patients who received no other therapy for UCDs prior to NaPB (n = 61). Four of 16 neonatal rescue patients died within approximately 15 months. Four of six patients prospectively treated from birth discontinued NaPB treatment within the first 2.5 years of life. Three of 13 late-onset patients ceased treatment after an unknown time. Three of 26 OTC females withdrew from therapy, and none died.

b) Cohort 2 (1985 to 1996)

In Cohort 2, 82 patients had been treated with NaPB only. Of these patients, 18 died during a hyperammonemic episode, with 15 patients in the neonatal rescue group. Some of these patients died after the parents' decision to withdraw their child from therapy.

3.6.2 Hyperammonemic Episodes

a) Cohort 1 (1985 to 1994)

Of the 148 evaluable patients, 34 (23%) did not experience any hyperammonemic episodes that required hospitalization during the course of their follow-up (up to nine years) and 114 patients (77%) experienced at least one episode that required hospitalization.

b) Cohort 2 (1985 to 1996)

Of the 183 evaluable patients, 51 (28%) did not experience any hyperammonemic episodes that required hospitalization during the course of their follow-up, and 132 patients (72%) experienced at least one episode that required hospitalization.

3.6.3 Cognitive Development

Cognitive development was difficult to estimate because only some patients were evaluated repeatedly, and different tests were occasionally used to assess the same patient. In addition, the reliability of estimates during the first months of life is unknown.

a) Cohort 1 (1985 to 1994)

Of the OTC female patients who had their IQ evaluated, six of 25 patients had normal mental capacity. The neonatal rescue patients demonstrated the greatest impairment in cognitive performance. In the prospectively treated from birth group, no patients exceeded a score of average/borderline (4/3), but none of these patients were in the severely retarded (1) category.

3.6.4 Anthropometric Measurements

At study entry, patients had lower height and weight than average, with neonatal rescue patients having the largest deviation from normal. Height and weight-for-age z scores remained relatively stable over time throughout the study. Values were not reported.

3.6.5 Plasma Ammonia and Glutamine Levels

Plasma ammonia levels were monitored for 85 patients during stable periods (i.e., not hyperammonemic episodes). Based on 281 measurements, 45 patients (53%) had at least one measurement exceeding the upper limit of normal (ULN) and 6% of measurements were greater than two times the ULN. The normal range of plasma ammonia was not reported.

Plasma glutamine levels were presented for subgroups according to diagnosis, onset, and age (Table 7). The normal range was 337 to 673 µmol/L. Mean glutamine levels were lower in the young patient groups: neonatal-rescue and prospectively treated from birth groups (677 ± 343 µmol/L) and late-onset OTC males younger than 18 years (700 ± 331 µmol/L) than for the patient groups older than 18 years (> 1,000 µmol/L).

TABLE 7: MEAN GLUTAMINE LEVELS

Diagnosis and Onset	N	Mean Glutamine Levels (SD), µmol/L Normal Range: 337 to 673 µmol/L
Neonatal rescue and prospectively treated from birth	77	677 (343)
Late-onset OTC males aged < 18 years	17	700 (331)
Late-onset OTC and CPSI aged > 18 years	8	1,001 (426)
OTC females aged > 18 years	19	1,004 (298)
OTC females aged < 18 years	47	1,074 (369)

ASS = argininosuccinate synthetase; CPSI = carbamoyl phosphate synthetase I; EMA = European Medicines Agency; FDA = Food and Drug Administration; HCRR = Health Canada Reviewer's Report; IND/NDA = Investigational New Drug and New Drug Application programs; OTC = ornithine transcarbamylase; UCD = urea cycle disorder.
Source: HCRR,[31] EMA scientific discussion.[32]

3.6.6 Health-Related Quality of Life

Health-related quality of life was not assessed as an outcome in the US FDA IND/NDA Study.

3.6.7 Other Efficacy Outcomes

Hospitalization was not assessed as an outcome in the US FDA IND/NDA Study. However, hyperammonemic episodes were accompanied by hospitalization and this was reported (see section 3.6.2: Hyperammonemic Episodes).

Patient adherence and/or satisfaction and caregiver burden were not assessed.

3.7 Harms

Only those harms identified in the review protocol are reported below (see section 2.2.1: Protocol). Safety results are reported for Cohort 2 (N = 183).

3.7.1 Adverse Events

A total of 102 patients (56%) reported at least one adverse event. As safety data were obtained from investigator case reports, the data were dependent on spontaneous reporting. Instruments such as questionnaires or diaries were lacking. Because of the condition of many UCD patients, capture of adverse events would have been limited.

3.7.2 Serious Adverse Events

Serious adverse events were not differentiated from adverse events in the reports.

3.7.3 Withdrawals Due to Adverse Events

A total of 13 patients (7%) withdrew from the study due to poor compliance or upon a parent's request, which was often related to poor tolerance or acceptance of the drug by the child. Adverse events leading to discontinuation included nausea, vomiting, headache, unpleasant taste, behavioural changes, and unsteadiness and/or dizziness.

3.7.4 Notable Harms

A total of 248 adverse events were reported in 102 patients. Of the 248 adverse events, 90 (36%) were CNS-related and included hyperactivity, speech disorder, seizures, and mental retardation. However, it is unclear whether these were from the neurological effects of the disease.

Amenorrhea was reported in 23% of menstruating women. Decreased appetite was reported in 4% of patients. Body odour was reported in 3% of patients. Bad taste and taste aversion was reported in 3% of patients.

4. DISCUSSION

4.1 Summary of Available Evidence

One phase 3, open-label, single-arm study conducted in the US and Canada as part of the US FDA IND/NDA programs was considered pivotal by Health Canada and was included in this review. No other studies met the inclusion criteria for the systematic review. The US FDA IND/NDA Study spanned a time period of 15 years (1981 to 1996) and enrolled patients with a diagnosis of CPSI, OTC, or ASS deficiency, and treated them with various protocols as agents became available on the US market. NaPB was introduced into the protocol in 1985 as a maintenance therapy, and results were presented for a cohort of patients enrolled between 1985 and 1994 (Cohort 1; N = 148) and a cohort of patients enrolled between 1985 and 1996 (Cohort 2; N = 183). As some of these patients were started in the study prior to 1985, there were patients who received other maintenance therapies prior to NaPB, including sodium benzoate and NaPA. In Cohort 1, 61 patients were treated with NaPB alone as maintenance therapy. In Cohort 2, 82 patients were treated with NaPB alone as maintenance therapy.

