

PHEBURANE- sodium phenylbutyrate pellet
PHEBURANE- sodium phenylbutyrate
Medunik USA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PHEBURANE safely and effectively. See full prescribing information for PHEBURANE.

PHEBURANE[®] (sodium phenylbutyrate) oral pellets
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

PHEBURANE is a nitrogen-binding agent indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS). (1)

Limitations of Use

PHEBURANE is not indicated for the treatment of acute hyperammonemia. (1)

DOSAGE AND ADMINISTRATION

- PHEBURANE treatment should be supervised by a healthcare provider experienced in the treatment of UCDs. For administration, see full prescribing information. (2.1, 2.4)
- The recommended dosage measured as sodium phenylbutyrate is:
 - Patients weighing < 20 kg: 450–600 mg/kg/day of sodium phenylbutyrate orally. (2.1)
 - Patients weighing ≥ 20 kg: 9.9–13.0 g/m²/day of sodium phenylbutyrate orally. (2.1)
- Monitor plasma ammonia levels to determine the need for dosage adjustment. (2.2)
- Monitor patients for potential neurotoxicity. (2.2)
- For patients with hepatic impairment, start at the lower end of the recommended dosing range. (2.3)

DOSAGE FORMS AND STRENGTHS

Oral pellets: 84 g of sodium phenylbutyrate per bottle. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND 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. (5.1)
- Hypokalemia: Renal excretion of phenylacetylglutamine may induce urinary loss of potassium. Monitor serum potassium during therapy and initiate appropriate treatment when necessary. (5.2)
- 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. (5.3)
- 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 sucrase-isomaltase insufficiency. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 3%) are menstrual dysfunction, decreased appetite, body odor and bad taste or taste aversion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Medunik USA, Inc. at 1-844-884-5520 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Valproic Acid, Haloperidol, or Corticosteroids: May increase plasma ammonia level; monitor ammonia levels closely. (7.1)
- Probenecid: May inhibit renal excretion of metabolites of PHEBURANE including phenylacetate and phenylacetylglutamine; monitor for potential neurotoxicity. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Dosage Adjustment and Monitoring
- 2.3 Dosage Adjustment in Patients with Hepatic Impairment
- 2.4 Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Neurotoxicity of Phenylacetate
- 5.2 Hypokalemia
- 5.3 Conditions Associated with Edema
- 5.4 Diabetes Mellitus, Hereditary Fructose Intolerance, Glucose-Galactose Malabsorption or Sucrase-Isomaltase Insufficiency

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

- 7.1 Potential for Other Drugs to Affect Ammonia
- 7.2 Potential for Other Drugs to Affect PHEBURANE

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

PHEBURANE is indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS).

Limitations of Use

Episodes of acute hyperammonemia may occur in patients while on PHEBURANE. PHEBURANE is not indicated for the treatment of acute hyperammonemia, which can be a life-threatening medical emergency that requires rapid acting interventions to reduce plasma ammonia levels.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

PHEBURANE treatment should be supervised by a healthcare provider experienced in the treatment of urea cycle disorders.

The recommended dosage of PHEBURANE (measured as sodium phenylbutyrate) for patients with urea cycle disorders is:

- Patients weighing less than 20kg: 450 – 600 mg/kg/day of sodium phenylbutyrate orally. Divide the calculated total daily dose into three to six doses. Administer as three to six divided doses and take with food.
- Patients weighing greater than or equal to 20 kg: 9.9 – 13 g/m²/day of sodium phenylbutyrate orally. Divide the calculated total daily dose into three to six doses. Administer as three to six divided doses and take with food.

The maximum dosage is 20 grams per day. Combine PHEBURANE with dietary protein restriction and, in some cases, amino acid supplementation (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).

Measure the dose using only the calibrated spoon provided in the packaging. This calibrated dosing spoon directly measures PHEBURANE oral pellets as sodium phenylbutyrate [*see Dosage and Administration (2.4)*].

If a dose is missed, take the missed dose as soon as possible. There should be at least 3 hours between two doses and doses should not be doubled to make up for the missed dose.

2.2 Dosage Adjustment and Monitoring

Monitor plasma ammonia levels to determine the need for dosage adjustment. Adjust the PHEBURANE dosage to maintain the plasma ammonia level within the normal range for the patient's age, taking into consideration their clinical condition (e.g., nutritional requirements, protein intake, growth parameters, etc.).

