# CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

## SODIUM PHENYLBUTYRATE
## (Pheburane — Médunik Canada)
## Indication: Urea Cycle Disorders

This document was originally issued on May 16, 2016 and was revised on June 6, 2016 to correct an error in the Cost and Cost-Effectiveness section.

**Recommendation:**
The CADTH Canadian Drug Expert Committee (CDEC) recommends that sodium phenylbutyrate (NaPB) be listed as adjunctive therapy in the chronic management of urea cycle disorders (UCDs), involving deficiencies of carbamoyl phosphate synthetase I (CPSI), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS) in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.

**Reasons for the Recommendation:**
1. In one single-arm, open-label phase 3 trial in patients with UCDs, a lower mortality rate was reported in the setting of patients requiring neonatal rescue from hyperammonemic states with NaPB, compared with mortality rates reported in historical data from untreated patients. Although some of the improved survival may be due to improved supportive care, the magnitude difference suggests that NaPB has a mortality benefit.
2. The manufacturer provided a pharmacokinetic study that demonstrated bioequivalence between Pheburane and the uncoated formulation used in the pivotal study.
3. NaPB is the only Health Canada–approved treatment for UCDs. At the submitted price, the cost consequence of using NaPB appears to be similar to that of an alternative formulation of NaPB currently in use in Canada through the Special Access Programme (SAP). However, the true relative cost-effectiveness of these products cannot be determined based on available data.

**Of Note:**
- CDEC noted that the availability and method of reimbursement of Buphenyl is variable across jurisdictions. The continued availability of Buphenyl through the SAP is now uncertain, with the availability of Pheburane in Canada.

**Background:**
UCDs result from genetic mutations that cause defects in any of the enzymes of the urea cycle, which are responsible for the metabolism of nitrogen. Deficiencies in the urea cycle may result in hyperammonemia, which can be life-threatening and result in permanent neurological damage if left untreated. NaPB is a prodrug that is metabolized to sodium phenylacetate, which then conjugates to glutamine to form phenylacetylglutamine, providing an alternate route of nitrogen elimination.

NaPB 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 EU). NaPB is not recommended for the management of acute hyperammonemia.

**Summary of CDEC Considerations**
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of pivotal studies of NaPB, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with UCDs.

**Patient Input Information:**
The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- Patients with UCDs suffer progressive cognitive impairment due to hyperammonemic episodes, which include problems focusing, limited attention span, impulsive behaviours, and lack of judgment. UCDs also have a negative impact on the ability of adults to obtain or sustain employment and engage in social interactions.
- Parents experience great difficulty in administering medication to children due to the unpalatable taste of current therapies, particularly uncoated NaPB. Adult patients also find the taste unpalatable and sometimes decide to skip doses.
- Parents of patients and patients themselves who have used NaPB (Pheburane) report much greater tolerability than with uncoated NaPB and anticipate that the coated formulation will result in improved levels of adherence.

***Clinical Trials***
One phase 3, open-label, single-arm study conducted in the US and Canada as part of the US FDA Investigational New Drug and New Drug Application programs (US FDA IND/NDA Study) that spanned a time period of 15 years (1981 to 1996) was considered pivotal by Health Canada and was included in this review. Prospective FDA-approved therapeutic protocols were implemented and modified as new drugs became available. NaPB (Buphenyl; uncoated formulation) was introduced in 1985, and 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. 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.
Patients enrolled in this study had deficiencies in OTC (67%), ASS (21%), and CPSI (12%). A total of 39% of 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 of age at the time of the last visit to the investigator and 15% of patients had received NaPB for at least five years.

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 defined outcomes a priori, the lack of standardized data collection methods, poor reporting, and the use of the uncoated formulation of NaPB instead of the coated formulation being reviewed. The manufacturer conducted a study (LUC10001; N = 14) to demonstrate bioequivalence of the coated formulation of NaPB (Pheburane) to the uncoated formulation (Buphenyl) that was used in the pivotal trial. In addition, a French study (ATUc) was conducted in a cohort of UCD patients (N = 25) who could not tolerate the uncoated formulation of sodium phenylbutyrate (Ammonaps) and who were granted access to Pheburane.

***Outcomes***

No primary or secondary outcomes were defined in the US FDA IND/NDA Study. The outcomes that were reported included mortality, incidence of hyperammonemic episodes, cognitive development, anthropometric measurements, and plasma levels of ammonia and glutamine. No definition of hyperammonemia was reported. Cognitive development was evaluated using intelligence quotient (IQ) measurement scales when possible.