There were several limitations with the US FDA IND/NDA Study, including the lack of a comparator group, the use of treatment regimens that are no longer used in current clinical practice, the lack of defining outcomes a priori, the lack of standardized data collection methods, and poor reporting. In addition, patients often received treatment before official enrolment into the study. The dosing of NaPB used in earlier treatment protocols was lower than the Health Canada–recommended dose and earlier protocols used sodium benzoate, which is not used in current Canadian clinical practice. Relevant baseline characteristics such as age, compliance with therapy, and length of follow-up were not adequately reported, making it difficult to interpret the results. The three publications by Maestri et al.[28-30] that presented results from the US FDA IND/NDA Study did not present results for the entire cohort of patients who received NaPB treatment (see Appendix 4); therefore, the results from this study were taken from the HCRR for Pheburane[31] and the EMA Scientific Discussion for Ammonaps.[32]

The manufacturer conducted a study (LUC10001; N = 14) to demonstrate bioequivalence of the coated formulation of NaPB (Pheburane) being reviewed in this submission to the uncoated formulation that was used in the pivotal trial (see Appendix 6).[34] In addition, a French study was conducted in a cohort of UCD patients (N = 25) who could not tolerate the uncoated formulation of NaPB and who were granted access to Pheburane (see Appendix 7).[5]

4.2 Interpretation of Results

4.2.1 Efficacy

Results from the US FDA IND/NDA Study were difficult to interpret due to poor reporting and lack of a comparator group. In Cohort 1, 25% of neonatal rescue patients died within 15 months. Historical data from a French study (N = 217) in patients who did not receive nitrogen-scavenging therapy found that 84% of neonatal-onset patients died.[1] The US FDA IND/NDA Study also reported that no OTC female patients died. The clinical expert consulted for this review noted that it is rare for OTC female patients to experience a crisis severe enough to result in death. A retrospective evaluation of 88 patients in Europe found that the patients who used sodium benzoate and supplements in addition to protein restriction had improved survival compared with patients treated solely by protein restriction, but only in patients with neonatal onset and not in patients with later onset.[35-37]

Results for patients who discontinued NaPB treatment were also presented, but the reasons for discontinuation were not reported. According to the clinical expert, patients may discontinue a

treatment for a number of reasons, including if symptoms are mild, if they cannot tolerate the drug, if they switched to another therapy, or if funding runs out. According to the study, some patients died after their parents' decision to withdraw them from therapy, making the mortality results more difficult to interpret.

In the Health Canada–approved product monograph for Pheburane, there is a warning that episodes of acute hyperammonemic encephalopathy may occur in patients even when they are on therapy.[22] This was observed in the US FDA IND/NDA Study, where more than 70% of patients experienced at least one hyperammonemic episode that required hospitalization. No standard definition for hyperammonemia was reported in the publications, making it difficult to know how generalizable these results are. The clinical expert noted that the threshold at which a physician defines a hyperammonemic episode may differ between academic centres and community centres. A prospective, longitudinal observational study in 562 UCD patients found that the most common identifiable precipitant for an episode was infection (33%), followed by diet (11%).[38] As episodes may be triggered by infection and diet, a lack of reporting on the specific trigger and a lack of a standardized diet makes it difficult to interpret the results.

Results for cognitive development in this study were not well reported because different IQ tests were administered and only some patients were evaluated more than once throughout the study. Results suggested that the majority of patients who were evaluated had cognitive impairment. Neurological sequelae cannot be reversed, and therefore IQ scores are unlikely to improve over time. Results reported in the individual publications demonstrated declines in scores over time (see Appendix 4).[28-30] However, children who appeared to be developing normally were tested less frequently than children with evidence of developmental delay.[28] A study that performed neuropsychological assessments on 92 patients with UCDs found that children with neonatal-onset disease had a higher likelihood of having an intellectual disability, but children with late-onset disease also demonstrated neurocognitive and behavioural impairment.[2] The extent of brain damage appears to be associated with the duration of hyperammonemic coma, and neonatal-onset patients have been observed to have poor neurological outcomes in several observational studies.[1,39]

The study reported that patients had lower heights and weights at study entry than the national average, and that the mean height-for-age and weight-for-age z scores remained constant over time. The clinical expert noted that some patients would have normal growth curves while others may not, and that this variation is attributed to diet. Without height and weight information for individual patients, or data on the range of heights and weights, it is difficult to determine the precise variation in growth across the population.

Fasting plasma ammonia levels have been observed to correlate with the risk of hyperammonemic episodes.[40] According to the clinical expert consulted for this review, plasma ammonia and glutamine levels fluctuate throughout the day and differ depending on whether the patient is fasted or fed. Another source of variation is sample collection, handling, and analysis, which may have differed between laboratories and study centres.[17,37] As neither the timing nor method of sample collection was reported, it is difficult to draw any conclusions based on the plasma ammonia and glutamine levels reported for patients during stable periods. The clinical expert also noted that phenylacetylglutamine is a by-product of NaPB, and therefore it would be necessary to look at total glutamine levels to account for the extent to which NaPB binds glutamine.

Sodium benzoate is not as widely used in clinical practice as maintenance therapy for UCD patients in the US and Canada as it is in European countries.[14] The clinical expert confirmed that sodium benzoate is used much less frequently in current clinical practice. As several patients in this study received sodium benzoate during earlier protocols, this would limit generalizability of results to current Canadian clinical practice.

According to the clinical expert consulted for this review, maintenance therapy is effective for UCD patients not because it necessarily decreases the incidence of hyperammonemic episodes, but because it allows for the administration of protein nutrition without vomiting. In addition to excessive ammonia levels, a lack of proper protein intake can result in death. However, to ensure that these therapies work, proper compliance with medication regimens must be implemented. Compliance was not reported in the US FDA IND/NDA Study.

A major limitation of the US FDA IND/NDA Study was the lack of a control or comparator group. According to the clinical expert, placebo-controlled studies in UCDs are impossible because using a placebo would result in death in the majority of cases that are being managed for hyperammonemia. There is clinical heterogeneity such that even children with the same disease type can have differing levels of disease severity, and during periods of acute illness, the goal is in saving the life of the patient and not on the operation of a clinical trial. Therefore, the data, at best, can be gathered from cohort studies, case reports, and the considerable clinical experience with adverse outcomes when ammonia scavengers are unavailable. In this respect, NaPB (or NaPA) has shown improved ammonia control compared with diet alone or other ammonia scavengers, mortality, or increased tolerance to dietary protein.[28-30,39,41] Nevertheless, UCDs are severe diseases and patients continue to remain at risk for acute exacerbations of hyperammonemia, usually due to infections,[38] and these episodes have a high risk for mortality at any time. Early studies have shown that mortality can be improved in the short term, but long-term studies have not reported lower mortality since the introduction of ammonia scavengers.[10,35,36,42,43] Unfortunately, the long-term studies have serious limitations and do not contain sufficient information to determine which component of UCD management was related to the outcomes reported. Therefore, the long-term data cannot be used to demonstrate lack of effect. There is little doubt that NaPB can help to control ammonia levels, but in some patients, all therapies can fail to reduce ammonia levels.[28-30,42] Survivors of hyperammonemia tend to have severe neurological disease, but there is some evidence that early intervention to limit the ammonia peak at the first crisis and ongoing ammonia control result in better neurological outcomes.[44]