Monitor patients for potential neurotoxicity and obtain measurements of plasma phenylacetate and phenylacetylglutamine levels [*see Warnings and Precautions (5.1), Adverse Reactions (6)*]. If neurologic symptoms (e.g. vomiting, nausea, headache, somnolence or confusion) are present in the absence of high ammonia levels or other

intercurrent illnesses, consider reducing the dose of PHEBURANE.

2.3 Dosage Adjustment in Patients with Hepatic Impairment

For patients with hepatic impairment, start at the lower end of the recommended dosing range and maintain patients on the lowest dose necessary to control plasma ammonia levels [see *Use in Specific Populations (8.7)*] .

2.4 Administration Instructions

For oral administration only. Administration via gastrostomy or nasogastric tubes has not been evaluated.

1. Schedule PHEBURANE dosages at the same time as food consumption (meal or snack).
2. Use the calibrated dosing spoon to measure PHEBURANE oral pellets. The dosing spoon is directly calibrated in grams of sodium phenylbutyrate.
3. Swallow the coated oral pellets with a drink (e.g., water, fruit juices, protein-free infant formulas) or sprinkle onto spoonful of apple sauce or carrot puree. Do not chew PHEBURANE oral pellets directly or mix into liquids.
4. Swallow immediately to minimize dissolution of coating.

Administration of PHEBURANE oral pellets with other foods has not been studied and is not recommended. Additionally, administration with soft food is only recommended in patients old enough to consume soft foods.

3 DOSAGE FORMS AND STRENGTHS

Oral pellets: 84 g of sodium phenylbutyrate per PHEBURANE bottle as white to off-white coated pellets.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity of Phenylacetate

Increased exposure to phenylacetate, the major metabolite of PHEBURANE, may be associated with neurotoxicity in patients with UCDs. In a study of adult cancer patients receiving intravenous phenylacetate, 250-300 mg/kg/day for 14 days, repeated at 4-week intervals, signs and symptoms of neurotoxicity, which were reversible upon discontinuation, were seen at plasma concentrations ≥ 3.5 mmol/L, and included somnolence, fatigue, and light headedness [see *Adverse Reactions (6)*]. PHEBURANE is not approved for intravenous use or for treatment of patients with cancer.

If symptoms of vomiting, nausea, headache, somnolence or confusion are present in the absence of high ammonia levels or other intercurrent illnesses, consider reducing the dose of PHEBURANE [see *Dosage and Administration (2.2)*] .

Phenylacetate caused neurotoxicity when given subcutaneously in rat pups [see *Use in*

Specific Populations (8.4)] .

5.2 Hypokalemia

Renal excretion of phenylacetylglutamine may induce urinary loss of potassium. Monitor serum potassium during therapy and initiate appropriate treatment when necessary.

5.3 Conditions Associated with Edema

PHEBURANE contains 124 mg (5.4 mmol) of sodium per gram of sodium phenylbutyrate, corresponding to 2.5 g (108 mmol) of sodium in the maximum daily dose of 20 g of sodium phenylbutyrate. In order to decide if administration of PHEBURANE is appropriate in patients with diseases that involve edema such as heart failure, cirrhosis, or nephrosis, calculate the total amount of sodium patients will be exposed to based on their weight or body surface area (BSA) [*see Dosage and Administration (2.1)]* . If a patient develops new-onset edema or worsening edema while on treatment, discontinue administration of PHEBURANE and initiate appropriate therapy.

5.4 Diabetes Mellitus, Hereditary Fructose Intolerance, Glucose-Galactose Malabsorption or Sucrase-Isomaltase Insufficiency

PHEBURANE contains 768 mg of sucrose per gram of sodium phenylbutyrate, corresponding to 15.4 g of sucrose in the maximum daily dose of 20 g of sodium phenylbutyrate. This should be considered in patients with diabetes mellitus. Avoid use of PHEBURANE in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of sodium phenylbutyrate were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Most common adverse reactions (incidence \geq 3%) are amenorrhea or menstrual dysfunction (irregular menstrual cycles), decreased appetite, body odor and bad taste or taste aversion.

