Each gram of sodium phenylbutyrate powder contains 0.94 grams of sodium phenylbutyrate and the following inactive ingredients calcium stearate and colloidal silicon dioxide.

### PHARMACOKINETICS

Sodium phenylbutyrate is a pro-drug and is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine via an 

### CLINICAL PHARMACOLOGY

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### INDICATIONS AND USAGE

Sodium phenylbutyrate powder must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. (See Nutritional Supplementation subsection of the DOSAGE AND ADMINISTRATION section.)

Previously, neonatal-onset disease was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their 

### DOSAGE AND ADMINISTRATION

Oral Use Only.

The use of sodiumphenylbutyrate tablets is indicated for children weighing more than 

### CLINICAL ADVERSE EVENTS

There have been reported cases of hyperammonemia being induced by haloperidol and by valproic acid.

### PRECAUTIONS


### Gastrointestinal

Abdominal pain, gastritis, nausea and vomiting; constipation, rectal bleeding, pain in lower abdomen.

### Neurotoxicity of phenylacetate in animals: When given subcutaneously to rat pups, 190 to 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. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were fewer and thinner and normal and reduced in number.

### Information for Patients:

The full text of the separate insert of information for patients is reprinted at the end of the labeling. Laboratory Tests:

Plasma levels of ammonia, arginine, branched-chain amino acids, and serum proteins should be maintained within normal limits, and plasma glutamine should be maintained at levels less than 1,000 mcg/mL. Serum drug levels of phenylbutyrate and its metabolites, phenylacetate and phenylacetylglutamine, should be monitored periodically.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and fertility studies of sodium phenylbutyrate have not been conducted.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with sodium phenylbutyrate. It is also not known whether sodium phenylbutyrate can cause harm when administered to a pregnant woman.

Sodium phenylbutyrate should be given to a pregnant woman only if it clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium phenylbutyrate is administered to a nursing woman.

### CONTRAINDICATIONS

Sodium phenylbutyrate should not be used to manage acute hyperammonemia, which is a medical emergency.

### WARNINGS

Sodium phenylbutyrate powder contains 11.7 grams of sodium per 100 grams of powder, corresponding to 567 mg of sodium phenylbutyrate (12.4% w/w). Sodium phenylbutyrate should be used with great care, if at all, in patients with congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with edema.

Because sodium phenylbutyrate is metabolized in the liver and kidney, and phenylacetylglutamine is primarily excreted by the kidney, use caution when administering the drug to patients with hepatic or renal insufficiency or inborn errors of beta oxidation. Probenecid is known to inhibit the renal transport of many organic compounds, including hippuric acid, and may affect renal excretion of the conjugated product of sodium phenylbutyrate as well as its metabolite.

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

### PRECAUTIONS

General: Sodium phenylbutyrate should not be administered to patients with known hypersensitivity to sodium phenylbutyrate or any component of this preparation.

### ADVERSE REACTIONS

The assessment of clinical adverse events came from 206 patients treated with sodium phenylbutyrate. Adverse events (both clinical and laboratory) were not collected systematically in these patients, but were obtained from patient-visit reports by the 65 co-investigators. Causality of adverse effects is sometimes difficult to determine in this patient population because they may result from either the underlying disease, the patient’s restricted diet, intercurrent illness, or sodium phenylbutyrate. Furthermore, the rates may be under-estimated because they were reported primarily by parent or guardian and not the patient.

### CLINICAL ADVERSE EVENTS

In female patients, the most common clinical adverse event reported was amenorrhea/ menstrual dysfunction (irregular menstrual cycles), which occurred in 23% of the menstruating patients.

Decreased appetite occurred in 4% of all patients. Body odor (probably caused by the metabolite, phenylacetylglutamine) and bad taste or taste aversion were each reported in 3% of patients.

Other adverse events reported in 2% or fewer patients were:

Gastrointestinal: abdominal pain, gastritis, nausea and vomiting; constipation, rectal bleeding, pain in lower abdomen.

Cardiovascular: arrhythmia and edema each occurred in one patient.

Renal: renal tubular acidosis

Psychiatric: depression

Miscellaneous: headache, syncope, and weight gain

Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250 to 300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominately somnolence, fatigue, and lethargy, with less frequent headache, anorexia, hypogonadism, hypothyroidism, and exacerbation of a pre-existing neuropathy. These adverse events were mainly mild in severity. The acute onset and reversibility when the phenylacetate infusion was discontinued supported a drug effect.

### LABORATORY ADVERSE EVENTS

In patients with urea cycle disorders, the frequency of laboratory adverse events by body system were:

Metabolic: acidosis (14%), alkalosis and hyperchloremia (7%), hypophosphatemia (6%), hyperuricemia and hyperphosphatemia (each 2%), and hypotension and hypokalemia (each 1%).

