# PRIOR AUTHORIZATION POLICY

**POLICY:** Metabolic Disorders – Phenylbutyrate Products Prior Authorization Policy
- Buphenyl® (sodium phenylbutyrate tablets and powder for oral solution – Horizon, generic)
- Olpruva® (sodium phenylbutyrate for oral suspension – Acer)
- Pheburane® (sodium phenylbutyrate oral pellets – Medunik)
- Ravicti® (glycerol phenylbutyrate oral liquid – Horizon)

**REVIEW DATE:** 03/20/2024; selected revision 06/05/2024

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## OVERVIEW

Phenylbutyrate products are indicated in combination with dietary management for treatment of **urea cycle disorders (UCDs)**.

- **Sodium phenylbutyrate** products are indicated as adjunctive therapy in the chronic management of adult and pediatric patients with UCDs involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).[1-3]
  - **Buphenyl** and **Pheburane** can be administered orally in pediatric patients weighing less than 20 kg.
  - Buphenyl powder is compatible with feeding tube administration.
  - **Olpruva** is indicated for use in patients weighing $\geq$ 20 kg and with a body surface area of $\geq$ 1.2 $m^2$.

  Limitation of use: Sodium phenylbutyrate products are not indicated for the treatment of acute hyperammonemia, which can be a life-threatening medical emergency that requires rapid acting interventions to reduce plasma ammonia levels.
- **Ravicti** is indicated for the chronic management of patients with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[4]

  Limitation of use: Ravicti is not indicated for treatment of acute hyperammonemia in patients with UCDs. Safety and efficacy for treatment of N-acetylglutamate synthetase deficiency has not been established.

## Disease Overview

UCDs are rare inborn errors of metabolism which result from mutations in the genes encoding for enzymes necessary for normal function of the urea cycle: arginase, AS, N-acetyl glutamate synthetase, OTC, and CPS.[5,6] These defects lead to increased amounts of ammonia in the blood which may cause disturbed brain function and severe brain damage. Signs of disease include decreased mental awareness, vomiting, combativeness, slurred speech, unstable gait, and unconsciousness. Diagnosis begins with a clinical suspicion of hyperammonemia.[7] Typically, patients have normal glucose and electrolyte levels. Enzymatic diagnosis and/or genetic testing is also available; however, treatment should not be delayed while waiting for a final diagnosis. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy.[5,6] Treatment includes use of alternative waste nitrogen excretion pathways (e.g., Buphenyl, Ravicti); other treatments may include hemodialysis, dietary protein restriction, and, in some cases, essential amino acid supplementation.

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of phenylbutyrate products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with phenylbutyrate products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Automation**: None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of phenylbutyrate products is recommended in those who meet the following criteria:

### FDA-Approved Indication

1. **Urea Cycle Disorders.** Approve for the duration noted if the patient meets ALL of the following (A, B, C, and D):
   Note: Examples include deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.
   - **A)** According to the prescriber, the diagnosis was confirmed by ONE of the following (i or ii):
     - **i.** Approve for 1 year if genetic or enzymatic testing confirmed a urea cycle disorder; OR
     - **ii.** Approve for 3 months if the patient has hyperammonemia diagnosed with an ammonia level above the upper limit of the normal reference range for the reporting laboratory; AND
       Note: Reference ranges are dependent upon patient's age.
   - **B)** The medication is prescribed in conjunction with a protein-restricted diet; AND
   - **C)** Patient will not be receiving concurrent therapy with another phenylbutyrate product; AND
     Note: Examples of phenylbutyrate products that should not be taken concurrently include sodium phenylbutyrate (Buphenyl, generic), Pheburane, Olpruva, and Ravicti.
   - **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of phenylbutyrate products is not recommended in the following situations:

1. **Concomitant Therapy with Another Phenylbutyrate Product.** There are no data available to support concomitant use.
   Note: Examples of phenylbutyrate products include sodium phenylbutyrate, Olpruva, Pheburane, and Ravicti.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Buphenyl® tablets and powder for oral solution [prescribing information]. Lake Forest, IL: Horizon; July 2022.
2. Olpruva® oral powder for suspension [prescribing information]. Newton, MA: Acer; December 2022.
3. Pheburane® oral pellets [prescribing information]. Princeton, NJ: Medunik; August 2023.
4. Ravicti® oral liquid [prescribing information]. Lake Forest, IL: Horizon; September 2021.

5. Diaz GA, Krivitzky LS, Mokhtarani M, et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. *Hepatology*. 2013;57(6):2171-2179.
6. Hereditary urea cycle abnormality. Medline Plus. A service of the U.S. National Library of Science, National Institutes of Health (NIH). Updated November 1, 2021. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000372.htm. Accessed on March 15, 2024.
7. Summar M. Urea cycle disorders. National Organization of Rare Disorders [Website]. Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/. Accessed on March 15, 2024.