Patients who cannot take NaPB orally require administration of NaPB solution by nasogastric or gastronomy tube. The clinical expert noted that this would be difficult for patients in remote areas, because the solution would need to be prepared at a hospital centre and shipped at frequent intervals, as NaPB solution should be used within seven days.[22]

The NaPB formulation used in the US FDA IND/NDA Study was the unmasked formulation, while the NaPB formulation of interest in this review is the taste-masked formulation. The manufacturer conducted a pharmacokinetic study to demonstrate bioequivalence of the two formulations (see Appendix 6). The product monographs for both formulations of NaPB recommend a dose of 450 to 600 mg/kg/day in neonates, infants, and children less than 20 kg in weight.[22,23,25] The dose of NaPB used in the earlier protocol (Protocol II) of the US FDA IND/NDA Study was 250 mg/kg/day, in combination with sodium benzoate. This would further limit the generalizability of results from this study, although the numbers of patients who were enrolled into each protocol were not reported.

4.2.2 Harms

Adverse events in the US FDA IND/NDA Study were dependent on spontaneous reporting, and therefore may not have captured all adverse events experienced by patients. In addition, the condition of patients may have precluded proper capture of adverse events. There was no reporting of adverse events in the publications, and adverse event data reported in the HCRR and EMA Scientific Discussion were limited.

A total of 36% adverse events were related to the CNS and included hyperactivity, speech disorder, seizures, and mental retardation. Although it is unclear whether these CNS-related adverse events were due to disease progression rather than the drug, high plasma levels of phenylacetate, the major metabolite of NaPB, have been reported to be associated with reversible neurological adverse events in cancer patients receiving intravenous infusions of phenylacetate.[3] However, phenylacetate levels remain relatively low after NaPB administration and no relationship was identified between phenylacetate levels and neurological adverse events in a pooled analysis of 80 UCD patients from multiple studies of NaPB and glycerol phenylbutyrate.[3,45]

In the study, 3% of patients reported experiencing a bad taste or taste aversion to NaPB. The clinical expert noted that this number is much lower than expected, as unmasked NaPB is known to have a salty and bitter taste, leading to aversive reactions in the majority of patients.[4] In this submission, the taste-masked formulation (Pheburane) is being reviewed; thus essentially masking the salty and bitter taste of NaPB through the use of microgranular sucrose spheres and an outer ethylcellulose layer.[4,34] The clinical expert noted that this outer coating dissolves in 30 seconds once taken orally, implying that the granules must be swallowed immediately to preserve the coating and mask the unpleasant taste.[46] In a French program that granted UCD patients (N = 25) who could not tolerate the taste-unmasked formulation of NaPB (Ammonaps) access to the taste-masked formulation (Pheburane), patients rated the "acceptability" of Pheburane as higher than Ammonaps (see Appendix 7). Patient input also highlighted the burden of administration and tolerability associated with uncoated NaPB due to the taste profile, which may lead to non-compliance (Appendix 1).

Amenorrhea was reported in 23% of menstruating women. The clinical expert noted that this is higher than expected, and it is difficult to determine whether this is truly drug-related without data on contraceptive use.

NaPB is a histone deacetylase inhibitor that could potentially have unrecognized long-term side effects due to modification of gene expression.[14] NaPB has been observed to deplete branched chain amino acids (leucine, isoleucine, valine) and increase the risk of endogenous protein catabolism.[47] Therefore, it may be necessary to supply patients with essential amino acid mixture high in branched chain amino acids in order to maintain amino acid balance and promote growth.[47]

4.3 Potential Place in Therapy[1]

Currently, patients with UCDs are managed with the NaPB formulation Buphenyl, which has been available in Canada through the Health Canada Special Access Program (SAP) by request only. The SAP requires an approval from Health Canada. Although expedited approval can be requested, waiting for an approval invariably results in delays in the time to administer Buphenyl. Pheburane is currently the only medication specific to treatment of hyperammonemia in UCDs that has a Notice of Compliance from

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Health Canada, and an application has been made for CADTH review for formulary consideration. There is an unmet need for an approved and easily available drug through a formulary (at short notice without Special Access) for management of ammonia in UCDs in Canada.

Evidence for continuing the use of NaPB to control ammonia can easily be seen in patients who show immediate rises in ammonia after temporary interruption of NaPB in historical data (this would be unethical).[12] Reduction of blood ammonia levels is the principal target in the treatment of UCDs. Reducing blood ammonia levels not only reduces neurologic toxicity, but continued control of ammonia levels allows patients to consume sufficient protein, which is essential for growth in children and maintenance of health in adults. The goal for protein intake in children is considered to be between 1 g and 1.5 g protein/kg body weight per day,[48] and review of case reports prior to the use of scavengers shows historically lower protein intakes and protein aversion.[12,16,18,19,49]

There is limited experience with the specific product, Pheburane, for treating UCDs. There is a published report on experience with Pheburane in one patient[50] and a study on the palpability of the formulation, which showed that ammonia levels did not increase on Pheburane compared with Buphenyl.[5] The manufacturer has indicated that data from trials on NaPB can be used to show efficacy of Pheburane because the active ingredient is the same. This seems reasonable, since NaPB is quickly released from Pheburane and rapidly converted to its active metabolite NaPA after ingestion. [34] Of note, NaPB in Buphenyl has largely replaced the use of NaPA because of improved oral tolerance. The use of NaPB in the form of Pheburane does not imply improved control of ammonia levels, although one study showed that improved oral tolerance may improve adherence.[5] Buphenyl is largely still considered difficult to tolerate because of its taste, and nausea and vomiting after ingestion are not infrequent. Pheburane is considered a stepwise improvement in the oral tolerance of NaPB.

In Canada, newborn screening for UCDs is offered in many provinces, although newborns with severe hyperammonemia may present prior to the results of their newborn screen. Initial control of blood ammonia levels may require the use of intravenous scavengers and/or dialysis and temporary restriction of dietary protein. In children who survive, dietary protein is then reintroduced along with oral ammonia scavengers, usually NaPB, to control blood ammonia levels, with eventual discharge home while maintaining this therapy. The labelled doses of Pheburane may not be adequate to manage severe, acute hyperammonemic encephalopathy, but may be considered when intravenous ammonia scavengers are not available, and arrangements are in place to get access to more aggressive ammonia-lowering therapy. Most likely, NaPB would be used during and after the transition from intravenous scavengers to oral scavengers, with adequate dietary management.