Nutritional: hyperalbuminemia (11%) and decreased total protein (3%).

Hepatic: increased alkaline phosphatase (6%), increased liver transaminases (4%), and hyperbilirubinemia (1%).

Hematologic: anemia (9%), leukopenia and leucocytosis (each 4%), thrombocytopenia (3%), and thrombocytosis (1%).

The clinician is advised to routinely perform urinalysis, blood chemistry profiles, and hematologic tests.

### OVERDOSAGE

No adverse experiences have been reported involving overdoses of sodium phenylbutyrate in patients with urea cycle disorders.

In the event of an overdose, discontinue the drug and institute supportive measures. Hemodialysis or peritoneal dialysis may be beneficial.

### DOSAGE AND ADMINISTRATION

See table for reference. The use of tablets for neonates, infants and children to the weight of 20 kg is not recommended. (See DOSAGE AND ADMINISTRATION)
After Opening, Keep Bottle Tightly Closed.

Sodium phenylbutyrate powder should be stored in a tightly closed bottle at room temperature.

This leaflet provides a brief summary of the information available on a decrease in sodium phenylbutyrate powder. The information here is incomplete and is not designed to take the place of your doctor's instructions. For more information, consult your physician or call Par Pharmaceutical at 1-800-828-9393.

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PATIENT PACKAGE INSERT
Sodium Phenylbutyrate Powder
SOD-DEE-um feen-il-BUE-ty-rate

What is the most important information I should know about sodium phenylbutyrate powder?
Sodium phenylbutyrate powder is prescribed along with changes in diet for long-term treatment of urea cycle disorders. Sodium phenylbutyrate powder can only be obtained with your doctor.

Sodium phenylbutyrate powder must be taken exactly as the doctor prescribes; do not increase or decrease the dose of this medication without the doctor’s approval.

What are urea cycle disorders?
Urea cycle disorders include a group of diseases, each having a specific liver enzyme deficiency. Because they are inherited, other family members may be affected. These disorders vary in severity and may be first detected at various ages, from newborn infants to adults. They lead to increased amounts of ammonia in the blood, which may cause disturbed brain function and severe brain damage. Typical signs of the disease are decreased mental awareness, vomiting, combative behavior, slurred speech, unstable gait, and unconsciousness. The diagnosis of urea cycle disorders requires special laboratory tests. These typical signs of the disease may recur after the diagnosis is made if the condition is not under control. If they do, the doctor should be notified immediately because this is a medical emergency. An infection can cause the condition to go out of control. Therefore, if a fever develops, the doctor should be seen immediately.

A patient or carrier of these disorders should wear a Medic Alert tag stating the diagnosis. In the event that the patient has a sudden, rapid accumulation of ammonia in the blood, and, therefore, in the brain, leading to unconsciousness, the doctor will be alerted to treat the disease properly.

Periodically, depending upon the severity of a particular patient’s urea cycle disorder, it will be necessary to perform blood tests. These include plasma ammonia, plasma amino acid levels, and other more routine blood tests to evaluate nutritional status.

What is sodium phenylbutyrate powder?
Sodium phenylbutyrate powder is a drug that helps to prevent ammonia from accumulating in the blood. Sodium phenylbutyrate powder aids the body in eliminating substances that produce ammonia. However, despite drug treatment, blood ammonia levels may become elevated periodically and there may be episodes of altered brain function in association with these ammonia elevations. Patients who have disease onset as newborns have a high incidence of mental retardation. Medical attention should be obtained as soon as signs appear (see above under “What are urea cycle disorders?”). Sodium phenylbutyrate powder may be used as life-long therapy or as a temporary measure until liver transplantation is performed.

What diet should I or my child follow?
In addition to taking sodium phenylbutyrate powder, it is equally important that a prescribed diet be followed. Because there is great variability in the severity of urea cycle disorders, each patient’s diet should be custom designed by a physician and a nutritionist. Because the diet is so important, it is recommended that the prescribed diet be discussed with a nutritionist who is familiar with urea cycle disorders.

Who should not take sodium phenylbutyrate powder?
Sodium phenylbutyrate powder is prescribed only for patients with urea cycle disorders. It is not to be used for any other reason. Keep the medication in a safe place where children cannot reach it.

What other medical conditions may also be present that could increase the risk of taking sodium phenylbutyrate powder?
Heart failure or decreased kidney function may lead to retention of the sodium content of sodium phenylbutyrate powder with potentially serious consequences such as worsening heart failure, high blood pressure, and swelling. If these medical conditions are present, the doctor will determine if your child should take sodium phenylbutyrate powder.