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

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 AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

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.

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is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

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 COVERED

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is(are) considered experimental, investigational or unproven for ANY other use(s) 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 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/29/2023
Selected Revision	New formulation, Olpruva, was added to the policy.	07/12/2023
Annual Revision	No criteria changes.	03/20/2024
Selected Revision	**Urea Cycle Disorders**: Modified option of approval regarding genetic testing confirmation of a mutation to state genetic or enzymatic testing confirming a urea cycle disorder.	06/05/2024