Sodium Phenylbutyrate Tablets, 500 mg

Rx only

DESCRIPTION

Sodium phenylbutyrate tablets for oral administration contain sodium Phenylbutyrate. Sodium phenylbutyrate tablet is an off-white crystalline substance which is soluble in water and has a strong salty taste. Sodium phenylbutyrate also is freely soluble in methanol and practically insoluble in acetone and diethyl ether. It is known chemically as 4-phenylbutyric acid, sodium salt with a molecular weight of 186 and the molecular formula C_{8}H_{11}NaO_{3}.

Chemical Structure:

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\text{CH}_{3}\text{CH}_{2}\text{CH}_2\text{COONa}
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Each tablet of sodium phenylbutyrate tablets contains 500 mg of sodium phenylbutyrate and the inactive ingredients calcium stearate, colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Sodium phenylbutyrate is a pro-drug and is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutathione for excretion as phenylacetylglutaminate. Phenylacetate and phenylacetylglutaminate are then excreted by the kidneys. On a molar basis, it is comparable to urea (each containing two moles of nitrogen). Therefore, phenylacetylglutaminate provides an alternate vehicle for waste nitrogen excretion.

PHARMACOKINETICS

General:

Pharmacokinetic studies have not been conducted in the primary patient population (neonates, infants, and children), but pharmacokinetic data were obtained from normal adult subjects.

Absorption:

Peak plasma levels of phenylbutyrate occur within 1 hour after a single dose of 5 grams of sodium phenylbutyrate tablet with a C_{max} of 218 mg/mL under fasting conditions. The effect of food on phenylbutyrate's absorption is unknown.

Disposition:

The overall disposition of sodium phenylbutyrate and its metabolites has not been characterized fully. However, the drug is known to be metabolized to phenylacetate and subsequently to phenylacetylglutamate. Following oral administration of 5 grams (tablets), measurable plasma levels of phenylbutyrate and phenylacetate were detected 15 and 30 minutes after dosing, respectively, and phenylacetylglutamate was detected shortly thereafter. The pharmacokinetic parameters for phenylbutyrate for C_{max} (mg/mL), T_{max} (hours), and elimination half-life (hours) were 218.15 and 7.7, respectively, and for phenylacetate 48.5, 3.74, and 1.15, respectively.

The major sites for metabolism of sodium phenylbutyrate are the liver and kidney.

Excretion:

A majority of the administered compound (approximately 80% to 100%) is excreted by the kidneys within 24 hours as the conjugation product, phenylacetylglutamate. For each gram of sodium phenylbutyrate administered, it is estimated that between 0.12 to 0.15 grams of phenylacetylglutamate nitrogen are produced.

Pharmacodynamics:

In patients with urea cycle disorders, sodium phenylbutyrate decreases elevated plasma ammonia glucose levels. It increases waste nitrogen excretion in the form of phenylacetylglutaminate.

Special Populations

Gender:

Significant gender differences were found in the pharmacokinetics of phenylbutyrate and phenylacetate, but not for phenylacetylglutamate. The pharmacokinetic parameters (AUC and C_{max}) for both plasma phenylbutyrate and phenylacetate were about 30 to 50 percent greater in females than in males.

Hepatic insufficiency:

In patients who did not have urea cycle disorders but had impaired hepatic function, the metabolism and excretion of sodium phenylbutyrate were not affected. However, this information was obtained from unbalanced, uncontrolled case studies.

INDICATIONS AND USAGE

Sodium phenylbutyrate tablets is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency.

Sodium phenylbutyrate tablets 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.) Previous, 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 nitrogen-free analogs. However, with hemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate, and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in neonates diagnosed after birth but within the first month of life is almost 80%. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy. Patients with neonatal-onset disease have a high incidence of mental retardation. Those who had ICD-10 admin had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100%; 14/14 patients tested; argininosuccinate synthetase deficiency, 88%; 15/17 patients tested; and carbamyl phosphate synthetase deficiency, 31%; 4/7 patients tested. Retardation was severe in the majority of the retarded patients.

