Phenylbutyrate

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Related Coverage Resources

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. 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

This policy supports medical necessity review for the following phenylbutyrate products:

- **Pheburane**® (sodium phenylbutyrate) oral pellets
- **Ravicti**® (glycerol phenylbutyrate) oral liquid

Coverage for sodium phenylbutyrate (Pheburane) varies across plans and requires the use of preferred products in addition to the criteria listed below. Refer to the customer’s benefit plan document for coverage details.

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

Initial Approval Criteria

Phenylbutyrate products (Pheburane, Ravicti) are considered medically necessary for the treatment of Urea Cycle Disorders when the individual meets ONE of following criteria:

1. **Pheburane (sodium phenylbutyrate)**: Individual meets **ALL** of the following (1, 2, and 3):
1. Individual will NOT be receiving concurrent therapy with another phenylbutyrate product (for example, Buphenyl, Ravicti, sodium phenylbutyrate)
2. Medication is prescribed by, or in consultation with, a metabolic disease specialist or specialist who focuses in the treatment of metabolic diseases
3. There is documentation the individual has tried generic sodium phenylbutyrate (Buphenyl) powder for oral solution AND cannot take due to a formulation difference in the inactive ingredient(s) which resulted in a significant allergy or serious adverse reaction.

II. **Ravicti (glycerol phenylbutyrate):** Individual meets ALL of the following (1, 2, 3, and 4):

1. **ONE** of the following (a or b):
   a. Documented diagnosis of urea cycle disorder confirmed by enzymatic or genetic testing
   b. Initiation of treatment in an individual with suspected urea cycle disorder based on documented abnormal biochemical testing
2. The medication is prescribed in conjunction with a protein-restricted diet
3. Individual will NOT be receiving concurrent therapy with another phenylbutyrate product (for example, Buphenyl, Pheburane, sodium phenylbutyrate)
4. Medication is prescribed by, or in consultation with, a metabolic disease specialist or specialist who focuses in the treatment of metabolic diseases

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.

**Continuation of Therapy**

Continuation of Phenylbutyrate products (Pheburane, Ravicti) are considered medically necessary for continued use when BOTH of the following are met (1 and 2):

1. Initial criteria are met AND beneficial response is demonstrated
2. For an individual with abnormal biochemical test results with a suspected urea cycle disorder and treatment was initiated while confirmatory testing was pending, **ONE** of the following is met (A or B):
   A. Genetic testing has confirmed a mutation resulting in a urea cycle disorder
   B. Enzymatic testing has confirmed an enzyme deficiency resulting in a urea cycle disorder (for example deficiencies in carbamylphosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinate lyase or arginase)

**Authorization Duration**

Initial authorization and reauthorization approval duration is up to 12 months if genetic or enzymatic testing has confirmed a urea cycle disorder.

Authorization is one-time only, for 3 months, if there is no genetic or enzymatic testing confirmation.

**Conditions Not Covered**

Any other use is considered experimental, investigational or unproven including the following (this list may not be all inclusive):

1. Concomitant Therapy with Another Phenylbutyrate Product (for example, Buphenyl, Pheburane, Ravicti, sodium phenylbutyrate). There are no data available to support concomitant use.
2. **N-acetylglutamate synthase (NAGS) deficiency.** The safety and efficacy of Ravicti for the treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.

### Background

#### OVERVIEW
Phenylbutyrate products are indicated for treatment of **urea cycle disorders**.

- **Sodium phenylbutyrate** is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.¹

- **Ravicti** is indicated for chronic management patients with urea cycle disorders that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.²
  **Limitation of use:** Ravicti is not indicated for treatment of acute hyperammonemia in patients with urea cycle disorders. Safety and efficacy for treatment of N-acetylglutamate synthetase deficiency has not been established.

- **Pheburane** is indicated as adjunctive therapy for the chronic management of adults and pediatric patients with urea cycle disorders involving deficiencies of carbamyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.
  **Limitation of use:** Episodes of acute hyperammonemia may occur in patients while on Pheburane. Pheburane is 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.³

### Disease Overview

Urea cycle disorders 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, argininosuccinic acid synthetase, N-acetyl glutamate synthetase, ornithine transcarbamylase, and carbamyl phosphate synthetase.⁴,⁵ They 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, combative, slurred speech, unstable gait, and unconsciousness. Diagnosis begins with a clinical suspicion of hyperammonemia.⁶ 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.⁴,⁵ 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.

### References

1. Buphenyl® tablets and powder for oral solution [prescribing information]. Lake Forest, IL: Horizon; May 2021.
2. Ravicti® oral liquid [prescribing information]. Lake Forest, IL: Horizon; September 2021.