EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Phenylbutyrate Products

- Buphenyl (sodium phenylbutyrate tablets and powder for oral solution – Horizon Pharma, generics)
- Ravicti (glycerol phenylbutyrate oral liquid – Horizon Pharma)

TAC APPROVAL DATE: 03/13/2019

OVERVIEW

Buphenyl is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.[1] It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. Early diagnosis is important so that treatment is initiated early for improved survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. Buphenyl must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. Of note, Buphenyl tablet/powder contains 124 mg of sodium per gram of sodium phenylbutyrate (12.4% w/w) or about 2.5 grams of sodium in 40 tablets; safety or efficacy data unavailable for > 40 tablets/day. Therefore, it 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.

Ravicti is indicated for use as a nitrogen-binding agent for chronic management patients with urea cycle disorders that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[2] 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). Ravicti is not indicated for the treatment of acute hyperammonemia in patients with urea cycle disorders. Safety and efficacy for the treatment of N-acetyl glutamate synthase (NAGS) deficiency have not been established.

Disease Overview

Urea cycle disorders are rare inborn errors of metabolism which result from mutations in the genes encoding for one of the six enzymes necessary for normal function of the urea cycle: arginase, citrullinemia, arginosuccinic acid synthetase, N-acetyl glutamate synthetase, ornithine transcarbamylase, and carbamyl phosphate synthetase.[3-4] They lead to increased amounts of ammonia in the blood which may cause disturbed brain function and severe brain damage. Signs of disease include decreased mental awareness, vomiting, combativeness, slurred speech, unstable gait, and unconsciousness. Diagnosis begins with a clinical suspicion of hyperammonemia.[6] Typically, patients have normal glucose and electrolyte levels. Enzymatic diagnosis and/or genetic testing is also available; however, treatment should not be delayed while waiting for a final diagnosis. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy.[3-4] Treatment includes use of alternative waste nitrogen excretion pathways (e.g., Buphenyl, Ravicti); other treatments may include hemodialysis, dietary protein restriction, and, in some cases, essential amino acid supplementation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Phenylbutyrate Products (Buphenyl, Ravicti). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Phenylbutyrate Products (Buphenyl, Ravicti) as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Phenylbutyrate Products (Buphenyl, Ravicti) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Urea Cycle Disorders (e.g., Deficiencies of Carbamylphosphate Synthetase, Ornithine Transcarbamylase, or Argininosuccinic Acid Synthetase).** Approve for the duration noted if the patient meets ALL of the following (A, B, C, and D):
   - **A)** According to the prescriber, the diagnosis was confirmed by one of the following (i or ii):
     - **i.** Approve for 1 year if genetic testing confirmed a mutation resulting in a urea cycle disorder; OR
     - **ii.** Approve for 3 months if the patient has hyperammonemia (i.e., an ammonia level above the upper limit of the normal reference range for the reporting laboratory); AND
       Note: Reference ranges are dependent upon patient's age.
   - **B)** The medication is prescribed in conjunction with a protein-restricted diet; AND
   - **C)** The patient will not be taking Buphenyl and Ravicti concurrently; AND
   - **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Phenylbutyrate Products (Buphenyl, Ravicti) have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. **Concomitant Therapy with Buphenyl and Ravicti.** There are no data available to support concomitant use.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Buphenyl [prescribing information]. