UREA CYCLE DISORDERS (UCD) MEDICATIONS
PRIOR AUTHORIZATION CRITERIA
(Buphenyl, Carbaglu, and Ravicti)

A urea cycle disorder is a genetic disorder caused by a mutation that results in a deficiency of one of the six enzymes in the urea cycle. These enzymes are responsible for removing ammonia from the blood stream. In urea cycle disorders, nitrogen accumulates in the form of ammonia, a highly toxic substance, resulting in hyperammonemia. Ammonia reaches the brain through the blood, where it can cause irreversible brain damage, coma and/or death.

Drugs Addressed in this Policy

- Buphenyl (sodium phenylbutyrate)
- Carbaglu (carglumic acid)
- Ravicti (glycerol phenylbutyrate)

FDA-Approved Indications

Buphenyl

- Adjunct therapy to dietary protein restriction and occasionally essential amino acid supplementation in urea cycle disorders with neonatal-onset (complete enzyme deficiency and presents within the first 28 days of life) or late-onset (partial deficiency occurring after the first month of life) involving deficiencies of carbamylphosphate synthetase (CPS), argininosuccinic acid synthetase (ASS), or ornithine transcarbamylase (OTC).

Carbaglu

- Adult and pediatric patients as adjunctive therapy for acute hyperammonemia due to hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency.
- Adult and pediatric patients as maintenance therapy for chronic hyperammonemia due to hepatic enzyme NAGS deficiency.
Ravicti

- Use as a nitrogen-binding agent for chronic management of urea cycle disorders (UCDs) in adult and pediatric patients older than 2 years when the condition cannot be managed by dietary protein restriction with or without amino acid supplementation alone.

Approval Criteria

Buphenyl (sodium phenylbutyrate)
When a benefit, coverage for sodium phenylbutyrate may be approved if all of the following criteria are met:
1) Sodium phenylbutyrate is being used for chronic management of urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), argininosuccinic acid synthetase (ASS), or ornithine transcarbamylase (OTC)
2) Sodium phenylbutyrate is prescribed as an adjunct therapy to dietary protein restriction

Carbaglu (carglumic acid)
When a benefit, coverage for carglumic acid may be approved if one of the following criteria are met:
1) Carglumic acid is being used as an adjunct therapy for acute hyperammonemia
2) Carglumic acid is being used for maintenance therapy for chronic hyperammonemia due to hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency

Ravicti (glycerol phenylbutyrate)
When a benefit, coverage for glycerol phenylbutyrate may be approved if all of the following criteria are met:
1) Glycerol phenylbutyrate is being used for chronic management of a urea cycle disorders (UCDs)
2) The urea cycle disorder cannot be managed by dietary protein restriction alone
3) Glycerol phenylbutyrate is to be used in combination with dietary protein restriction

Background

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-acetylglutamate synthetase (NAGS), carbamoyl phosphate synthetase I (CPS1), and ornithine transcarbamylase (OTC). Genetic defects in these enzymes can result in a urea cycle disorder (UCD). The overall incidence of these defects has been estimated to be 1 in 20,000 to 1 in 30,000.

A urea cycle disorder (UCD) has two main biochemical consequences: arginine becomes an essential amino acid (excluding an arginase deficiency), and nitrogen accumulates in a variety of molecules, namely ammonium, which can result in brain damage, coma, or death.

Mechanism of Action

Buphenyl

- Sodium phenylbutyrate is a prodrug and is rapidly metabolized to phenylacetate, the active form. Phenylacetate conjugates with glutamine via acetylation to form phenylacetylglutamine, which provides a different vehicle for nitrogen waste excretion by the kidneys. Thus, sodium phenylbutyrate decreases elevated plasma ammonia glutamine concentrations in patients with UCDs.
Carbaglu

- Carglumic acid, a synthetic analogue of N-acetylglutamate (NAG), activates carbomoyl phosphate synthetase-1 in hepatic mitochondria which allows for the conversion of ammonia to urea.

Ravicti

- Glycerol phenylbutyrate, a triglyceride containing 3 phenylbutyrate (PBA) molecules, is released from the glycerol backbone by lipases in the gastrointestinal tract and hydrolyzed to phenylbutyrate (PBA), which is converted by beta-oxidation to form the active moiety, phenylacetate (PAA). PAA conjugates with glutamine (providing 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN). Two moles of nitrogen on PAGN provide an alternative to urea for nitrogen waste excretion for patients who cannot synthesize urea due to UCDs.

When any of these medications are approved, they must be obtained through our specialty pharmacy. Approvals will be given for a period of one year.

*Criteria is adapted from Highmark J-179*