Pharmacy Policy Bulletin: J-0179 Urea Cycle Disorder Medications - Commercial and Healthcare Reform	
Number: J-0179	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform**: Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):**
Version: J-0179-018	**Original Date:** 06/06/2013
Effective Date: 04/25/2025	**Review Date:** 04/09/2025

Drugs Product(s):	• Buphenyl (sodium phenylbutyrate) • Carbaglu (carglumic acid) • Olpruva (sodium phenylbutyrate) • Pheburane (sodium phenylbutyrate) • Ravicti (glycerol phenylbutyrate)
FDA-Approved Indication(s):	• **Buphenyl** ○ Adjunct therapy to dietary protein restriction and, in some cases, essential amino acid supplementation in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). Specifically: ▪ All patients with neonatal-onset deficiency (complete enzyme deficiency, presenting within the first 28 days of life) ▪ Patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy • **Carbaglu** ○ Indicated in pediatric and adult patients as: ▪ Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency. ▪ Maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency. ▪ Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA). • **Olpruva** ○ 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 m^2 or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate

	synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)
	• **Pheburane**
	  ○ 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)
	• **Ravicti**
	  ○ Chronic management of patients with 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.

Background:	• Sodium phenylbutyrate is a prodrug and is rapidly metabolized to phenylacetate (PAA), which conjugates with glutamine to form phenylacetylgutamine (PAGN). PAGN provides an alternative to urea for nitrogen waste excretion for patients who cannot synthesize urea due to UCDs.
	• Carbaglu (carglumic acid) is a synthetic analogue of N-acetylglutamate (NAG), which activates carbomoyl phosphate synthetase-1 in hepatic mitochondria to allow for the conversion of ammonia to urea.
	• Ravicti (glycerol phenylbutyrate) is a triglyceride containing 3 phenylbutyrate (PBA) molecules. PAA, the active moiety of PBA, conjugates with glutamine to form PAGN which provides an alternative to urea for nitrogen waste excretion for patients who cannot synthesize urea due to UCDs.
	• The normal urea cycle in an individual utilizes six enzymes that, through multiple steps, facilitate the removal of ammonia through the metabolism of amino acids. The six enzymes include arginosuccinic acid synthetase (ASS), arginosuccinase acid lyase (ASL), arginase (ARG), N-actetylglutamate synthetase (NAGS), carbamoyl phosphate synthetase I (CPS1), and ornithine transcarbamylase (OTC). Genetic defects in these enzymes can result in a UCD. The overall incidence of these defects has been estimated to be 1 in 20,000 to 1 in 35,000. In patients with a UCD, nitrogen accumulates in a variety of molecules, namely ammonium, which can result in brain damage, coma, or death. Neonatal-onset UCD is often related to a complete enzyme deficiency and is typically more severe than what is seen in patients with a partial deficiency (“late-onset” disease).
	• The 2019 Journal of Inherited Metabolic Disease for the Diagnosis and Management of Urea Cycle disorders recommend sodium phenylbutyrate, glycerol phenylbutyrate, sodium benzoate, sodium phenylacetate, L-arginine, L-citrulline, and carbamylglutamate as first line therapies for chronic management of UCDs. The guidelines state that there are no consistent recommendations for drug treatment; however, nitrogen-binding agents are stated as a mainstay of therapy for UCD patients. These guidelines have been updated to include Pheburane as a first-line treatment option for patients.
	• Prescribing Considerations:
	  ○ Prescribing and treatment should be supervised by a healthcare provider experienced in the treatment of UCDs.
	  ○ Buphenyl (sodium phenylbutyrate)
	  ▪ Plasma levels of ammonia, arginine, branched-chain amino acids, and serum proteins should be maintained within normal limits, and plasma glutamine should be maintained at levels less than 1,000 µmol/L.
	  ▪ The powder formulation can be administered via nasogastric (NG) tube, but the tablet formulation cannot.

