BlueCross BlueShield
Federal Employee Program

BUPHENYL tablet, powder for solution (sodium phenylbutyrate)
OLPRUVA packets for oral suspension (sodium phenylbutyrate)
PHEBURANE oral pellets (sodium phenylbutyrate)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Urea cycle disorders include a group of diseases, each having a specific liver enzyme deficiency. Because they are inherited, other family members may be affected. These disorders vary in severity and may be first detected at various ages, from newborn infants to adults. They lead to increased amounts of ammonia in the blood, which may cause disturbed brain function and severe brain damage (1-3).

Buphenyl is available both as tablets and a powder for oral use (via mouth, gastrostomy, or nasogastric tube) with meals or feedings and helps dispose of ammonia in the body. Olpruva is available as packets for oral suspension. Pheburane is available as a taste-masked oral pellet. Sodium phenylbutyrate is intended for patients who have UCD that cannot be managed by a protein-restricted diet or amino acid supplements alone. Buphenyl, Olpruva, and Pheburane must be used with a protein-restricted diet and, in some cases, dietary supplements (1-3).

Regulatory Status

FDA-approved indication: Buphenyl, Olpruva, and Pheburane are indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) (1-3).

Limitations of Use**:**
Buphenyl, Olpruva, and Pheburane are not indicated for treatment of acute hyperammonemia in patients with UCDs (1-3).

Caution should be used when using haloperidol and valproic acid. Buphenyl, Olpruva, and Pheburane should be used with great care, if at all, in patients with congestive heart failure or severe renal insufficiency and in clinical states in which there is sodium retention with edema. Probenecid may inhibit renal transport of Buphenyl, Olpruva, and Pheburane. Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels.

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The use of tablets for neonates, infants, and children under the weight of 20kg is not recommended (1-3).

Plasma phenylacetate and 24 hour urinary phenylacetylgutamine (a metabolite of phenylbutyrate) should be evaluated when initiating therapy (for 1 to 2 days) to monitor for drug toxicity and inadequate response to therapy. The metabolite of sodium phenylbutyrate and glycerol phenylbutyrate (phenylacetate) can cause neurotoxicity if plasma levels are elevated. The 24 hour test correlates well with the bioconversion and metabolism of these molecules (4).

Summary

Buphenyl, Olpruva, and Pheburane are indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). Patients with urea cycle disorders should not take valproic acid, haloperidol, or steroids as these drugs have been reported to increase blood ammonia levels, and probenecid may affect the kidneys' excretion. Use with great care, if at all, in patients with congestive heart failure or severe renal insufficiency, and in clinical states where there is sodium retention with edema. Use caution when administering to patients with hepatic or renal insufficiency or inborn errors of beta oxidation. The safety or efficacy of doses in excess of 20 grams (40 tablets) per day has not been established (1-3).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Buphenyl, Olpruva, and Pheburane while maintaining optimal therapeutic outcomes.

References

1. Buphenyl [package insert]. Lake Forest, IL: Horizon Therapeutics, Inc. March 2023.
2. Pheburane [package insert]. Bryn Mawr, PA: Medunik USA, Inc. June 2022.
3. Olpruva [package insert]. Newton, MA: Acer Therapeutics, Inc.; December 2022.
4. Mokhatarani M, Diaz GA, Rhead W et al. Urinary phenylacetylgutamine as dosing biomarker for patients with urea cycle disorders. *Mol. Genet Metab.* 2012,107(3):308-14.