Less Common Clinical Adverse Reactions

Blood and lymphatic system disorders: aplastic anemia ,ecchymoses

Cardiac disorders: arrhythmia

Gastrointestinal disorders: abdominal pain, decreased appetite, gastritis, nausea and vomiting, constipation, rectal bleeding, peptic ulcer disease, pancreatitis

Metabolism and nutrition disorders: increased weight, edema

Nervous system disorders: syncope, headache

Psychiatric disorders: depression

Renal and urinary disorders: renal tubular acidosis

Skin and subcutaneous tissue disorders: rash

Laboratory Adverse Reactions

Blood and lymphatic system disorders: anemia, leukopenia and leukocytosis, thrombocytopenia, thrombocytosis

Hepatobiliary disorders: hyperbilirubinemia, increased blood alkaline phosphatase, increased transaminases

Metabolism and nutrition disorders: acidosis, alkalosis, hyperchloraemia, hypophosphataemia, hyperuricemia, hyperphosphatemia, hyponatremia, hypokalemia, hypoalbuminemia, decreased total protein

Clinical Adverse Reactions with Use of Phenylacetate

Nervous system disorders: Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, the major metabolite of PHEBURANE (PHEBURANE is not approved for intravenous use or for treatment of patients with cancer). Signs and symptoms were predominately somnolence, fatigue, and dizziness (lightheadedness); less frequently reported were headache, dysgeusia, hypoacusis, disorientation, memory impairment, and exacerbation of a pre-existing neuropathy.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect Ammonia

Corticosteroids

Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels.

Valproic Acid and Haloperidol

Hyperammonemia may be induced by haloperidol and by valproic acid.

Monitor plasma ammonia levels closely when corticosteroids, valproic acid, or haloperidol is used concomitantly with PHEBURANE.

7.2 Potential for Other Drugs to Affect PHEBURANE

Probenecid

Probenecid may inhibit renal excretion of the metabolites of PHEBURANE including phenylacetate and phenylacetylglutamine. Monitor patients for potential neurotoxicity and measure plasma phenylacetate and phenylacetylglutamine levels when probenecid is used concomitantly with PHEBURANE [see *Dosage and Administration* (2.2)] .

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with sodium phenylbutyrate use in pregnant women are insufficient to identify a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with sodium phenylbutyrate. Based on published animal data, phenylacetate may be neurotoxic to the developing brain (*see Data*) .

There are serious risks to the mother and fetus associated with untreated urea cycle disorders during pregnancy which can result in serious morbidity and mortality to the mother and fetus (*see Clinical Considerations*) .

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnancy is a time of increased metabolic demand which increases the risk for hyperammonemic episodes when metabolic demands are not met. Hyperammonemic episodes in pregnancy are associated with impaired cognition in the mother and an increased risk of maternal and fetal death.

Data

In rats, intrauterine exposure to phenylacetate produced lesions in the neonatal brain in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number.

8.2 Lactation

Risk Summary

There are no data on the presence of sodium phenylbutyrate and its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PHEBURANE and any potential adverse effects on the breastfed infant from PHEBURANE or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of PHEBURANE have been established as adjunctive therapy to the standard of care, which includes dietary management, in the chronic management of pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS).

PHEBURANE is not indicated for the treatment of acute hyperammonemia, which can be a life-threatening medical emergency that requires rapid acting interventions to reduce plasma ammonia levels.

The sodium content of PHEBURANE has the potential to cause new-onset edema or worsening edema from salt and water retention, particularly in patients with underlying

predisposing conditions [see *Warnings and Precautions (5.3)*] .

Neurotoxicity has been observed in juvenile animals with phenylacetate exposure [see *Warnings and Precautions (5.1)*] .

Juvenile Animal Toxicity Data

When given subcutaneously to rat pups, 190–474 mg/kg phenylacetate caused decreased proliferation and increased loss of neurons, and it reduced CNS myelin. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth.

8.5 Geriatric Use

Clinical studies of PHEBURANE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Renal Impairment

No studies with PHEBURANE were conducted in subjects with renal impairment. Monitor plasma ammonia levels when starting patients with impaired renal function on PHEBURANE [see *Clinical Pharmacology (12)*] .

8.7 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 necessary to control plasma ammonia levels [see *Clinical Pharmacology (12.3), Dosage and Administration (2.3)*] .

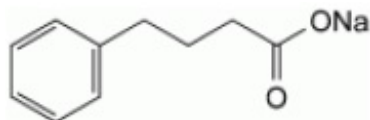
10 OVERDOSAGE

Overdoses of PHEBURANE exceeding ten-fold the maximum recommended dosage may produce emesis, CNS depression, metabolic acidosis with or without respiratory alkalosis, hypernatremia, hypokalemia, and hypophosphatemia. Symptoms of overdose overlap with those of acute hyperammonemia. If overdose occurs, discontinue PHEBURANE, monitor plasma phenylacetate and ammonia levels closely, and institute appropriate emergency management, which may include hemodialysis, continuous veno-venous hemofiltration (CVVH) or extracorporeal membrane oxygenation (ECMO).