	▪ Generic sodium phenylbutyrate is highly emetic and is usually only tolerated with NG tube administration. This formulation may be contraindicated in patients taking medication orally. ○ Carbaglu (carglumic acid) ▪ Therapeutic monitoring for NAGS deficiency: closely monitor plasma ammonia and titrate dosage to maintain the ammonia level within normal range for the patient's age, taking into consideration their clinical condition. ▪ Acute hyperammonemia due to PA or MMA: continue treatment until ammonia level is less than 50 micromol/L and for a maximum duration of 7 days. ▪ Carbaglu must be dispersed in water and can be administered orally or through a NG tube. ○ Olpruva or Pheburane ▪ Monitor plasma ammonia levels to determine the need for dosage adjustment. ▪ If a patient develops new-onset edema or worsening edema while on treatment, discontinue administration and initiate appropriate therapy. ▪ Olpruva and Pheburane cannot be administered through a NG tube. ▪ Olpruva and Pheburane are formulated to have a masked taste. ▪ Generic sodium phenylbutyrate is highly emetic and is usually only tolerate with administration through an NG tube. This formulation may be contraindicated in patients taking medication orally. ○ Ravicti ▪ Ravicti is approved for chronic management of UCDs regardless of the specific protein deficiency present. Possible protein deficiencies include AS, ASL, ARG, NAGS, CPS, and OTC. ▪ Follow plasma ammonia levels to determine the need for dosage titration. ▪ Ravicti can be administered through a NG tube. ▪ Ravicti is formulated to have a masked taste.

Approval Criteria

I. Initial Authorization

A. Buphenyl (sodium phenylbutyrate) or Pheburane

When a benefit, coverage of Buphenyl (sodium phenylbutyrate) or Pheburane may be approved when all of the following criteria are met **(1. through 4.)**:

1. The member meets both of the following criteria **(a. and b.)**:
   a. The member is using Buphenyl (sodium phenylbutyrate) or Pheburane for chronic management of urea cycle disorders. (ICD -10: E72.20)
   b. The member is using Buphenyl (sodium phenylbutyrate) or Pheburane involving deficiencies of carbamylphosphate synthetase (CPS), argininosuccinic acid synthetase (AS), or ornithine transcarbamylase (OTC).

2. The member is using Buphenyl (sodium phenylbutyrate) or Pheburane as adjunctive therapy to dietary protein restriction.

3. If the request is for brand Buphenyl, the member has experienced therapeutic failure, intolerance, or contraindication to generic sodium phenylbutyrate.

4. If the request is for brand Pheburane, the member has experienced therapeutic failure, intolerance, or contraindication to plan-preferred generic sodium phenylbutyrate.

B. Carbaglu (carglumic acid)

When a benefit, coverage of Carbaglu (carglumic acid) may be approved when one (1) of the following criteria is met **(1. through 4.)**:

1. The member meets both of the following criteria **(a. and b.)**:
   - **a.** The member is using Carbaglu (carglumic acid) as adjunctive therapy to standard of care for acute hyperammonemia (ICD-10: E72.20)
   - **b.** The member is using Carbaglu (carglumic acid) for acute hyperammonemia due to hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency.
2. The member is using Carbaglu (carglumic acid) as maintenance therapy for chronic hyperammonemia due to hepatic enzyme NAGS deficiency.
3. The member is using Carbaglu (carglumic acid) as adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA).
4. If the request is for brand Carbaglu, the member has experienced therapeutic failure or intolerance to generic carglumic acid.

C. Olpruva

When a benefit, coverage of Olpruva may be approved when all of the following criteria are met **(1. through 4.)**:

1. The member meets both of the following criteria **(a. and b.)**:
   - **a.** The member is using Olpruva for chronic management of urea cycle disorders. (ICD-10: E72.20)
   - **b.** The member is using Olpruva for urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), argininosuccinic acid synthetase (ASS), or ornithine transcarbamylase (OTC).
2. The member is using Olpruva as adjunctive therapy to dietary management.
3. If the member is less than 18 years of age, the member weighs 20 kg or greater and has a body surface area (BSA) of 1.2 m^2 or greater.
4. The member has experienced therapeutic failure, intolerance, or contraindication to plan-preferred generic sodium phenylbutyrate.