In patients diagnosed during perinatal or late-onset hyperammonemic encephalopathy, survival is 100%, but even in these patients, most subsequently manifest cognitive impairment or other neurologic deficits. In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate tablets and dietary protein restriction to prevent mental deterioration and recurrence of hyperammonemic encephalopathy if carefully adhered to. The majority of these patients tested (30/46 or 66%) had IQ's in the low average/low normal mentally retarded range. Reversal of pre-existing neurologic impairment is not likely to occur with treatment and neurologic deterioration may continue in some patients.

Even on therapy, acute hyperammonemic encephalopathy recurred in the majority of patients for whom the drug is indicated. Sodium phenylbutyrate tablets may be required life-long unless orthotopic liver transplantation is elected. (See CLINICAL PHARMACOLOGY, Pharmacodynamics subsection for the biochemical effects of sodium phenylbutyrate tablets).

CONTRAINDICATIONS

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

WARNINGS

Each sodium phenylbutyrate tablet contains 62 mg of sodium (0.2 % w/w) (corresponding to 124 mg of sodium per gram 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 phenylacetylglutamate is primarily excreted by the kidney, use caution when administering the drug to patients with hepatic or renal insufficiency or inherent errors of beta oxidation. Probencidine is known to inhibit the renal transport of many organic compounds, including hippuric acid, and may affect renal excretion of the conjuncted 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. There have been published reports of hyperammonemia being induced by haloperidol and by valproic acid.

Neurotoxicity of phenylacetate in animals:

When given subcutaneously to rats, 100 to 474 mg/kg phenylacetate caused decreased prolferation and increased loss of neurons, and it reduced CBS mRNA. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was decreased, and the process was not reversed in impaired brain growth. Premature exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dentritic spines were longer and thinner than normal and reduced in number.

For information on drug interactions:

The full text of the separate insert for information 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 μmol/L. Serum drug levels of phenylbutyrate and its metabolites, phenylacetate and phenylacetylglutamate, should be monitored from time to time.

Carcinogenicity, 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 fetal harm when administered to a pregnant woman or can affect reproduction capacity.

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

Pediatric Use:

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.

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

Gastrointestinal: abdominal pain, gastritis, nausea and vomiting, constipation, rectal bleeding, peptic ulcer disease, and pancreatitis each occurred in 1 patient.

Hematologic: aplastic anemia and eosinophils each occurred in one patient.

Cardiovascular: arrhythmias and edema each occurred in one patient.

Respiratory: tendency for irritation.

Psychiatric: depression

Allergic:

rash

Neurologic: headache, syncope, and weight gain

Psychotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250 to 300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominantly somnolence, fatigue, and lightheadedness; with less frequent headache, dyspnea, dysconjugation, impaired memory, and exacerbation of a pre-existing neuropsychiatric deficit. These adverse events were mainly severe in the acute onset and reversibility when the phenylbutyrate infusion was discontinued suggested 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%), azotemia, and hyperammonemia (each 1%); hypophosphatemia (6%); hyperuricemia, and hyperphosphatemia (each 2%), and hyperglycemia and hyperuricemia (each 1%).

Hematologic: anemia (9%), leukopenia and leukocytosis (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

For oral use only.

The use of sodium phenylbutyrate tablets is indicated for children weighing more than 20 kg and for adults.
**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 neonatal 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, convulsions, slowed speech, unstable gait, and unconsciousness. The diagnosis of a urea cycle disorder 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 tablets?**

Sodium phenylbutyrate tablets is a drug that helps to prevent ammonia from accumulating in the blood. Sodium phenylbutyrate tablets 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 this 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 tablets 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 tablets, 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 tablets?**

Sodium phenylbutyrate tablets 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 tablets?**

Heart failure or decreased kidney function may lead to retention of the sodium content of sodium phenylbutyrate tablets 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 tablets.

**How should I or my child take sodium phenylbutyrate tablets?**

The dose of sodium phenylbutyrate tablets prescribed for adults and children is based upon the patient’s weight or size. It is very important that the full amount prescribed for 24-hour period be taken. If a dose is missed it should be administered as soon as possible that same day. The total daily dose should be administered in equally divided amounts with meals.