NaPB in North America is considered a suitable ammonia scavenger in chronically treated patients with UCDs such as CPSI, ASS, ASL, and OTC deficiency. Hyperammonemia in organic acid disorders such as propionic academia and methyl-malonic academia, and transporter defects such as lysinuric protein intolerance and hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, may also require treatment with NaPB in some cases. Not all UCDs require the use of NaPB to control hyperammonemia. Examples include NAGS deficiency, which is treated with carglumic acid; ASL deficiency, which may be controlled with L-arginine; and ARG deficiency, which is not commonly associated with hyperammonemia. Hyperammonemia from inborn errors of metabolism can quickly be fatal, and metabolic specialists may require the use of NaPB in circumstances other than those listed above. Sodium benzoate can also be used as an ammonia scavenger, but has potentially lower ammonia-scavenging potential per mole than NaPB and is only available through Special Access. A newer product,

glycerol phenylbutyrate, did not have a Notice of Compliance from Health Canada at the time of this review and was not available through Special Access, either.

NaPB is currently viewed as an indispensable drug in the management of UCDs and some organic acidurias, as no other formulary product is available in Canada. Barriers to the use of ammonia scavengers would likely reduce accessibility to treatments that reduce morbidity and mortality in patients with UCDs.

5. CONCLUSIONS

One phase 3, open-label, single-arm study conducted in the US and Canada that spanned a time period of 15 years (1981 to 1996) was considered pivotal by Health Canada and was included in this review. The US FDA IND/NDA Study enrolled patients with a diagnosis of CPSI, OTC, or ASS deficiencies and treated patients with 250 mg/kg/day NaPB and 250 mg/kg/day sodium benzoate between 1985 and 1987, and with 450 to 600 mg/kg/day NaPB after 1987. A total of 148 evaluable patients were enrolled between 1985 and 1994, and 183 patients between 1985 and 1996. Results were difficult to interpret due to the lack of a control or comparator group; the lack of a rigorous study design; the lack of methods and objectives defined a priori; the use of treatment regimens and doses that are no longer used in current Canadian practice; and poor reporting of relevant data, including compliance with therapy, length of follow-up, and age of patients. When the results of this trial are compared with historical data in patients who received no maintenance therapy for UCDs from other studies, treatment with NaPB maintenance therapy reduced the mortality rate in neonatal rescue patients, although the mortality in late-onset patients was similar. Results also suggested that the majority of patients on maintenance therapy treatment still experience hyperammonemic episodes despite lowered ammonia levels, and that almost all patients evaluated had evidence of cognitive impairment that worsened over time.

CNS-related adverse events were reported, although it was unclear whether these were due to disease progression or phenylacetate, the active component of NaPB. Few patients reported experiencing taste aversion, which is unexpected, given the bitter and salty taste profile of uncoated NaPB. The NaPB formulation used in the US FDA IND/NDA Study was the uncoated formulation, while the NaPB formulation of interest in this review is the taste-masked formulation. The manufacturer conducted a pharmacokinetic study to demonstrate bioequivalence of the two formulations. In a study of a subgroup of patients who could not tolerate uncoated NaPB (Ammonaps) and who were granted access to coated NaPB (Pheburane), patients rated the acceptability of Pheburane as higher than Ammonaps.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The National Urea Cycle Disorders Foundation (NUCDF) was the only patient group that submitted input.

The NUCDF is an advocacy organization that represents patients affected by urea cycle disorders (UCDs), their families, and medical professionals in more than 38 countries. The NUCDF is dedicated to saving and improving the lives of children and adolescents with UCDs. Its goals are to stimulate and support scientific research, provide guidance to affected patients and their families, educate health care professionals and policy-makers, increase public awareness, and provide a caring community.

The NUCDF declared largely receiving funding support from the general public via fundraisers and private donations, as well as small, unrestricted educational grants and nominal annual conference sponsorships from corporations, in the last 12 months, including Cytonet, Recordati Rare Diseases, Vitaflo, and Médunik.

2. Condition-Related Information

According to the NUCDF, the information presented below was gathered through individual correspondences with patients with UCDs, as well as their families, focus groups and annual NUCDF conferences; reports from medical professionals; and formal surveys of patients, their caregivers, and physicians.

The submission highlighted the impact of the result of acute and chronic hyperammonemia and related neurotoxins associated with UCDs. Specifically, short- and long-term effects on executive and cognitive function were noted, including problems with focusing, inattention, impulsive behaviour, and lack of insight and judgment. Further, in a few adults, the resulting implications on quality of life include an inability to obtain or sustain employment, and difficulties with social interactions. In addition, the submission noted "countless activities that affected patients are unable to do," although these were not described in further detail. The submission also revealed the "Herculean" effort that parents face in administering current therapies to their children due to the "horrible and noxious" taste of the treatments. Specifically, it highlighted the emotional challenges that parents (and other caregivers) face, including developing negative coping mechanisms, as well as concerns that their children will become mistrustful of parents, caretakers, or school staff, and develop behaviours to avoid receiving and/or administering the drug therapy. Parents of affected children sometimes have to resort to physical confrontations, especially with respect to administering the drugs multiple times over a day. In response, families often elect for gastric tube placement.

3. Current Therapy-Related Information

The submission mentioned two current therapies: sodium phenylbutyrate (NaPB) and sodium benzoate. NaPB is accessible as Buphenyl (US) or Ammonaps (Europe). It highlighted serious challenges with these therapies, specifically with regard to burden of administration and tolerability associated with NaPB, which ultimately lead to non-compliance. In young children, the noxious taste of existing treatments often causes gagging and vomiting, which leads to the need for placement of gastric tubes to administer the drugs. This could lead to children feeling socially isolated, as well as experiencing other issues, including feeling mistrust toward parents and food. Adults too are non-compliant with treatment

(e.g., missing doses, reducing doses on their own) due to the above burdens. The submission highlighted that the unmet needs of patients are improved taste and administration profiles, affordability, and accessibility.

4. Expectations About the Drug Being Reviewed

According to the NUCDF, the information presented below was gathered through individual correspondences with patients using Pheburane as well as their families, published medical literature, and product development information.

According to the submission, it is expected that Pheburane's improved administration profile and taste-masked formulation will improve compliance with the drug, optimize control of the disorder, and ultimately improve the lives of patients and their caregivers. This would involve fewer hospital visits; reduced burden on caregivers, including less time off work; and a reduction in associated health care costs. Pheburane is not anticipated to be associated with any serious adverse effects, and the NUCDF did not reporting receiving any reports of negative effects from patients, families, or physicians.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 17, 2015
Alerts:	Bi-weekly search updates until March 16, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. *Arylbutyric Acid Derivative/
2. (sodium phenylbutyrate or 4-phenylbutyric acid or 1- phenylbutyric acid or 4-phenylbutanoic acid or AI3-12065 or benzenebutyric acid or EINECS 217-341-8 or gamma-phenylbutyric acid or NSC 295 or omega-phenylbutanoic acid or benzenebutanoic acid or butyric acid, 4-phenyl).ti,ab,kw.

