Drug Coverage Policy

Effective Date……6/15/2025
Coverage Policy Number……IP0169
Policy Title…. Phenylbutyrate Products

Metabolic Disorders – Phenylbutyrate Products

- 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)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Phenylbutyrate products are indicated in combination with dietary management for treatment of **urea cycle disorders (UCDs)**.[1-4]

- **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 < 20 kg.
    - Buphenyl powder is compatible with feeding tube administration.
    - **Olpruva** is indicated for use in patients weighing ≥ 20 kg and with a body surface area of ≥ 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.

Coverage Policy

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 Phenylbutyrate products to be prescribed by a physician who has consulted with or who specializes in the condition.

Phenylbutyrate products are considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Urea Cycle Disorders.** Approve for the duration noted if the patient meets ALL of the following (A, B, C, D, and E):

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 on the treatment of metabolic diseases); AND
E. Preferred product criteria are met for the product(s) as listed in the below tables

Employer Plans:

Product	Criteria
Buphenyl Powder (sodium phenylbutyrate powder for oral solution)	The patient has tried the bioequivalent generic product, **sodium phenylbutyrate powder for oral solution**, AND cannot take due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result, per the prescriber, in a significant allergy or serious adverse reaction.
Buphenyl Tablets (sodium phenylbutyrate tablets)	The patient has tried the bioequivalent generic product, **sodium phenylbutyrate tablets**, AND cannot take due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result, per the prescriber, in a significant allergy or serious adverse reaction.
Olpruva (sodium phenylbutyrate for oral suspension)	Patient meets **ONE** of the following: 1. Trial of Pheburane (sodium phenylbutyrate oral pellets) 2. Patient has a feeding tube AND has tried sodium phenylbutyrate powder for oral solution (Buphenyl powder)
Ravicti (glycerol phenylbutyrate oral liquid)	Patient meets **ONE** of the following: 1. Has tried Pheburane (sodium phenylbutyrate oral pellets) 2. Patient has a feeding tube AND has tried sodium phenylbutyrate powder for oral solution (Buphenyl powder) 3. Weighs < 20 kg AND meets **ONE** Of the following: a. Patient has tried Pheburane (sodium phenylbutyrate oral pellets) b. Patient is not eating solid food AND does NOT have a feeding tube (for example, young infant) 4. Patient is on a sodium restricted diet OR, according to the prescriber, a high sodium diet is contraindicated

Individual and Family Plans:

Product	Criteria
Buphenyl Powder (sodium phenylbutyrate powder for oral solution)	The patient has tried the bioequivalent generic product, **sodium phenylbutyrate powder for oral solution**, AND cannot take due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result, per the prescriber, in a significant allergy or serious adverse reaction.
Buphenyl Tablets (sodium phenylbutyrate tablets)	The patient has tried the bioequivalent generic product, **sodium phenylbutyrate tablets**, AND cannot take due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result, per the prescriber, in a significant allergy or serious adverse reaction.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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.

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 December 31, 2023. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000372.htm. Accessed on February 24, 2025.
7. Hyperammonemia in the emergency department. National Urea Cycle Disorders Foundation [Website]. Available at: https://nucdf.org/about-ucd/for-medical-professionals.html. Accessed on February 24, 2025.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	• Buphenyl (sodium phenylbutyrate) powder for oral solution and tablets added to the policy (effective 7/1/2024). • Removed Pheburane preferred product requirements (effective 7/1/2024). • Added Ravicti preferred product requirements (effective 7/1/2024).	04/01/2024
Annual Revision	**Urea Cycle Disorders: Added** note listing examples of urea cycle disorders. **Removed** the requirement for initiating treatment in individuals with suspected urea cycle disorder based on abnormal biochemical testing. **Updated** approval criteria for 3 months to require a diagnosis of hyperammonemia, with ammonia levels exceeding the upper limit of the normal reference range for the reporting laboratory and added a note indicating that reference ranges vary depending on the patient's age. **Removed** Pheburane preferred product step requirement for Employer Plans. **Added** preferred product step requirement for Buphenyl powder and tablets for Individual and Family Plans. **Conditions Not Covered: Removed** N-acetylglutamate synthase (NAGS) deficiency.	10/01/2024
Annual Revision	No criteria change.	6/15/2025

The policy effective date is in force until updated or retired.