D. Ravicti

When a benefit, coverage of Ravicti may be approved when all of the following criteria are met **(1. through 5.)**:

1. The member is using Ravicti for the chronic management of UCDs. (ICD-10: E72.20)
2. Documentation of specific protein deficiency subtype (e.g. carbamylphosphate synthetase [CPS], ornithine transcarbamylase [OTC] or argininosuccinic acid synthetase [AS]).
3. The UCD cannot be managed by dietary protein restriction and/or amino acid supplementation alone.
4. The member is using Ravicti as adjunctive therapy to dietary protein restriction.
5. If the member has a deficiency of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS), the member has experienced therapeutic failure, intolerance, or contraindication to both of the following plan-preferred medications **(a. and b.)**:
   - **a.** Generic sodium phenylbutyrate
   - **b.** Pheburane

II. Reauthorization

A. Buphenyl (sodium phenylbutyrate), Olpruva, or Pheburane
When a benefit, reauthorization of Buphenyl (sodium phenylbutyrate), Pheburane, or Olpruva may be approved when both of the following criteria are met **(1. and 2.)**:
1. The prescriber attests that the member has experienced positive clinical response to therapy (e.g., reduction in blood ammonia levels).
2. The member is continuing use of requested drug with standard of care (e.g., dietary protein restriction and/or amino acid supplementation).

B. Carbaglu (carglumic acid)
When a benefit, reauthorization of Carbaglu (carglumic acid) may be approved when both of the following criteria are met **(1. and 2.)**:
1. The prescriber attests that the member has experienced positive clinical response to therapy (e.g., reduction in blood ammonia levels).
2. If Carbaglu (carglumic acid) is being used for the treatment of acute hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency or treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA), the member meets the following criterion **(a.)**:
    a. The member is continuing use of requested drug with standard of care (e.g., dietary protein restriction and/or amino acid supplementation).

C. Ravicti
When a benefit, reauthorization of Ravicti may be approved when both of the following criteria are met **(1., 2., and 3.)**:
1. The prescriber attests that the member has experienced positive clinical response to therapy (e.g., reduction in blood ammonia levels).
2. The member is continuing use of Ravicti with standard of care (e.g., dietary protein restriction and/or amino acid supplementation).
3. If the member has a deficiency of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS), the member has experienced therapeutic failure, intolerance, or contraindication to both of the following plan-preferred medications **(a. and b.)**:
    a. Generic sodium phenylbutyrate
    b. Pheburane

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Ravicti, Buphenyl (sodium phenylbutyrate), Olpruva, or Pheburane will not be approved for coverage for treatment of acute hyperammonemia in patients with UCDs.
II. Ravicti will not be approved for coverage of UCDs due to NAGS deficiency.
III. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
IV. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Olpruva [package insert]. Newton, MA: Acer Therapeutics; December 2022.
2. Pheburane [package insert]. Bryn Mawr, PA: Medunik USA; August 2023.
3. Buphenyl [package insert]. Deerfield, IL: Horizon Therapeutics USA, Inc.; March 2023.
4. Carbaglu [package insert]. Lebanon, NJ: Recordati Rare Diseases Inc.; January 2024.
5. Ravicti [package insert]. Deerfield, IL. Horizon Therapeutics USA, Inc.; September 2021.
6. National Organization on Rare Disease (NORD). Urea Cycle Disorders. Available at https://www.filiere-g2m.fr/images/NORD_Physician_Guide_to_Urea_Cycle_Disorders.pdf. Accessed February 11, 2025.
7. Summar ML, Koelker S, Freedenberg D, et al. The incidence of urea cycle disorders. *Mol Genet Metab*. 2013; 110(0):179-180.
8. Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012; 7:32.
9. Clinical Pharmacology powered by ClinicalKey Online. Tampa, FL: Elsevier; 2025. Accessed February 11, 2025.
10. DRUGDEX System (Micromedex 2.0), Greenwood Village, CO, Truven Health Analytics; 2025. Accessed February 11, 2025.