MULTI-DATABASE STRATEGY

3. (buphenyl or pheburane or ammonaps or phenylbutyrate* or TriButyrate or NaPBA).ti,ab,kw.
4. (NSC 657802 or NSC657802 or NT6K61736T).ti,ab,kw.
5. 1 or 2 or 3 or 4
6. exp Urea Cycle Disorder/
7. Hyperammonemia/ or Argininosuccinate Synthase/ or Ornithine Carbamoyltransferase/ or Ornithine Transcarbamylase Deficiency/
8. Urea/ or Ammonia Blood Level/ or Urea Nitrogen Blood Level/
9. (urea or hyperammon?emi* or citrullin* or CTLN or argininosuccin* or arginase or arginosuccin* or ASAuria or inborn error* or ornithin* or ammonia or nitrogen or arginine).ti,ab.
10. ((carbamylphosphate or carbamyl phosphate or carbamoyl phosphate or carbamoylphosphate or CPS1 or N-acetylglutamate or N-acetyl glutamate or NAGS or ASS) adj1 synthetase).ti,ab.
11. ((citrin or CPSID or NICCD or ARG or ASL or OTC or ASA or ONRT 1) adj1 deficien*).ti,ab.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12
14. conference abstract.pt.
15. 13 not 14
16. 15 use oemezd
17. Phenylbutyrates/
18. (sodium phenylbutyrate or 4-phenylbutyric acid or 1- phenylbutyric acid or 4-phenylbutanoic acid or AI3-12065 or benzenebutyric acid or EINECS 217-341-8 or gamma-phenylbutyric acid or NSC 295 or omega-phenylbutanoic acid or benzenebutanoic acid or butyric acid, 4-phenyl).ti,ab,ot,sh,hw,nm,kf.
19. (buphenyl or pheburane or ammonaps or phenylbutyrate* or TriButyrate or NaPBA).ti,ab,ot,sh,hw,nm,kf.
20. (NSC 657802 or NSC657802).ti,ab,ot,sh,hw,nm,kf.
21. NT6K61736T.ti,ab,ot,sh,hw,nm,kf,rn.
22. (1716-12-7 or 1821-12-1 or 7WY7YBi87E).rn,nm.
23. 17 or 18 or 19 or 20 or 21 or 22
24. exp Urea Cycle Disorders, Inborn/ or Hyperammonemia/ or Argininosuccinate Synthase/
25. Urea/ or Ammonia/blood or Nitrogen/blood
26. (urea or hyperammon?emi* or citrullin* or CTLN or argininosuccin* or arginase or arginosuccin* or ASAuria or inborn error* or ornithin* or ammonia or nitrogen or arginine).ti,ab,ot,sh,hw,nm.
27. ((carbamylphosphate or carbamyl phosphate or carbamoyl phosphate or carbamoylphosphate or CPS1 or N-acetylglutamate or N-acetyl glutamate or NAGS or ASS) adj1 synthetase).ti,ab,ot,sh,hw,nm.
28. ((citrin or CPSID or NICCD or ARG or ASL or OTC or ASA or ONRT 1) adj1 deficien*).ti,ab,ot,sh,hw,nm.
29. 24 or 25 or 26 or 27 or 28
30. 23 and 29
31. 30 use pmez
32. 16 or 31
33. exp animals/
34. exp animal experimentation/ or exp animal experiment/
35. exp models animal/
36. nonhuman/
37. exp vertebrate/ or exp vertebrates/

MULTI-DATABASE STRATEGY
38. animal.po.
39. or/33-38
40. exp humans/
41. exp human experimentation/ or exp human experiment/
42. human.po.
43. or/40-42
44. 39 not 43
45. 32 not 44

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 11, 2015
Keywords:	Pheburane (sodium phenylbutyrate) and urea cycle disorders
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Lichter-Konecki et al. 2011[51]	Study design
Smith et al. 2013[52]	
Kibleur et al. 2014[5]	
Guffon et al. 2012[34]	
Diaz et al. 2013[53]	Wrong intervention

APPENDIX 4: PUBLICATIONS OF US FDA INVESTIGATIONAL NEW DRUG AND NEW DRUG APPLICATION STUDY

Aim

To summarize the findings of the three publications of the US FDA Investigational New Drug and New Drug Application (IND/NDA) Study.

Findings

Three publications were identified presenting data from the US FDA IND/NDA Study that were included in the main review (Maestri et al. 1991, 1995, 1996).[28-30] These publications presented data from specific subgroups of patients and grouped patients treated from all protocols together. One publication presented results in patients who were prospectively treated from birth (Maestri et al. 1991).[28] One publication presented data for patients with argininosuccinate synthetase (ASS) deficiency (Mastri et al. 1995).[29] One publication presented data for females with ornithine transcarbamylase (OTC) deficiencies (Maestri et al. 1996).[30]

The results presented here differ from the results presented in the main report due to different time frames of follow-up and the different subgroups of patients who were analyzed.

The protocols used in the US FDA IND/NDA Study were as follows:

Protocol I

In the first protocol, patients received 250 mg/kg/day sodium benzoate as maintenance therapy (protocol I) prior to 1984.

Protocol II

The second protocol added 250 mg/kg/day sodium phenylacetate (NaPA) (protocol IIa) in 1984 or 250 mg/kg/day sodium phenylbutyrate (NaPB) (protocol IIb) in 1985 as maintenance therapies, to be taken in combination with 250 mg/kg/day sodium benzoate. NaPB was administered as tablets or granules.

Protocol III

The dosing regimen for NaPA and NaPB was modified in 1987 to 450 to 600 mg/kg/day (protocol III), during which sodium benzoate was no longer administered.

All treatment protocols included natural protein and calories for all patients, and essential amino acids for patients with a carbamoyl phosphate synthetase I (CPSI) or OTC deficiency. Arginine freebase was administered to all patients. All patients received hemodialysis or hemofiltration during episodes of hyperammonemia.

Prospectively Treated From Birth (Maestri et al. 1991)[28]

From 1981 to 1988, a total of 32 parents agreed to have their at-risk fetus (two ASL, four ASS, six CPSI, and 20 OTC) treated prospectively from birth. The identification of fetuses at risk for a UCD was based on the diagnosis of a previously affected sibling with neonatal onset. After birth, a priming infusion of sodium benzoate and sodium phenylacetate (250 mg/kg each) and arginine was given to patients with deficiencies of OTC, CPSI, and ASS. If the infant had plasma ammonia levels within normal limits after

24 to 48 hours of life, an amino acid protein infusion was administered. If plasma ammonia levels remained normal, protein intake can be increased. Patients with ASL deficiencies were given arginine. All patients were given glucose and lipids to sustain an appropriate total daily caloric intake.

A UCD was ruled out in 17 at-risk neonates based on plasma citrulline and ammonia levels. Three OTC infants died during the neonatal period and 12 infants with symptomatic UCD (one ASL, three ASS, three CPSI, five OTC) survived the neonatal period free of hyperammonemia and developmental delay. The ASL patient received arginine as maintenance therapy. The three ASL and three CPSI patients all did receive protocol 3 regimens for a period of time, which may have included NaPB. Only one OTC patient received protocol 3 regimens.