11 DESCRIPTION

PHEBURANE (sodium phenylbutyrate) oral pellets is a nitrogen binding agent. Sodium phenylbutyrate is a white or yellowish-white powder, freely soluble in water and in methanol, and practically insoluble in methylene chloride. It is known chemically as sodium 4-phenylbutanoate with a molecular weight of 186.19 and the molecular formula $C_{10}H_{11}NaO_2$.

Structural formula:



Each bottle of PHEBURANE contains 84 g of sodium phenylbutyrate (equivalent to 74 g of phenylbutyrate) in 174 g of oral pellets. Each gram of pellets contains 483 mg of sodium phenylbutyrate (equivalent to 423 mg of phenylbutyrate). PHEBURANE contains the following inactive ingredients: ethylcellulose, hypromellose, polyethylene glycol 1500, povidone K25, and sugar spheres.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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.

12.2 Pharmacodynamics

In patients with urea cycle disorders, sodium phenylbutyrate decreased elevated plasma ammonia and glutamine levels.

12.3 Pharmacokinetics

The pharmacokinetics of phenylbutyrate and its metabolite phenylacetate were characterized in healthy adult subjects following a single oral administration of PHEBURANE (3 g of sodium phenylbutyrate) under fasted and fed conditions.

Absorption

Under fasted condition, the mean (SD) maximum plasma concentration (C_{max}) of phenylbutyrate ranged from 146 (30) to 169 (33) $\mu\text{g/mL}$, which was achieved at approximately 0.6 hour after PHEBURANE administration. The mean (SD) area under the plasma concentration-time curve (AUC) of phenylbutyrate ranged from 272 (78) to 283 (68) $\text{h}\cdot\mu\text{g/mL}$.

Effect of Food

Compared to fasted condition, AUC of phenylbutyrate decreased by 40-45% and C_{max} of phenylbutyrate decreased by 55%, when PHEBURANE was administered with a high-fat, high-calorie meal (total 800 to 1000 calories with approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). When PHEBURANE was administered with a normal-fat, normal-calorie, low-protein meal (total 600 to 700 calories with approximately 60, 200, and 400 calories from protein, fat, and carbohydrate, respectively), AUC of phenylbutyrate decreased by 56-63% and C_{max} decreased by 43-45% compared to fasted condition.

Elimination

The mean half-life of phenylbutyrate ranged from 0.5 to 0.8 hour.

Metabolism

Following oral administration, sodium phenylbutyrate is metabolized by β -oxidation into phenylacetate, which is converted to its coenzyme A ester, phenylacetyl-coenzyme A and further conjugated with glutamine to form phenylacetylglutamine.

Phenylacetylglutamine is excreted by the kidneys. The major sites for metabolism of sodium phenylbutyrate are the liver and kidneys. Phenylacetate is also hydrolysed by esterases in liver and blood.

Excretion

Approximately 80–100% of sodium phenylbutyrate is excreted by the kidneys within 24 hours as phenylacetylglutamine. For each gram of sodium phenylbutyrate administered, it is estimated that between 0.12–0.15 grams of phenylacetylglutamine nitrogen are produced.

Specific Populations

Patients with Renal Impairment or Hepatic Impairment

PHEBURANE has not been studied in patients with renal impairment or in patients with hepatic impairment.

Drug Interaction Studies

In vitro or clinical studies with PHEBURANE for determination of potential drug-drug interaction have not been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies of sodium phenylbutyrate have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

PHEBURANE (sodium phenylbutyrate) oral pellets consists of white to off-white pellets and is available in a child-resistant high-density polyethylene (HDPE) bottle with a desiccant in the cap.

Each bottle contains 84 g of sodium phenylbutyrate (equivalent to 74 g of phenylbutyrate) in 174 g of oral pellets (NDC 71770-200-10). Each gram of pellets contains 483 mg of sodium phenylbutyrate (equivalent to 423 mg of phenylbutyrate).

A calibrated measuring spoon that dispenses up to 3 g of sodium phenylbutyrate in increments of 0.25 g is provided in the packaging.

Store PHEBURANE at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Discard any remaining PHEBURANE 45 days after first opening of the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Neurotoxicity

Advise the patient or caregiver that neurotoxicity may occur during PHEBURANE treatment. Inform the patient or caregiver of the signs and symptoms of this risk and to contact the healthcare provider immediately if signs and symptoms occur [see *Warnings and Precautions (5.1)*] .

