Urea Cycle Disorders (UCDs): Pheburane (sodium phenylbutyrate), Olpruva (sodium phenylbutyrate) and Ravicti (glycerol phenylbutyrate)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

1. Pheburane is a nitrogen-binding agent indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).
2. Olpruva is a nitrogen-binding agent indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients weighing 20 kg or greater and with a body surface area (BSA) of 1.2 m2 or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).
3. Ravicti 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. Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

Limitations of Use

1. Pheburane and Olpruva are not indicated for the treatment of acute hyperammonemia.
2. Ravicti is not indicated for treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.
3. The safety and efficacy of Ravicti for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.

POLICY

Documentation

A. Initial Requests:
   1. Enzyme assay, biochemical, or genetic testing results supporting diagnosis
   2. Lab results documenting baseline plasma ammonia levels
   3. Member's chart notes or medical record documentation and claims history of trial and failure of all forms of sodium phenylbutyrate including dosage, duration, response to therapy, dietary restriction of sodium intake, and clinical rationale for using Pheburane or Ravicti
   4. If therapy with generic sodium phenylbutyrate is not advisable due to a condition requiring sodium restriction, documentation of comorbid condition(s) requiring restriction of sodium intake is required
B. Continuation of therapy requests: lab results documenting a reduction in plasma ammonia levels from baseline

Criteria for Initial Approval

A. Pheburane (sodium phenylbutyrate oral pellets) and Olpruva (sodium phenylbutyrate for oral suspension)

Authorization of 12 months may be granted for chronic management of urea cycle disorders (UCDs) when all of the following criteria are met:

1. Diagnosis was confirmed by enzymatic, biochemical, or genetic testing
2. The medication is prescribed by, or in consultation with, a specialist in metabolic disorders
3. Member has elevated plasma ammonia levels at baseline
4. Member is unable to manage the disorder by dietary protein restriction and/or amino acid supplementation alone
5. The medication will be used along with a protein restricted diet and in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements)
6. Member has tried and failed generic sodium phenylbutyrate due to experiencing adverse event(s) or intolerance(s). If member has a nasogastric or gastrostomy tube, treatment failure would not be caused by poor palatability and smell.
   a. Failure of generic sodium phenylbutyrate occurred despite limiting dietary sodium intake
   b. Adverse event(s) or intolerance(s) were not attributed to the active ingredient (phenylbutyrate)
7. The medication is not being used for the treatment of acute hyperammonemia

B. Ravicti

Authorization of 12 months may be granted for chronic management of urea cycle disorders (UCDs) when all of the following criteria are met:

1. Diagnosis was confirmed by enzymatic, biochemical, or genetic testing
2. The medication is prescribed by, or in consultation with, a specialist in metabolic disorders
3. Member has elevated plasma ammonia levels at baseline
4. Member is unable to manage the disorder by dietary protein restriction and/or amino acid supplementation alone
5. The medication will be used along with a protein restricted diet and in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements)

6. Member meets ANY of the following criteria:
   a. Member has tried and failed generic sodium phenylbutyrate due to experiencing adverse event(s) or intolerance(s)
      i. Failure of generic sodium phenylbutyrate occurred despite limiting dietary sodium intake
      ii. Adverse event(s) or intolerance(s) were not attributed to the active ingredient (phenylbutyrate)
   b. Member trial of generic sodium phenylbutyrate resulted in worsening of renal function, cardiac output, or blood pressure attributed to the high sodium content of sodium phenylbutyrate and was not due to other causes
   c. Member has a clinical reason to restrict sodium intake (i.e., severe renal impairment, congestive heart failure, hypertension, or other comorbid condition where there is sodium retention with edema) prohibiting a trial of sodium phenylbutyrate due to its sodium content
7. Member meets ANY of the following criteria:
   a. Member has tried and failed Pheburane (sodium phenylbutyrate oral pellets) or Olpruva (sodium phenylbutyrate for oral suspension) due to experiencing adverse events(s)
      i. Failure of Pheburane (sodium phenylbutyrate oral pellets) or Olpruva (sodium phenylbutyrate for oral suspension) occurred despite limiting dietary sodium intake
      ii. Adverse event(s) was not attributed to the active ingredient (phenylbutyrate)
   b. Member trial of Pheburane (sodium phenylbutyrate oral pellets) or Olpruva (sodium phenylbutyrate for oral suspension) resulted in worsening of renal function, cardiac output, or blood pressure attributed to the high sodium content of Pheburane and was not due to other causes
   c. Member has a clinical reason to restrict sodium intake (i.e., severe renal impairment, congestive heart failure, hypertension, or other comorbid condition where there is sodium retention with edema) prohibiting a trial of Pheburane (sodium phenylbutyrate oral pellets) or Olpruva (sodium phenylbutyrate for oral suspension) due to the sodium content
   d. Member has a nasogastric or gastrostomy tube
8. The medication is not being used for the treatment of acute hyperammonemia

C. No prior authorization is required for generic sodium phenylbutyrate oral tablets for the chronic management of urea cycle disorders (UCDs).

