09-J1000-97

Original Effective Date: 07/15/13

Reviewed: 05/10/23

Revised: 07/01/23

Subject: Sodium Phenylbutyrate (Buphenyl®, Olpruva®, and Pheburane®)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Sodium phenylbutyrate (Buphenyl®) 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.

Sodium phenylbutyrate (Buphenyl®, Olpruva®, Pheburane®) is FDA-approved as adjunctive therapy for the chronic management of hyperammonemia in subjects with urea cycle disorders, including deficiencies in carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) enzymes. Sodium phenylbutyrate (Buphenyl®) is FDA-approved in individuals with neonatal-onset deficiency (i.e., complete enzymatic deficiency, presenting within the first 28 days of life) and in those with late-onset disease (i.e., partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy.

Many individuals continue to have hyperammonemic episodes while receiving sodium phenylbutyrate therapy; however, sodium phenylbutyrate should not be used to treat acute hyperammonemia, because uncontrolled hyperammonemia can rapidly result in brain damage or death. Any episode of acute symptomatic hyperammonemia should be treated as a life-threatening emergency, and prompt use of all therapies necessary to reduce ammonia concentrations is essential. Hemodialysis is the most rapid and effective method for removing ammonia in subjects with acute neonatal hyperammonemic coma, moderate to severe episodes of hyperammonemic encephalopathy, or episodes of hyperammonemia that fail to respond to an initial course of sodium phenylacetate and sodium benzoate therapy.

POSITION STATEMENT:

Initiation of sodium phenylbutyrate (Buphenyl, Olpruva, Pheburane) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. **Urea Cycle Disorders (UCDs)**
    a. The member has a diagnosis of urea cycle disorders (UCD) involving known or proven deficiencies of **ANY** of the following:
        i. carbamylphosphate synthetase (CPS)
        ii. ornithine transcarbamylase (OTC)
        iii. argininosuccinic acid synthetase (AS)
    b. The member is on a protein restrictive diet
    c. The drug is not being used to manage acute hyperammonemia
    d. For brand Buphenyl or Olpruva, the member has tried and had intolerable adverse effects to an adequate trial of generic sodium phenylbutyrate, and **ALL** of the following must be submitted:
        i. The specific intolerance(s) and rationale for use must be specified
        ii.
        iii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
        iv. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
    e. Dosage does not exceed 20 grams per day

Continuation of sodium phenylbutyrate therapy **meets the definition of medical necessity** for the treatment of urea cycle disorders when **ALL** of the following criteria are met:

1. Member has a history of beneficial clinical response with sodium phenylbutyrate therapy for the treatment of urea cycle disorders (does not include use of samples)
2. Member has been previously approved for sodium phenylbutyrate by Florida Blue or another health plan in the past 2 years, or the member has previously met all indication-specific initiation criteria for coverage
3. Dosage does not exceed 20 grams per day

Approval duration: 1 year

Generic sodium phenylbutyrate **meets the definition of medical necessity** when used for **ANY** of the following designated Orphan Drug indications (http://www.fda.gov/orphan/designat/list.htm):

1. Treatment of spinal muscular atrophy

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Sodium Phenylbutyrate Tablets (500 mg): indicated for children weighing more than 20 kg and for adults.

Sodium Phenylbutyrate Powder (level teaspoon = 3 gm): 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. When dissolved in water, sodium phenylbutyrate powder has been shown to be stable for up to one week at room temperature or refrigerated.

The usual total daily dose of sodium phenylbutyrate tablets and powder for urea cycle disorders is 450–600 mg/kg/day in subjects weighing less than 20 kg, or 9.9–13.0 g/m^2/day in larger individuals. 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).

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

Sodium Phenylbutyrate Pellets (Pheburane):

Measure the dose using only the calibrated spoon provided in the packaging. See prescribing information.

Patients weighing less than 20kg: 450 – 600 mg/kg/day of sodium phenylbutyrate orally (oral only). 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/m^2/day of sodium phenylbutyrate orally (oral only). 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 with dietary protein restriction and, in some cases, amino acid supplementation (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).

Sodium Phenylbutyrate Pellets for Oral Suspension (Olpruva):

For adult and pediatric patients weighing 20 kg or greater with a body surface area of 1.2 m^2 or greater, the dose is 9.9 – 13 g/m^2/day orally. Divide the calculated total daily dose into three to six doses. Administer as three to six divided doses and take with food.

Round each dose to the nearest available strength. The maximum dosage is 20 grams per day. Combine with dietary protein restriction and, in some cases, amino acid supplementation (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).

See prescribing information for preparation of the oral suspension.

PRECAUTIONS:

Contraindication:

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

Warnings:

Because of its high sodium content, sodium phenylbutyrate should be used with great care, if at all, in individuals with congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with edema.

Adverse neurotoxic effects, principally somnolence, fatigue, and lightheadedness have been reported in cancer subjects receiving IV phenylacetate, a metabolite of sodium phenylbutyrate. Also reported were headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of existing neuropathy but less frequently.

Monitoring: serum protein concentrations and plasma concentrations of ammonia, arginine, and branched-chain amino acids should be monitored and maintained within normal limits. Plasma glutamine concentrations should be maintained at less than 1000 mcmol/L. Serum phenylbutyrate, phenylacetate, and phenylacetylglutamine concentrations should be monitored periodically. Urinalysis, blood chemistry profiles, and hematologic tests should be monitored routinely.

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 individuals with hepatic or renal insufficiency.

Use of sodium phenylbutyrate tablets in neonates, infants and children weighing less than 20 kg is not recommended.

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

There have been published reports of hyperammonemia being induced by haloperidol and by valproic acid.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

E72.20	Disorder of urea cycle metabolism, unspecified
E72.22	Arginosuccinic aciduria
E72.29	Other disorders of urea cycle metabolism
E72.4	Disorders of ornithine metabolism

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Urea Cycle Disorder: a genetic disorder caused by a mutation that results in a deficiency of one of the six enzymes in the urea cycle. These enzymes are responsible for removing ammonia from the blood stream.

RELATED GUIDELINES:

Glycerol Phenylbutyrate (Ravicti ®), 09-J1000-98

OTHER:

None

REFERENCES:

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4. Micromedex® 2.0, ©2022 Truven Health Analytics Inc. Accessed 01/19/23.
5. National Urea Cycle Disorders Foundation. Copyright© 2005-2014. Available at http://www.nucdf.org/ucd.htm. Accessed 10/09/20.
6. Olpruva (sodium phenylburate pellet) [package insert]. Acer Therapeutics Inc. Newton, MA. December 2022.

7. Phenburane (sodium phenylburate pellet) [package insert]. Medunik USA, Inc. Bryn Mawr, PA. June 2022.
8. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. National Institutes of Health, Rare Diseases Clinical Research Network. Available at http://rarediseasesnetwork.epi.usf.edu/ucdc/physicians/guidelines-main.htm. Accessed 10/09/20.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/10/23.

GUIDELINE UPDATE INFORMATION:

07/15/13	New Medical Coverage Guideline.
01/15/15	Review and revision to guideline; consisting of updating references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/20	Review and revision to guideline; consisting of updating the position statement.
01/01/23	Revision to guideline; consisting of adding Pheburane to the position statement, dosing, and updating dosing and references.
04/01/23	Review and revision to guideline; consisting of adding Olpruva to the position statement, and updating description, dosing and references.
07/01/23	Review and revision to guideline; consisting of updating the step in the position statement.