Administration

Instruct the patient or caregiver to only use the calibrated dosing spoon supplied with PHEBURANE to measure the oral pellets. Inform the patient or caregiver that the dosing spoon is directly calibrated in grams of sodium phenylbutyrate. Inform the patient or caregiver to consume the pellets immediately after preparation [see *Dosage and Administration (2.4)*] .

Inform the patient or caregiver that if a dose is missed, take the missed dose as soon as possible. Instruct the patient or caregiver that there should be at least 3 hours between two doses and doses should not be doubled to make up for the missed dose [see *Dosage and Administration (2.1)*] .

Storage and Handling

Advise the patient or caregiver to discard any remaining PHEBURANE 45 days after first opening of the bottle.

Distributed by:

Medunik USA, Inc.

2 Research Way, Suite 1B

Princeton, NJ 08540



PHEBURANE ® is a registered trademark of Lucane Pharma

<p style="text-align: center;">Patient Information PHEBURANE (FE bue rayne) (sodium phenylbutyrate) oral pellets</p>
--

<p>What is PHEBURANE?</p>

- | |
|---|
| <ul style="list-style-type: none">• PHEBURANE is a prescription medicine, used along with a specific diet, for the long-term management of adults and children with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinate synthetase (AS).• Episodes of sudden, rapid increase of ammonia in the blood (acute hyperammonemia) may happen in people during treatment with PHEBURANE. |
|---|

PHEBURANE is not used for the treatment of acute hyperammonemia, which can be life-threatening and requires emergency medical treatment.

Before taking PHEBURANE, tell your or your child's healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have kidney or liver problems.
- have diabetes (PHEBURANE contains sucrose), or have a history of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.
- are pregnant or plan to become pregnant. It is not known if PHEBURANE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if PHEBURANE passes into your breastmilk. Talk to your healthcare provider about the best way to feed your baby during treatment with PHEBURANE.

Tell your healthcare provider about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Certain medicines may increase the level of ammonia in your blood or cause serious side effects when taken during treatment with PHEBURANE.

Especially tell your healthcare provider if you or your child take:

- corticosteroids
- valproic acid
- haloperidol
- probenecid

Know the medicines you take. Keep a list of them to show your or your child's healthcare provider and pharmacist when you get a new medicine.

How should I take PHEBURANE?

Read the detailed Instructions for Use that comes with PHEBURANE for information about the right way to prepare and take a dose of PHEBURANE.

- Take PHEBURANE exactly as prescribed by your healthcare provider.
- Your healthcare provider may change your dose if needed. Do not change your dose unless your healthcare provider tells you to.
- Your healthcare provider will prescribe PHEBURANE based on your or your child's weight.
- Schedule your PHEBURANE dose at the same time you eat a meal or snack.
- Use the calibrated dosing spoon to measure PHEBURANE oral pellets.
- PHEBURANE oral pellets should be taken with a drink such as water, fruit juices or protein-free infant formulas, **or** soft food, such as apple sauce or carrot puree. It is not recommended to use other foods to take your dose of PHEBURANE oral pellets.
- Do not chew PHEBURANE oral pellets directly or mix PHEBURANE oral pellets into liquids.
- If you miss a dose of PHEBURANE, take it as soon as possible. Each dose of PHEBURANE should be taken at least 3 hours apart. If you have missed a dose within 3 hours of the next dose, take only one dose the next time it is scheduled.

- **Do not** give or take PHEBURANE through a gastrotomy or nasogastric tube.
- If you take too much PHEBURANE, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of PHEBURANE?

PHEBURANE can cause serious side effects, including:

Nervous system problems (neurotoxicity). Call your healthcare provider right away if get any of the following symptoms during treatment with PHEBURANE:

- sleepiness
- tiredness
- lightheadedness
- vomiting
- nausea
- headache
- confusion

Low potassium levels in your blood (hypokalemia). Your healthcare provider will monitor your blood potassium levels during treatment with PHEBURANE and treat if needed.

Conditions related to swelling (edema). PHEBURANE contains salt (sodium), which can cause swelling from salt and water retention. Your healthcare provider will decide if PHEBURANE is right for you if you have certain medical conditions that can cause swelling, such as heart failure, liver problems or kidney problems.

The most common side effects of PHEBURANE include:

- absent or irregular menstrual periods
- decreased appetite
- body odor
- bad taste or avoiding foods that you ate prior to getting sick (taste aversion)

Your healthcare provider may do certain blood tests to check you or your child for side effects during treatment with PHEBURANE.

These are not all of the possible side effects of PHEBURANE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PHEBURANE?