Of the 12 survivors, three died (one CPSI, two OTC) at seven months, 33 months, and 46 months of life during a hyperammonemic episode that did not respond to treatment. The patients who died at seven and 33 months were treated with sodium benzoate only. No patients with ASS or ASL deficiency died.

All patients experienced intercurrent hyperammonemic episodes. Plasma ammonia and glutamine levels were not reported.

Standardized tests used to assess cognitive development were not specified. Children who appeared to be developing normally were tested less frequently than children who showed evidence of developmental delay. Nine of the 12 patients who survived the neonatal period had evidence of developmental delay, and almost all reported problems with expressive or receptive language.

The weight of the ASL patient was at or above average after one year. In most patients with CPSI deficiencies, weights fell between the fifth and 50th percentiles. There was no apparent relationship between weight and outcome in patients with OTC deficiencies. No patients had height measurements above the mean for age.

Argininosuccinate Synthetase Deficiencies (Maestri et al. 1995)[29]
From 1979 to 1989, 23 infants were born who had ASS deficiencies diagnosed within the first month of life and were rescued from hyperammonemic coma and maintained on therapeutic protocols from birth (23 white, two Hispanic, one black, five unknown or mixed). One patient was enrolled just before age five years, after being identified as at risk on the basis of an affected older sibling. These 24 patients were enrolled in institutions across the US and Canada.

Fourteen patients were born before 1984 and initially treated with oral sodium benzoate therapy. Nine patients were born between 1983 and 1989 and initially given sodium benzoate with NaPA. At age five years, patients' cumulative survival was 87.5%, and at 10 years, the survival was 72%.

All patients had intercurrent episodes of hyperammonemia, often associated with viral or bacterial infections. The average frequency was 0.9 episodes per patient-year. The frequency of hyperammonemic episodes varied between protocols, with a higher frequency of episodes on treatment with sodium benzoate alone (1.4 episodes/patient-year) compared with NaPA alone (0.4 episodes/patient-year) and NaPB alone (0.7 episodes/patient-year) (Table 8).

TABLE 8: HYPERAMMONEMIC EPISODES DURING TREATMENT PROTOCOLS

Protocol	N	Total Hyperammonemic Episodes	Patient-Years of Treatment	Frequency (Episodes per Patient-Year)
I (NaB)	12	41	29.3	1.4
IIa (NaB+NaPA)	22	71	74.7	1.0
IIIa (NaPA)	8	3	7.0	0.4
IIb (NaB+NaPB)	7	18	25.9	0.7
IIIb (NaPB)	18	52	71.7	0.7
Total	-	185	208.6	0.9

NaB = sodium benzoate; NaPA = sodium phenylacetate; NaPB = sodium phenylbutyrate.
Source: Maestri et al. 1995.[29]

Of the 15 surviving patients, 12 had plasma ammonia levels in the neonatal period ranging from 400 to 2,000 µmol/L, which resulted in coma for 24 to 168 hours. Eleven patients had intelligence quotient (IQ) measurements < 55 at age eight years (severely mentally retarded). One patient had an IQ of 80 at age 3.5 years, but declined to 55 at age eight years. Among three patients who had neonatal ammonia levels ranging from 266 to 396 µmol/L, two had earlier IQ measurements between 75 and 100, which then decreased to 50 and 70, as did the third patient.

All patients had normal anthropometric measurements at birth. The height-for-age z scores of patients were consistent with time, with approximately two standard deviations (SDs) below the mean, indicating inadequate nutritional intake. The weight-for-age z scores fluctuated over time between 1.2 and 1.9 SDs of the mean.

The most recently taken mean plasma glutamine level in the 15 surviving patients was 688 (SD 246) µmol/L and 95% of the values were less than 1,080 µmol/L.

Ornithine Transcarbamylase Deficiencies in Females (Maestri et al. 1996)[30]
From 1979 to 1990, 39 girls younger than 18 years across North and South America with a confirmed diagnosis of OTC deficiency were enrolled in the study (33 white, three Hispanic, one black, two mixed or ethnic). The girls ranged in age from one to 17 years (median five). Of the 39 patients, seven withdrew before five years of follow-up, and data on the 32 remaining patients are presented.

There were three deaths during the study, two of which occurred during a hyperammonemic episode.

After enrolment, 23 patients had episodes of hyperammonemia requiring hospitalization. The patients receiving NaPA or NaPB (protocol 2 or 3) had fewer episodes than patients receiving sodium benzoate alone (protocol 1) (Table 9). The frequency of episodes declined with increasing age, with patients younger than five years having a frequency of 1.0 episodes per patient-year, and patients older than five years having a frequency of < 0.5 episodes per patient-year.

TABLE 9: HYPERAMMONEMIC EPISODES DURING TREATMENT PROTOCOLS

Protocol	N	Total Hyperammonemic Episodes	Patient-Years of Treatment	Frequency (Episodes per Patient-Year)
I	11	25	35	0.7
II	22	32	81	0.4
III	28	76	165	0.5
Total	**61**	**133**	**281**	**0.5**

NaB = sodium benzoate; NaPA = sodium phenylacetate; NaPB = sodium phenylbutyrate.
Source: Maestri et al. 1996.[30]

Standardized intelligence tests were administered to 23 patients at least twice. The initial test scores ranged from 56 to 111 (mean 84), with 10 girls scoring below 80. At follow-up, the scores ranged from 36 to 116. The correlation between follow-up and initial scores was 0.9 ($P < 0.001$). Only four patients had decreases in IQ scores that exceeded 15 points. The change in IQ was not affected by the length of the interval between tests, the age at first testing, initial IQ score, or the number of years of treatment.

The mean (SD) birth weight of patients at enrolment was 3.8 (0.8) kg. The mean weight-for-age and height-for-age z scores were below the national mean, but remained relatively constant with increasing age. The mean z scores were all less than one SD from the mean.

Mean glutamine levels were not reported in this publication.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize evidence that evaluates the extent to which ammonia and glutamine levels correlate with clinical outcomes among patients with urea cycle disorders (UCDs).

Findings

Four studies were identified that investigated the relationship between ammonia levels and clinical outcomes among patients with UCDs.

Bachmann et al. (2003) evaluated 88 patients (41 females) with UCD in Switzerland.[35] The most common UCDs were ornithine transcarbamylase (OTC) deficiency – hemizygous (20%), OTC deficiency — heterozygous (20%), citrullinemia type I (16%), and argininosuccinic aciduria (16%). Forty-four patients (50%) received conservative long-term management using protein restriction, while the other half received protein restriction combined with more extensive therapy; i.e., arginine and citrulline, essential amino acid supplements, and sodium benzoate as alternate pathway therapy. The authors concluded that all patients with normal developmental outcome had initial ammonia concentrations less than 300 µmol/L and peak ammonia concentrations less than 480 µmol/L. The authors did not describe the manner in which they evaluated psychomotor outcome; instead, they classified patients as "normal," "retarded," and "dead."

