NEW DRUG APPROVAL

Brand Name	Pheburane®
Generic Name	sodium phenylbutyrate
Drug Manufacturer	Medunik USA, Inc

New Drug Approval

FDA approval date: June 17, 2022

Review designation: Standard; Orphan

Type of review: Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 216513

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Urea cycle disorders (UCDs) are inherited deficiencies in one or more of the enzymes involved in the urea cycle pathway. These deficiencies cause ammonia to build up in the body. UCDs are generally rare, with an overall incidence of at least 1:35,000 births. Signs and symptoms of UCDs depend heavily on which exact enzyme is involved. Enzymes that are involved earlier on in the urea cycle are more important, and thus a deficiency causes more severe symptoms that onset in the first few days of life. Symptoms can include failure to feed, hypothermia, cerebral edema, seizures, and coma. Deficiencies in less important enzymes in the cycle may not manifest until adulthood, when triggered by an eliciting event. Symptoms tend to be more subtle, like loss of appetite, lethargy, and vomiting.

UCDs are a type of inborn error in hepatic metabolism caused by the lack of enzymatic activities that control the transfer of nitrogen from ammonia to urea. With an average prevalence of at least 1 in 2500, these conditions often lead to lethal hyperglutaminemia and hyperammonemia. The manifestations of UCDs vary with independent of the age, although they are most probably to appear during the late infancy, neonatal stage, and at the time of puberty. Early signs are generally nonspecific, so it is crucial to regularly screen for hyperammonemia to determine a diagnosis rapidly and avoid complications. A disorder known as transient hyperammonemia of the newborn is of the differential diagnosis in neonates, while in older infants the defects of fatty acid oxidation may be taken into consideration.The toxic ammonia is eliminated by the urea cycle through renal excretion which is generated by the amino acid deamination by transforming it into nontoxic urea. If the urea cycle fails to function, ammonia builds up in the blood and thus causes impaired mental state, fatigue, cerebral edema, lethargy, and eventually, coma, and death

Efficacy

To date, two clinical trials have shown the results of the use of taste-masked NaPB granules in patients with UCD under a French-cohort temporary utilization authorization (ATU) protocol.43,44 In September 2012, the French medicines agency granted a cohort-ATU protocol for NaPB granules, allowing its use in UCD patients not able to tolerate the marketed product due to its unpalatability. NaPB granules were granted market authorization in the EU on July 31, 2013, and thus the last date for inclusion in the cohort-ATU protocol was October 31, 2013. In 2014, Kibleur et al published the results of the first French nationwide 1-year cohort study on 25 patients, of whom 21 were children. The aim of this study was to describe a nationwide system for premarketing follow-up of NaPB granules in France and to analyze safety and efficacy in this cohort of patients treated with UCDs. Most patients

joined the study due to major issues with the taste of the marketed formulations of NaPB, as indicated by the results from patients' surveys for assessment of palatability and ease or difficulty of administration of the available marketed drug. After just one dose of NaPB granules, taste and global acceptability evaluations indicated a dramatic increase in acceptability, a decrease in perceived bitterness, and an inverse correlation between general acceptability and bitterness compared with after one dose of the licensed marketed product. In addition, no patient in the ATU protocol reported any adverse event related to vomiting following administration of NaPB granules compared to when receiving marketed NaPB prior to entry into the cohort-ATU protocol. The absence of such vomiting reflex following drug intake with NaPB granules obviates the need for redosing and thus the risk of overdose or the risk of underdosing in those cases when the dose was not adequately readministered. Moreover, no additional measure, such as reformulation into capsules, was required to administer NaPB granules, which were taken orally in all patients in the ATU follow-up. This represents a dramatic improvement in care for these patients. The most important clinical outcome was the change in episodes of hyperammonemia. In the cohort-ATU protocol, the number of hyperammonemic episodes decreased from 20, as reported in ten licensed NaPB-treated patients in the previous 6 months, to 0 in the same patients treated with NaPB granules over a period of 3–11 months. Although the cohort-ATU protocol was not designed to collect any measurement of compliance or quality of life (QoL), analysis of the data indicated that the QoL of UCD patients and their families improved greatly with NaPB granules, as assessed on ease of administration and meaningfully reduced incidence of adverse events, notably vomiting and dysgeusia, which impair patients' well-being and/or their acceptance/compliance with pharmaceutical treatments.