- Store PHEBURANE at room temperature between 68°F and 77°F (20°C and 25°C).
- PHEBURANE comes in a child-resistant bottle. The bottle cap contains a desiccant to help keep PHEBURANE dry.
- Throw away (discard) any remaining PHEBURANE 45 days after first opening of the bottle.

Keep PHEBURANE and all medicines out of the reach of children.

General information about the safe and effective use of PHEBURANE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PHEBURANE for a condition for which it was not prescribed. Do not give PHEBURANE to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or

pharmacist for information about PHEBURANE that is written for health professionals.

What are the ingredients in PHEBURANE?

Active ingredient: sodium phenylbutyrate

Inactive Ingredients: ethylcellulose, hypromellose, polyethylene glycol 1500, povidone K25, and sugar spheres.

Distributed by: Medunik USA, Inc., 2 Research Way, Suite 1B, Princeton, NJ 08540
For more information, go to www.medunikusa.com

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: August 2023

**INSTRUCTIONS FOR USE
PHEBURANE[®] (FE bue rayne)
(sodium phenylbutyrate)
oral pellets**

Read this Instructions for Use before taking PHEBURANE oral pellets and each time you get a refill. There may be new information. This Instructions for Use does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk to your healthcare provider or pharmacist if you have any questions about how to take a dose of PHEBURANE.

This Instructions for Use contains information on how to measure and take PHEBURANE.

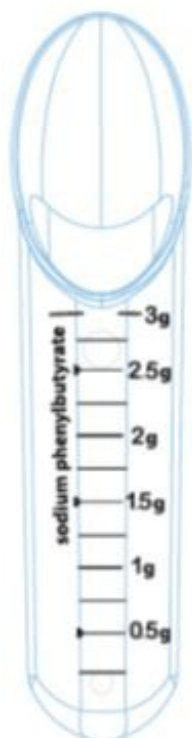


Figure A: Calibrated dosing spoon provided

Important information you need to know before taking PHEBURANE

- The total daily dose of PHEBURANE must be given in divided doses and taken with food (meal or snack). Your healthcare provider will tell you when to take PHEBURANE and the dose to take.
- Schedule PHEBURANE doses at the same time as eating a meal or snack.
- Only use the calibrated dosing spoon provided with PHEBURANE to measure the dose (See **Figure A**).

Supplies needed for measuring and taking PHEBURANE

- Bottle of PHEBURANE oral pellets.
- Calibrated dosing spoon provided with PHEBURANE.
- A drink such as water, fruit juices or protein-free infant formulas, **or** soft food, such as apple sauce or carrot puree. It is not recommended to use other foods to take your dose of PHEBURANE oral pellets.

Measuring PHEBURANE

Repeat Steps 1 through 3 throughout the day as prescribed by your healthcare provider to get the total daily dose.

Step 1

- Use the calibrated dosing spoon to measure the prescribed divided dose of PHEBURANE oral pellets (See **Figure A**).

The calibrated dosing spoon measures PHEBURANE oral pellets as grams (g) of sodium phenylbutyrate. The calibrated dosing spoon dispenses up to 3 g of sodium phenylbutyrate, in increments of 0.25 g.

- Pour the oral pellets directly into the calibrated dosing spoon until it reaches the black line for the prescribed dose of sodium phenylbutyrate in grams (See **Figure B**).

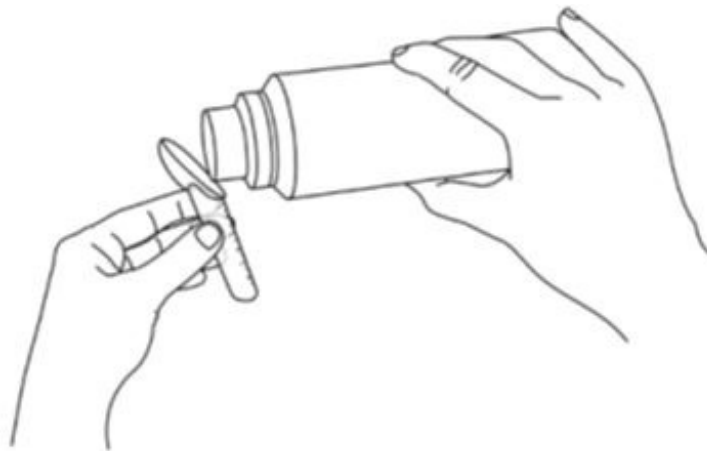


Figure B: Pour the PHEBURANE oral pellets directly into the calibrated dosing spoon.