Uchino et al. (1998) evaluated 108 patients with UCD in Japan.[15] No information was provided about the demographic or disease characteristics of the patients. The researchers noted that patients did not develop severe neurological damage when their peak blood ammonia concentration during the initial hyperammonemic episode was less than 180 µmol/L, but when it exceeded 350 µmol/L, all patients sustained severe brain damage or died. Patients whose peak ammonia concentration ranged from 180 µmol/L to 350 µmol/L had variable outcomes. The authors did not describe the manner in which they evaluated cognitive outcome.

Msall et al. (1984) studied 26 children with inborn errors of urea synthesis who survived neonatal hyperammonemic coma in the United States.[39] The distribution of patients by enzyme deficiencies were as follows: three patients with carbamoyl phosphate synthetase, seven with OTC, eight with argininosuccinate synthetase, and eight with argininosuccinase. The age of the children ranged from 12 to 74 months. Two patients with deficiencies in OTC died of hyperammonemic coma before one year of age. The researchers did not find a statistically significant correlation between peak ammonium level (351 to 1800 µmol/L) and intelligence quotient (IQ) scores at 12 months, as measured by the Bayley Scales of Infant Development among those aged six to 30 months, Stanford–Binet Scales among those aged 30 to 54 months, and Wechsler Preschool and Primary Scale of Intelligence among those aged 54 to 74 months. They conducted IQ testing at least six months after the neonatal hyperammonemic episode and during a period of normal or nearly normal ammonium levels — i.e., less than 60 µmol/L.

Kido et al. (2012) studied 151 patients with UCD in Japan.[44] No information was provided about the demographic or disease characteristics of the patients. Overall, they found that among the 77 patients whose maximum ammonia concentration during the first hyperammonemic attack was less than 360 µmol/L, no patient died. Further, of the 74 patients with a maximum ammonia concentration greater than 360 µmol/l, 11 (15%) died, 38 (51%) developed mental retardation, 11 (15%) did not develop mental retardation but had abnormal brain computed tomography (CT) and magnetic resonance imaging (MRI) results or an abnormal electroencephalogram (EEG), and six (8%) did not develop mental retardation and had normal brain CT and MRI images and a normal EEG. There were eight (11%) patients for whom information about mental retardation was unknown.

APPENDIX 6: SUMMARY OF PHEBURANE BIOEQUIVALENCE STUDY

Objective

To summarize the results of a randomized, open-label, crossover study between Pheburane and a marketed sodium phenylbutyrate (NaPB) formulation.[34]

Study Population

The study enrolled 14 healthy Caucasian participants, of whom six were females. The overall mean (SD) ages for females were 36.0 (13.9) and 21.5 (2.8) years, respectively. One female participant withdrew due to an adverse event (vomiting) after receiving the marketed NaPB. A single 5 g oral dose of Pheburane was administered in these participants.

Results

The drug dissolution tests demonstrated that the marketed NaPB formulation was released completely within 60 seconds, whereas Pheburane had a lag time of 10 seconds before being released slowly and progressively (60%) over the eight-minute test. According to the authors, "This delay should prevent interaction of NaPB with the taste receptors in the mouth, indicating typical taste-masking properties."

The in vitro taste assessment (using an "electronic tongue") revealed that marketed NaPB formulation is mainly characterized as bitter, sour, salty, and astringent.

Table 10 presents the results of the pharmacokinetic analyses of Pheburane versus the marketed NaPB formulation.

TABLE 10: RESULTS OF PHARMACOKINETIC ANALYSES OF PHEBURANE VERSUS MARKETED NAPB FORMULATION

Pharmacokinetic Parameter	Pheburane	Marketed NaPB Formulation	Statistical Analysis (94.12% CI)[a]
C_{max} (µg/mL)			
Mean (SD)	212.4 (46.6)	225.2 (49.3)	NS (87.0 to 102.3)
Median (range)	218 (137 to 318)	218 (146 to 326)	
T_{max} (h)			
Mean (SD)	0.75 (0.23)	0.5 (0.25)	NS (*P* = 0.5205)
Median (range)	0.75 (0.5 to 1.25)	0.5 (0.25 to 1.25)	
AUC_{0-t} (mcg/mL·h)			
Mean (SD)	445.4 (172.4)	464.9 (190.4)	NS (90.34 to 101.19)
Median (range)	445.3 (234.9 to 809.5)	476.8 (265.5 to 867.1)	
$AUC_{0-\infty}$ (mcg/mL·h)			
Mean (SD)	448.2 (171.9)	466.9 (190.4)	NS (90.80 to 101.08)
Median (range)	446.4 (235.6 to 810.5)	481.8 (267.2 to 867.7)	

AUC = area under the plasma concentration-time curve; CI = confidence interval; C_{max} = maximum concentration; h = hour; NaPB = sodium phenylbutyrate; NS = not significant; SD = standard deviation; T_{max} = time to maximum plasma concentration.
[a] CI adjusted for multiple testing.
Source: Guffon N, Kibleur Y, Copalu W, Tissen C, Breitkreutz J. Developing a new formulation of sodium phenylbutyrate. Arch Dis Child. 2012 Dec;97(12):1081-5.

The authors reported that the confidence intervals (above) were within the acceptable bioequivalence standard range of 80% to 125%.

The authors also evaluated the taste of the two drugs in the study population at various times after ingestion, including immediately after, 0.5 hours after, and two hours after. They reported using a taste test questionnaire, although they did not provide details about its properties, including the range of possible scores, or its psychometric properties, in the report.

TABLE 11: RESULTS OF TASTE PARAMETER SCORES BETWEEN PHEBURANE AND MARKETED NAPB FORMULATION

Taste Parameter	Difference in Scores (Test – Reference)[a] (95% CI)
Acceptability	–34.25 (–56.79 to –11.71)
Bitterness	–47.93 (–62.20 to –33.65)
Saltiness	–30.88 (–49.26 to –12.50)

CI = confidence interval; NaPB = sodium phenylbutyrate.
[a] Test agent was Pheburane; reference was the marketed NaPB formulation.
Source: Guffon et al.[34]

The authors noted that, after taking the marketed NaPB formulation, five participants experienced a loss of taste perception (ageusia), and one participant experienced severe vomiting that led to study withdrawal.

Conclusions

Overall, based on the results, the authors concluded that the two drugs were bioequivalent "with respect to the rate and extent of absorption of phenylbutyrate."

External Review

An assessment of the study by the European Medicines Agency did not identify any issues with respect to safety or pharmacokinetic properties of Pheburane versus the licensed NaPB formulation.

