BUPHENYL® (sodium phenylbutyrate) Tablets
BUPHENYL® (sodium phenylbutyrate) Powder

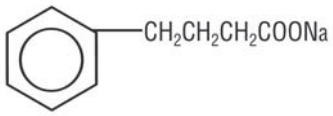
[bu'fen-əl]
(sodium phenylbutyrate)

Rx Only

DESCRIPTION

BUPHENYL® (sodium phenylbutyrate) Tablets for oral administration and BUPHENYL® (sodium phenylbutyrate) Powder for oral, nasogastric, or gastrostomy tube administration contain sodium phenylbutyrate. Sodium phenylbutyrate 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 $C_{10}H_{11}O_2Na$.

Chemical Structure:



Each tablet of BUPHENYL contains 500 mg of sodium phenylbutyrate and the inactive ingredients microcrystalline cellulose NF, magnesium stearate NF, and colloidal silicon dioxide NF.

Each gram of BUPHENYL Powder contains 0.94 grams of sodium phenylbutyrate and the inactive ingredients calcium stearate NF, and colloidal silicon dioxide NF.

CLINICAL PHARMACOLOGY

Sodium phenylbutyrate is a pro-drug and is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine then is excreted by the kidneys. On a molar basis, it is comparable to urea (each containing two moles of nitrogen). Therefore, phenylacetylglutamine 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 µg/mL under fasting conditions; peak plasma levels of phenylbutyrate occur within 1 hour after a single dose of 5 grams of sodium phenylbutyrate powder with a C_{max} of 195 µg/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 phenylacetylglutamine. Following oral administration of 5 grams (tablets), measurable plasma levels of phenylbutyrate and phenylacetate were detected 15 and 30 minutes after dosing, respectively, and phenylacetylglutamine was detected shortly thereafter. The pharmacokinetic parameters for phenylbutyrate for C_{max} (µg/mL), T_{max} (hours), and elimination half-life (hours) were 218, 1.35, and 0.77, respectively, and for phenylacetate were 48.5, 3.74, and 1.15, respectively.

Following oral administration of 5 grams of the powder, measurable plasma levels of phenylbutyrate and phenylacetate were detected 15 and 30 minutes after dosing, respectively, and phenylacetylglutamine was detected shortly thereafter. The pharmacokinetic parameters for phenylbutyrate for C_{max} (µg/mL), T_{max} (hours), and elimination half-life (hours) were 195, 1.00, and 0.76, respectively, and for phenylacetate were 45.3, 3.55, and 1.29, respectively.

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

Excretion:

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

Pharmacodynamics:

In patients with urea cycle disorders, BUPHENYL® decreased elevated plasma ammonia glutamine levels. It increases waste nitrogen excretion in the form of phenylacetylglutamine.

Special Populations

Gender:

Significant gender differences were found in the pharmacokinetics of phenylbutyrate and phenylacetate, but not for phenylacetylglutamine. 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 unvalidated, uncontrolled case studies.

INDICATIONS AND USAGE

BUPHENYL® is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). 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.

BUPHENYL 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 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 newborns 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 IQ tests administered had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100% (14/14 patients tested); argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested); and carbamylphosphate synthetase deficiency, 57% (4/7 patients tested). Retardation was severe in the majority of the retarded patients.

In patients diagnosed during gestation and treated prior to any episode of hyperammonemic encephalopathy, survival is 100%, but even in these patients, most subsequently demonstrate 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 and dietary protein restriction, the survival rate is 98%. The two deaths in this group of patients occurred during episodes of hyperammonemic encephalopathy. However, compliance with the therapeutic regimen has not been adequately documented to allow evaluation of the potential for BUPHENYL 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 65%) have IQ's in the average to low average/borderline 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.

BUPHENYL may be required life-long unless orthotopic liver transplantation is elected.

(See CLINICAL PHARMACOLOGY, Pharmacodynamics subsection for the biochemical effects of BUPHENYL).

CONTRAINDICATIONS

BUPHENYL® should not be used to manage acute hyperammonemia, which is a medical emergency.

WARNINGS

Each BUPHENYL® Tablet contains 62 mg of sodium (9.2% w/w) (corresponding to 124 mg of sodium per gram of sodium phenylbutyrate [12.4% w/w]) and BUPHENYL Powder contains 11.7 grams of sodium per 100 grams of powder, corresponding to 125 mg of sodium per gram of sodium phenylbutyrate (12.4% w/w). BUPHENYL 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 BUPHENYL 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 BUPHENYL as well as its metabolite.

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

PRECAUTIONS

General:

BUPHENYL® 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 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. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than 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 µmol/L. 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 BUPHENYL®. It is also not known whether BUPHENYL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

BUPHENYL should be given to a pregnant woman only if 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 BUPHENYL® is administered to a nursing woman.

Pediatric Use:

The use of tablets for neonates, infants and children to the weight of 20 kg is not recommended. (See Dosage and Administration.)

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 BUPHENYL®. 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, phenylacetate) 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, peptic ulcer disease, and pancreatitis each occurred in one patient.
Hematologic: aplastic anemia and ecchymoses each occurred in one patient.
Cardiovascular: arrhythmia and edema each occurred in one patient.
Renal: renal tubular acidosis
Psychiatric: depression
Skin: rash
Miscellaneous: headache, syncope, and weight gain

Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250–300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominately somnolence, fatigue, and lightheadedness; with less frequent headache, dysgeusia, hypoacusis, disorientation, impaired memory, 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 suggest 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 (each 7%), hypophosphatemia (6%), hyperuricemia and hyperphosphatemia (each 2%), and hypernatremia and hypokalemia (each 1%).
Nutritional: hypoalbuminemia (11%) and decreased total protein (3%).
Hepatic: increased alkaline phosphatase (6%), increased liver transaminases (4%), and hyperbilirubinemia (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 BUPHENYL® Tablets is indicated for children weighing more than 20 kg and for adults.

The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450–600 mg/kg/day in patients weighing less than 20 kg, or 9.9–13.0 g/m^2/day in larger patients. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day).

BUPHENYL® Powder is indicated for oral use (via mouth, gastrostomy, or nasogastric tube) only. The powder is to be mixed with food (solid or liquid), for immediate use; however, when dissolved in water, BUPHENYL Powder has been shown to be stable for up to one week at room temperature or refrigerated. Sodium phenylbutyrate is very soluble in water (5 grams per 10 mL). When BUPHENYL Powder is added to a liquid, only sodium phenylbutyrate will dissolve, the excipients will not. The effect of food on sodium phenylbutyrate has not been determined.

Each level teaspoon (enclosed) dispenses 3.2 grams of powder and 3.0 grams of sodium phenylbutyrate.
Each level tablespoon (enclosed) dispenses 9.1 grams of powder and 8.6 grams of sodium phenylbutyrate.

Shake lightly before use.

The safety or efficacy of doses in excess of 20 grams (40 tablets) per day has not been established.

NUTRITIONAL MANAGEMENT

To promote growth and development, plasma levels of ammonia, arginine, branched-chain amino acids, and serum protein should be maintained within normal limits while plasma glutamine is maintained at levels less than 1,000 µmol/L. Minimum daily protein intake for a patient of a particular age should be taken from, for example, “Recommended Dietary Allowances”, 10th ed., Food and Nutrition Board, National Academy of Sciences, 1989. The allocation of dietary nitrogen into natural protein and essential amino acids is a function of age, residual urea-cycle enzyme activity, and the dose of sodium phenylbutyrate.

At the recommended dose of sodium phenylbutyrate, it is suggested that infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period.

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