Taking PHEBURANE

Step 2

- Tap the bottom of the calibrated dosing spoon 1 time on a hard surface to give a flat level of oral pellets and continue filling until you reach the prescribed dose.

Step 3

- Swallow PHEBURANE oral pellets with a drink such as water, fruit juices, or protein-free infant formulas.

or

- Sprinkle PHEBURANE oral pellets onto a spoonful of apple sauce or carrot puree and swallow right away. It is important to swallow right away to prevent coating from dissolving.

Do not chew PHEBURANE oral pellets directly or mix PHEBURANE oral pellets into liquids.

If the prescribed divided dose is more than 3 grams, repeat Steps 1 through 3 to get the prescribed divided dose of sodium phenylbutyrate.

Storing PHEBURANE

- Store PHEBURANE at room temperature between 68°F and 77°F (20°C and 25°C).
- PHEBURANE comes in a child-resistant bottle. The bottle cap contains a desiccant to help keep PHEBURANE dry.
- Throw away (discard) any remaining PHEBURANE 45 days after first opening of the bottle.
- **Keep PHEBURANE and all medicines out of the reach of children.**

Disposing of PHEBURANE

- Throw away (dispose of) the bottle of PHEBURANE 45 days after first opening by dropping off the medicine at a drug take back site or following the steps below.
 - Mix medicine with an unappealing substance such as dirt, cat litter, or used coffee grounds
 - Place the mixture in a container such as a sealed plastic bag
 - Throw away the container in your trash at home, and
 - Delete all personal information on the prescription label of the empty medicine bottle, then throw away or recycle the empty bottle.
- Throw away (dispose of) used calibrated dosing spoon in the household trash.
- Do not use the calibrated dosing spoon to measure any other medicine.

If cleaning is necessary, rinse the calibrated dosing spoon with water and dry it completely.

To replace the calibrated dosing spoon, contact Medunik USA at 1-844-884-5520.

Distributed by: Medunik USA, Inc. 2 Research Way, Suite 1B, Princeton, NJ 08540



PHEBURANE[®] is a registered trademark of Lucane Pharma.

PRINCIPAL DISPLAY PANEL - Carton

NDC 71770-200-10

Pheburane[®]