The aforementioned drugs are considered **not medically necessary** for patients who do not meet the criteria set forth above.

Continuation of Therapy

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for chronic management of a urea cycle disorder (UCD) who meet Criteria for Initial Approval above AND are experiencing benefit from therapy as evidenced by a reduction in plasma ammonia levels from baseline.

Quantity Limit

Trade Name	Generic Name	Quantity Limit
Pheburane (sodium phenylbutyrate) 483mg/1gm coated pellets	sodium phenylbutyrate	Maximum daily dose: 20 grams Maximum 8 bottles (84 grams per bottle) per 30 days
Ravicti	glycerol phenylbutyrate	Maximum daily dose: 19 grams (17.5 mL)
Olpruva (sodium phenylbutyrate) 2gm, 3gm,	Sodium phenylbutyrate	90 envelopes (1 kit) per 30 days

Trade Name	Generic Name	Quantity Limit
4gm, 5gm, 6gm, 6.67gm per envelope)		

Non-Formulary Exception Criteria

Non-Formulary Exception Criteria applies to formularies which do not include the requested product(s) on the formulary drug list. Meeting the criteria above may satisfy some, or all, portions of the Non-Formulary Exception Criteria. A medication that is non-formulary may be covered when the Criteria for Approval AND the following criteria are met:

1. The requested drug must be used for an FDA-approved indication, or an indication supported in the compendia of current literature (examples: AHFS, Micromedex, current accepted guidelines). Diagnostic testing/lab results required when applicable.
2. The prescribed dose/quantity must fall within the FDA-approved labeling or dosing guidelines found in the compendia of current literature.
3. All covered formulary alternative drugs on any tier will be ineffective, have been ineffective, would not be as effective as the non-formulary drug, or would have adverse effects. Documentation is required and must include chart note(s) or other documentation indicating prior treatment failure, severity of the adverse event (if any), and dosage and duration of the prior treatment, or contraindication to formulary alternatives.

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

CLINICAL RATIONALE

Ravicti (glycerol phenylbutyrate) must be taken with food or formula and used with dietary protein restriction and, in some cases, dietary supplements. Ravicti is commercially available as a tasteless, odorless liquid that is preferably administered orally, but is suitable for administration via nasogastric or gastrostomy tube if oral administration is not feasible. It is noteworthy that Ravicti (glycerol phenylbutyrate) does not contain any sodium unlike Buphenyl (sodium phenylbutyrate), Olpruva (sodium phenylbutyrate), and Pheburane (sodium phenylbutyrate). In comparison to glycerol phenylbutyrate, these sodium phenylbutyrate products provide approximately 125 mg of sodium per gram of sodium phenylbutyrate. Usual dosing of sodium phenylbuterate products would provide more sodium than recommended daily allowances and should be used with caution in populations who must maintain a low sodium intake.

Buphenyl is available as oral tablets and powder for administration via the oral route or via nasogastric or gastrostomy tube but is known for having poor palatability among patients. Olpruva and Pheburane offer improved palatability over Buphenyl, but the availability of nasogastric or gastrostomy tube administration is unique to only Buphenyl and Ravicti. Olpruva is available in packet form for oral suspension only. Similarly, Pheburane is available for oral administration in a pellet form that may be swallowed with a drink or sprinkled on soft food, but administration via nasogastric or gastrostomy tubes has not been evaluated.

Both glycerol phenylbutyrate and sodium phenylbutyrate are metabolized to the same active compound, phenylacetate. There are no data to suggest that either product is safer or more efficacious. A randomized, double-blind, study evaluated Ravicti and sodium phenylbutyrate among adults with urea cycle disorders. The primary endpoint was the 24-hour AUC for venous ammonia at steady state and included a prespecified noninferiority threshold. Forty-four patients were evaluated and the prespecified noninferiority threshold was met. The mean 24-hour AUCs for ammonia were 866 µmol·hr/L with Ravicti versus 977 µmol·hr/L with

sodium phenylbutyrate. Additionally, Ravicti was compared to sodium phenylbutyrate in an open-label, switchover study enrolling pediatric patients 2 to 17 years of age with urea cycle disorders which resulted in similar 24-hour AUCs for ammonia between Ravicti and sodium phenylbutyrate. Despite variations in sodium content, palatability, and available routes of administration the available clinical data do not demonstrate a significant safety or efficacy advantage of glycerol phenylbutyrate over sodium phenylbuturate.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- Code(s), if applicable

REFERENCES

- Pheburane [package insert]. Bryn Mawr, PA: Medunik USA, Inc.; June 2022.
- Ravicti [package insert]. Lake Forest, IL: Horizon Pharma USA, Inc; September 2021.
- Mew NA, Lanpher BC. Urea Cycle Disorders Overview. In: Pagon RA, Adam MP, Ardinger HH, et. al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017 [updated April 9, 2015]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1217/?report=printable.
- Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *J Inherit Metab Dis*. 2019;42(6):1192-1230.
- 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.
- Smith W, Diaz GA, Lichter-Konecki U, et al. Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. J Pediatr. 2013;162(6):1228-1234.

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POLICY HISTORY

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