APPENDIX 7: SUMMARY OF COHORT UTILIZATION AUTHORIZATION PHEBURANE STUDY

Background

In France, the cohort temporary utilization authorization (ATU) is a program that provides access to drugs not approved for marketing. In September 2012, the French National Agency of Medicine granted a cohort ATU for Pheburane. The main inclusion criterion into the cohort ATU was the unacceptability of any of the marketed sodium phenylbutyrate (NaPB) formulations. Specifically, patients were eligible if they could not take the drug or required additional measures to facilitate administration; e.g., nasogastric tubing.

The purpose of the study by Kibleur et al. (2014) was to report the findings of patients who received Pheburane via the cohort ATU between October 2012 and October 2013.[5] The authors also report some of the results of a bioequivalence study — by Guffon et al. (2012) — of Pheburane versus the granule formulation of NaPB.[34] This study is summarized (in greater detail) separately in Appendix 6.

Original Publication From Kibleur et al.

Patient Demographics

Twenty-five patients were enrolled in the cohort ATU to receive Pheburane following unacceptability of any of the marketed NaPB formulations. The mean (SD) age at enrolment was 12.6 (13.0) years. The distribution of patients by type of enzyme deficiency was as follows: 15 with ornithine transcarbamylase (OTC), five with argininosuccinate synthetase (ASS), two with carbamoyl phosphate synthetase I (CPSI), and one each with argininosuccinate lyase (ASL), hyperornithinemia-hyperammonemia-homocitrullinuria (HHH), and lysinuric protein intolerance. Sixteen patients were female, eight were male, and gender information for one patient was not available. In the cohort ATU, Pheburane was given orally at doses between 1.5 g and 15 g per day (mean dose of 5.2 g) for one to 11 months. Follow-up data were available for 20 patients.

Fourteen individuals participated in the bioequivalence study, which, in brief, was an open-label crossover study in which healthy volunteers received Pheburane and the marketed NaPB formulation. One participant withdrew after receiving the licensed NaPB. A single 5 g oral dose of Pheburane was administered in these participants.

Results

The authors reported the results of several effectiveness outcomes among patients in the cohort ATU, as well as the participants of the bioequivalence study.

1. Acceptability and Other Measures of Taste Characteristics

In the bioequivalence study, there was a statistically significant increase in ratings of acceptability (as measured by the 100 mm visual analogue scale [VAS]) when participants received Pheburane versus the marketed NaPB formulation ($P < 0.05$). Table 12 presents the acceptability and bitterness ratings on the 100 mm VAS among patients in the cohort ATU and healthy volunteers in the bioequivalence study who received both formulations.

TABLE 12: ASSESSMENT OF ACCEPTABILITY AND OTHER MEASURES OF TASTE CHARACTERISTICS

	Marketed NaPB	Pheburane
Acceptability rating (100 mm VAS)		
Cohort ATU patients (n = 25)		
N[a]	9	
Mean (SE)	17 (7)	85 (1)
Healthy volunteers		
N	14	
Mean (SE)	42 (1)	78 (8)
Bitterness rating (100 mm VAS)[b]		
Healthy volunteers (n = 14)		
N	14	
Mean (SE)	55 (2)	11 (6)

ATU = utilization authorization; NaPB = sodium phenylbutyrate; SE = standard error; VAS = visual analogue scale.
[a] Patients receiving doses of 2.5 g to 10 g per day.
[b] Not assessed in cohort ATU patients.
Source: Kibleur et al. 2014[5]

According to the authors of the study, all 25 patients in the cohort ATU reported that the marketed NaPB formulation was unacceptable. Further, they stated that four patients reported it was "totally impossible" to take the marketed NaPB formulation. One patient in the cohort ATU discontinued due to issues with granularity of Pheburane.

In the bioequivalence study, while receiving the licensed NaPB formulation, five of 14 participants reported taste disturbances, and one individual reported severe vomiting — this was the same participant who withdrew from the study. None of the 13 participants who received Pheburane reported any disturbances or vomiting. In the cohort ATU, no patient reported any adverse events following administration of Pheburane, whereas four patients complained of vomiting reflexes while receiving the marketed NaPB formulation.

2. Ease of Administration

Among the 25 patients in the cohort ATU, two patients required the licensed NaPB product to be reformulated into capsules, four required administration via a nasogastric tube, and one required administration via gastronomy. Conversely, none of the patients receiving Pheburane required additional measures for administration.

No information on this outcome was presented for the bioequivalence study in this report.

3. Number of Hyperammonemic Episodes and Ranges of Biological Values (Ammonia, Glutamine)

In the cohort ATU, among 10 patients, there were 20 hyperammonemic episodes during the six-month period when receiving the marketed NaPB, whereas there were no episodes (in the same patients) up to 11 months after treatment with Pheburane. The median (interquartile range [IQR]) concentrations of plasma ammonia and glutamine were significantly higher when patients received the marked NaPB versus Pheburane, as follows: ammonia (marketed NaPB vs. Pheburane: 124 µmol/L [68 to 221] versus 49 µmol/L [39.5 to 54.5]; $P = 0.019$) and glutamine (marketed NaPB vs. Pheburane: 1,027 µmol/L [905 to 1,310] versus 845 µmol/L [707 to 1,075] $P = 0.028$).

No information on this outcome was presented for the bioequivalence study in this report.

Additional Follow-Up of Utilization Authorization Cohort

A long-term follow-up was conducted in eight of the original 25 patients in the French cohort ATU.[54] The follow-up comprised unsystematic clinical examinations that were scheduled every six to 12 months. Three of the patients had OTC deficiency, three had ASS deficiency, one had CPSI deficiency, and one had HHH. Their mean (SD) age and weight were 9.1 (4.7) years and 25.4 (12.0) kg, respectively. Three of the patients were female. At the latest follow-up, Pheburane was administered between eight and 30 months, and the mean (SD) daily dose was 5.6 g (2.7). The mean (SD) exposure to Pheburane was 13.6 (5.0) patient-years. The results indicated that neurological status was normal in all patients, but mild cognitive delays were reported in four patients. Among the six patients for whom staturo-pondéral data were available, the results indicated, according to the authors, a "slow by steady growth in weight, height, and body surface area." No decompensation episodes occurred among the eight patients. The median (IQR) maximal plasma ammonal levels significantly decreased among the eight patients, from 115 (75 to 185) µmol/L (at the beginning of the ATU) to 49 (40 to 55) µmol/L (at the end of the ATU) to 45 (30 to 76) µmol/L (at the latest follow-up) (P = 0.039, Wilcoxon test). The median (IQR) maximal glutamine ammonal levels decreased among the eight patients, from 995 (898 to 1,098) µmol/L (at the beginning of the ATU) to 845 (707 to 1,045) µmol/L (at the end of the ATU) to 593 (478 to 975) µmol/L (at the latest follow-up), although the changes were not significant (P = 0.1, Wilcoxon test). The researchers did not report any adverse effects among the eight patients during the long-term follow-up period.

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