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## Subject: Urea Cycle Disorders

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<a href="#">Dosage/ Administration</a>	<a href="#">Position Statement</a>	<a href="#">Billing/Coding</a>	<a href="#">Reimbursement</a>	<a href="#">Program Exceptions</a>
<a href="#">Definitions</a>	<a href="#">Related Guidelines</a>	<a href="#">Other</a>	<a href="#">References</a>	<a href="#">Updates</a>

### DESCRIPTION:

[Urea cycle disorders](#) (UCDs), are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH<sub>3</sub>, NH<sub>4</sub><sup>+</sup>). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected individuals.

Sodium phenylbutyrate (Buphenyl<sup>®</sup>, Olpruva<sup>®</sup>, Pheburane<sup>®</sup>) 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<sup>®</sup>) 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.

Glycerol phenylbutyrate (Ravicti<sup>®</sup>) is a nitrogen-binding agent indicated for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. The product must be used with dietary protein restriction and, in some cases, dietary supplements. It is not indicated for treatment of acute hyperammonemia in patients

with UCDs. The safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.

## **POSITION STATEMENT:**

I. 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. Completed Medwatch reporting form (FDA 3500) - <https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda>
  - iii. 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

II. 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

III. 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

IV. Initiation of glycerol phenylbutyrate (Ravicti®) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. The member has a diagnosis of urea cycle disorders (UCD) involving known or proven deficiencies of **ANY** of the following- documentation must be submitted:
  - a. carbamylphosphate synthetase (CPS)
  - b. ornithine transcarbamylase (OTC)
  - c. argininosuccinic acid synthetase (AS)
2. The member has documentation of a protein restrictive diet
3. The drug is not being used to manage acute hyperammonemia or N-acetylglutamate synthase (NAGS) deficiency
4. For Brand Ravicti only, generic glycerol phenylbutyrate is **NOT** available due to a national drug shortage<sup>a</sup> – documentation must be submitted
5. The member has tried and had intolerable adverse effects to an adequate trial of sodium phenylbutyrate **AND** Pheburane and **ALL** of the following must be submitted:
  - a. The specific intolerance(s) and rationale for using glycerol phenylbutyrate must be specified
  - b. Completed Medwatch reporting form (FDA 3500) - <https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda>
  - c. Completed Naranjo Adverse Drug reaction probability scale - <https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf>
6. Dosage does not exceed 17.5 mL (19 grams) daily

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

1. Member has a beneficial response to glycerol phenylbutyrate for the treatment of urea cycle disorders (does not include use of samples)
2. Member has been previously approved for glycerol 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. For Brand Ravicti only, generic glycerol phenylbutyrate is **NOT** available due to a national drug shortage<sup>a</sup> – documentation must be submitted
4. Dosage does not exceed 17.5 mL (19 grams) daily

**Approval duration:** 1 year

<sup>a</sup> To verify non-availability, the status of generic glycerol phenylbutyrate must be listed as “Currently in Shortage” on the ASHP Current Shortages webpage (Drug Shortages List ([ashp.org](http://ashp.org))) AND all listed manufactures must have all strengths unavailable

## 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<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup> or greater, the dose is 9.9 – 13 g/m<sup>2</sup>/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.

## **Glycerol phenylbutyrate (Ravicti)**

Glycerol phenylbutyrate oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles.

Glycerol phenylbutyrate should be taken with food, administered directly into the mouth via oral syringe or dosing cup.

### **Switching From Sodium Phenylbutyrate to Glycerol Phenylbutyrate**

Individuals switching from sodium phenylbutyrate to glycerol phenylbutyrate should receive the dosage of glycerol phenylbutyrate that contains the same amount of phenylbutyric acid. The conversion is as follows:

Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.86

Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate powder(g) x 0.81

### **Initial Dosage in Phenylbutyrate-Naïve Individuals:**

The recommended dosage range, based upon body surface area, in individuals naïve to phenylbutyrate (PBA) is 4.5

to 11.2 mL/m<sup>2</sup>/day (5 to 12.4 g/m<sup>2</sup>/day).

For individuals with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m<sup>2</sup>/day. See prescribing information for an estimation of 24 hr dosing based on the total grams of dietary protein ingested. Follow plasma ammonia levels to determine the need for dose titration.

The total daily dosage should not exceed 17.5 mL (19 grams).

### **Dose Adjustments**

- Hepatic impairment: start dosage at lower end of range.

### **Drug Availability**

- Glycerol phenylbutyrate oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles. The bottles are supplied in the following configurations:
  - Single 25-mL bottle per carton
  - Four 25-mL bottles per carton

## **PRECAUTIONS:**

### **Sodium Phenylbutyrate**

#### **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  $\mu\text{mol/L}$ . 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.

**Glycerol phenylbutyrate (Ravicti)**

**Contraindication:**

Known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

**Warnings:**

The major metabolite of glycerol phenylbutyrate is phenylacetate (PAA) which is associated with neurotoxicity. Signs and symptoms of PAA neurotoxicity include somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting neuropathy.

If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or other intercurrent illnesses, reduce the glycerol phenylbutyrate dosage.

Monitor ammonia levels closely in individuals with pancreatic insufficiency or intestinal malabsorption. Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels.

Monitor ammonia levels closely when corticosteroids and glycerol phenylbutyrate are used concomitantly.

Hyperammonemia may be induced by haloperidol and by valproic acid. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in UCD individuals.

See prescribing information for additional drug interactions.

## BILLING/CODING INFORMATION:

### HCPSC Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS
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### 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 Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#).

## 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:

None.

## OTHER:

None.

## REFERENCES:

1. Buphenyl® Prescribing Information. Horizon Therapeutics, USA, Inc. Deerfield, IL July 2022.
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3. Micromedex® 2.0, ©2020 Truven Health Analytics Inc. Accessed 11/26/25.
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5. Olpruva (sodium phenylburate pellet) [package insert]. Acer Therapeutics Inc. Newton, MA. December 2022.
6. Phenburane (sodium phenylburate pellet) [package insert]. Medunik USA, Inc. Bryn Mawr, PA. June 2022.
7. Ravicti® Prescribing Information. Horizon Therapeutics USA, Inc. Lake Forest (IL). Revised 09/2025.
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 05/20/13.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

## GUIDELINE UPDATE INFORMATION:

03/15/26	New medical coverage guideline to consolidate policies into one guideline.
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