Clinical Policy: Sodium Phenylbutyrate (Buphenyl, Pheburane)

Reference Number: ERX.SPA.21
Effective Date: 07.01.16
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Sodium phenylbutyrate (Buphenyl®, Pheburane®) is a nitrogen-binding agent.

FDA Approved Indication(s)
Buphenyl is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).

Pheburane is indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with UCDs, involving deficiencies of CPS, OTC or AS.

Limitation(s) of use: Buphenyl and Pheburane should not be used to manage acute hyperammonemia, which is a medical emergency.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Buphenyl and Pheburane are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Urea Cycle Disorders: CPS, OTC, AS (must meet all)**:**

1. Diagnosis of a UCD caused by one or more of the following, confirmed by enzymatic, biochemical, or genetic analysis:
   a. CPS deficiency;
   b. OTC deficiency;
   c. AS deficiency;
2. Prescribed by or in consultation with a physician experienced in treating metabolic disorders;
3. Dose does not exceed 20 grams per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Urea Cycle Disorders: CPS, OTC, AS (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 20 grams per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ASL: argininosuccinate lyase
AS: argininosuccinate synthetase
CPSI: carbamyl phosphate synthetase I
CTLN1: type I citrullinemia
FDA: Food and Drug Administration
NAGS: N-acetyl glutamate synthetase
OTC: ornithine transcarbamylase
UCD: urea cycle disorder

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): should not be used to manage acute hyperammonemia (Buphenyl only)
- Boxed warning(s): none reported

Appendix D: Urea Cycle Disorders

UCDs are caused by a deficiency in any of the below enzymes in the pathway that transforms nitrogen to urea:

- Carbamyl phosphate synthetase I (CPSI) deficiency
- Ornithine transcarbamylase (OTC) deficiency
- Argininosuccinate synthetase (AS) deficiency (also known as classic citrullinemia or type I citrullinemia, CTLN1)
- Argininosuccinate lyase (ASL) deficiency (also known as argininosuccinic aciduria)
- N-acetyl glutamate synthetase (NAGS) deficiency
- Arginase deficiency

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
UCD	• Weight < 20 kg: 450-600 mg/kg/day PO in three to six equally divided doses with each meal or feeding • Weight ≥ 20 kg: 9.9-13 g/m^2/day PO in three to six equally divided doses with each meal or feeding	20 grams/day

VI. Product Availability

Drug Name	Availability
Sodium phenylbutyrate (Buphenyl)	• Tablet: 500 mg • Powder: 250 grams (each level teaspoon dispenses 8.6 grams of Buphenyl)
Sodium phenylbutyrate (Pheburane)	Oral pellets: 84 g of sodium phenylbutyrate per bottle

VII. References

1. Buphenyl Prescribing Information. Lake Forest, IL: Horizon Pharma USA, Inc.; March 2021. Available at https://www.horizontherapeutics.com. Accessed September 16, 2021.

2. Pheburane Prescribing Information. Bryn Mawr, PA: Medunik USA, Inc; June 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216513s000lbl.pdf. Accessed August 28, 2022.
3. Haberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J Inherit Metab Dis*. 2019;42(6):1192-1230. doi:10.1002/jimd.12100.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Removed dietary protein restriction requirements as this cannot be confirmed.	11.15.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.25.18	02.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.20.19	02.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	10.28.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.16.21	02.22
RT4: added Pheburane oral pellets dosage formulation.	08.29.22	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.