***Efficacy***

- Of patients treated with NaPB alone between 1985 and 1994 (Cohort 1), 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. Of the 82 patients treated with NaPB alone between 1985 and 1996 (Cohort 2), 18 died during a hyperammonemic episode and 15 of these patients were neonatal-rescue patients.
- 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.
- 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. Height and weight values were not reported.

- 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. 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 of age (> 1,000 µmol/L).
- In the French ATUc study that enrolled UCD patients (N = 25) who could not tolerate the taste-unmasked formulation of NaPB (Ammonaps), patients rated the "acceptability" of the taste-masked formulation (Pheburane) as higher than Ammonaps.

***Harms (Safety and Tolerability)***

- In the US FDA IND/NDA Study, a total of 102 patients (56%) reported at least one adverse event. Safety data were obtained from investigator case reports and were dependent on spontaneous reporting. Instruments such as questionnaires or diaries were not used. Serious adverse events were not differentiated from adverse events in the reports.
- A total of 13 patients (7%) withdrew from the study due to poor compliance or upon a parent's request, 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 and included hyperactivity, speech disorder, seizures, and mental retardation. However, it is unclear whether these were attributable to the neurological effects of the disease. Amenorrhea was reported in 23% of menstruating women. Decreased appetite was reported in 4% of patients, body odour in 3%, and bad taste and taste aversion in 3%.

***Cost and Cost-Effectiveness***

The manufacturer submitted a cost-consequence analysis (CCA) comparing Pheburane (NaPB) to Buphenyl (NaPB) and Ravicti (glycerol phenylbutyrate), over a 25-year time horizon from the perspective of a Canadian Ministry of Health. The manufacturer assumed equivalent clinical efficacy of Pheburane and Buphenyl, based on a bioequivalence study, and Ravicti and NaPB formulations, based on results of non-inferiority trials. Ravicti is currently being reviewed by Health Canada. Based on the assumption of equal harms and efficacy, the manufacturer concluded that Pheburane is expected to cost between $35,674 and $54,752 per patient per year, depending on patients' age and weight. Pheburane is expected to result in cost savings between $3,913 and $6,061 per patient per year compared with Buphenyl, and $74,899 and $115,873 per patient per year compared with Ravicti, if Ravicti costs the same in Canada as in the US.

CDR identified the following key limitations with the manufacturer's economic submission:

- The model was based on a primary assumption of equal efficacy and harms among the treatments; this assumption effectively rendered the submitted analysis a cost-minimization analysis.

- The costs of each treatment were based on drug acquisition costs and total hospitalization costs. It was unclear what resources and costs were included within hospitalization costs.
- The manufacturer relied on the survival and hospitalization information from the study by Enns et al. (2007), a 25-year study of intravenous Ammonul (NaPB and sodium benzoate) for in-patient treatment of acute hyperammonemic episodes, to inform the effects of NaPBs and Ravicti on hyperammonemia. The study investigated a different product that was administered intravenously in hospital, Ammonul, which is indicated for the treatment of acute hyperammonemia, while Pheburane is an oral product that is indicated for chronic management of UCDs. The clinical expert indicated that Pheburane is not considered a rescue medication for UCDs in clinical practice and that rescue doses of Ammonul as used in the Enns study were considered to be double the expected dosage for Pheburane. The use of efficacy data for Ammonul to inform that of other drugs is highly uncertain.
- The cost per hospitalization used by the manufacturer in the analysis was $8,503, which was considered low by the clinical expert.
- The manufacturer assumed that 10.38% of patients will not survive the index hyperammonemic episode when treated with Pheburane, Buphenyl, or Ravicti. The clinical expert felt that this percentage is likely much higher.
- The manufacturer based the cost of Ravicti on US sources. It is unknown how the price of Ravicti in Canada will compare with that of the US.

Due to limited information, CDR was unable to conduct reanalyses to address the identified limitations. CDR was able to validate the analyses presented by the manufacturer.

At the submitted price of $0.01919 per mg ($1,612.80 per 174 g bottle), considering drug acquisition cost only, Pheburane ($10,401 to $140,087 per patient per year, depending on dosage and patient weight) may be less expensive than Buphenyl ($11,599 to $156,220 per patient per year).

**Research Gaps:**
CDEC noted that there is insufficient evidence regarding the following:

- The trial included did not prospectively define outcomes, nor have a standardized protocol for collecting data on outcomes of interest.
- The trial included did not use the formulation under review in the assessment of the impact of NaPB on clinical outcomes.
- The relative tolerability and associated adherence of available drugs is uncertain.

**CDEC Members:**
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

**March 16, 2016 Meeting**

**Regrets:**
Dr. Anatoly Langer, Dr. Harindra Wijeysundera.

**Conflicts of Interest:**
None

**About this Document:**
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH addressed the request in accordance with *the CDR Confidentiality Guidelines.*

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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