In January 2016, Kibleur and Guffon reported the results of further follow-up of part of the original ATU-cohort protocol. The aim of this study was to describe the status of patients with UCDs at the latest long-term clinical follow-up of treatment with NaPB granules. Patients from the original ATU cohort were followed up every 6–12 months at one reference center. Long-term follow-up data supported the previously observed improvements in drug tolerability. Moreover, follow-up data also confirmed the protective effect of NaPB granules against metabolic decompensations. Indeed, in the long term, improved biochemical control, as assessed by an absence of episodes of clinical decompensation, reduction in plasma ammonia and glutamine levels, and improved neurocognitive and height:weight status, were observed in the group of patients treated with NaPB granules. This observed improved clinical status after long-term administration of NaPB granules may reflect efficacy and improved compliance with this tasteless formulation of NaPB, as well as indicating an improvement in patients' and their families' QoL, as expected with tasteless products. It is worth mentioning that the safety of NaPB granules was also confirmed from experience in other patients in Sweden and in Turkey who received the drug under a named patient program prior to marketing approval.

In 2015, Uçar et al reported on 1-year usage of NaPB granules in a case of late-onset ASL deficiency on a named patient program in Turkey. The family reported the child's refusal to eat or drink due to the taste and smell of NaPB, as well as their unsuccessful attempts to mask the taste of the drug in food. The consequences of the child not taking the medication added a significant burden to the stress already experienced by the parents, as indicated by their QoL score. For these reasons, the tasteless and odor-free formulation NaPB granules was prescribed. After 1 month of treatment, the patient became fully compliant with the drug. In addition, no hyperammonemia episodes occurred over 1 year of treatment. Moreover, a decrease in family stress and anxiety was observed, with QoL measurement indicating a significant improvement.

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence ≥ 3%) are menstrual dysfunction, decreased appetite, body odor and bad taste or taste aversion.

WARNINGS & PRECAUTIONS

- **Neurotoxicity of Phenylacetate**:
  Increased exposure to phenylacetate, the major metabolite of Pheburane®, may be associated with neurotoxicity in patients with UCDs. Consider reducing the dose if neurotoxicity symptoms are present.
- **Hypokalemia**:
  Renal excretion of phenylacetylglutamine may induce urinary loss of potassium. Monitor serum potassium during therapy and initiate appropriate treatment when necessary
- **Conditions Associated with Edema**:
  Calculate the total amount of sodium patients will be exposed to based on their weight or body surface area. If a patient develops new-onset edema or worsening edema while on treatment, discontinue administration of Pheburane® and initiate appropriate therapy.
- **Diabetes Mellitus, Hereditary Fructose Intolerance, Glucose Galactose Malabsorption or Sucrase-Isomaltase Insufficiency**:
  Avoid use of Pheburane® in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucraseisomaltase insufficiency.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Sodium phenylbutyrate is a pro-drug and is metabolized to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is excreted by the kidneys, hence providing an alternate vehicle for waste nitrogen excretion.

Dose & Administration

ADULTS

The recommended dosage measured as sodium phenylbutyrate is:

- Patients weighing < 20 kg: 450–600 mg/kg/day of sodium phenylbutyrate orally.
- Patients weighing ≥ 20 kg: 9.9–13.0 g/m2 /day of sodium phenylbutyrate orally.

PEDIATRICS

Refer to adult weight-based dosing.

GERIATRICS

Refer to adult weight-based dosing.

RENAL IMPAIRMENT

Monitor plasma ammonia levels when starting patients with impaired renal function on Pheburane®.

HEPATIC IMPAIRMENT

No studies with Pheburane® were conducted in subjects with hepatic impairment. Start at the lower end of the recommended dosing range and maintain patients with hepatic impairment on the lowest dose.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral pellets: 84 gm of sodium phenylbutyrate per bottle.