**(sodium phenylbutyrate)
oral pellets**

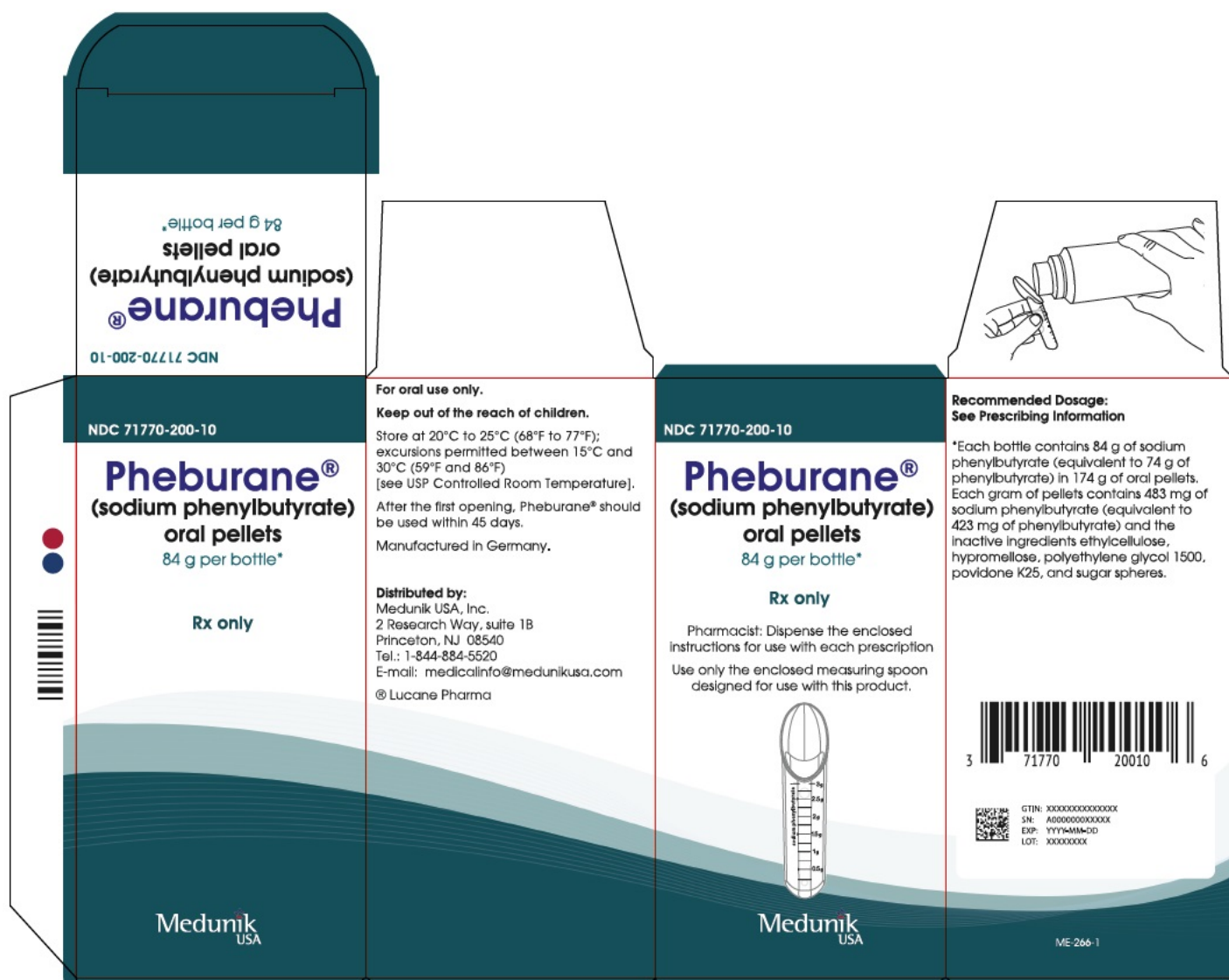
84 g per bottle*

Rx only

Pharmacist: Dispense the enclosed instructions per use with each prescription

Use only the enclosed measuring spoon designed for use with this product.

Medunik USA



PRINCIPAL DISPLAY PANEL - Container

NDC 71770-210-10

Pheburane[®]

(sodium phenylbutyrate)
oral pellets

84 g per bottle*

For oral use only

Rx only

Use only the enclosed
measuring spoon designed for
use with this product.

*Each bottle contains 84 g of sodium phenylbutyrate (equivalent to 74 g of phenylbutyrate) in 174 g of oral pellets. Each gram of pellets contains 483 mg of sodium phenylbutyrate (equivalent to 423 mg of phenylbutyrate).

Recommended Dosage:
See Prescribing Information.
Keep out of the reach of children.

LOT:
EXP:

NDC 71770-210-10

Pheburane[®]
(sodium phenylbutyrate)
oral pellets
84 g per bottle*
For oral use only
Rx only

Use only the enclosed measuring spoon designed for use with this product.



Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature).

Date of first opening __/__/__. **Discard unused Pheburane 45 days after first opening the bottle.**

Manufactured in Germany.

Distributed by:
Medunik USA, Inc.
2 Research Way, suite 1B
Princeton, NJ 08540
Tel.: 1-844-884-5520
E-mail:
medunica@medunikusa.com

© Lucane Pharma



Medunik USA

ME-267-3

PHEBURANE

sodium phenylbutyrate pellet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:71770-210
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM PHENYL BUTYRATE (UNII: NT6K61736T) (PHENYL BUTYRIC ACID - UNII: 7WY7YBI87E)	SODIUM PHENYL BUTYRATE	483 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
POLYETHYLENE GLYCOL 1500 (UNII: 1212Z7S33A)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE K25 (UNII: K0KQV10C35)	
SUCROSE (UNII: C151H8M554)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71770-210-10	174 g in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	09/14/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216513	09/14/2022	

PHEBURANE

sodium phenylbutyrate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:71770-200
--------------	-------------------------	--------------------	---------------

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71770-200-10	1 in 1 CARTON	08/26/2022	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 BOTTLE	174 g

Part 1 of 1

PHEBURANE

sodium phenylbutyrate pellet

Product Information**Item Code (Source)** NDC:71770-210**Route of Administration** ORAL**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
SODIUM PHENYLBUTYRATE (UNII: NT6K61736T) (PHENYLBUTYRIC ACID - UNII:7WY7YBI87E)	SODIUM PHENYLBUTYRATE	483 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
POLYETHYLENE GLYCOL 1500 (UNII: 1212Z7S33A)	
STARCH, CORN (UNII: O8232NY3SJ)	
POVIDONE K25 (UNII: K0KQV10C35)	
SUCROSE (UNII: C151H8M554)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71770-210-10	174 g in 1 BOTTLE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216513	09/14/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA216513	08/26/2022	

Labeler - Medunik USA (080318531)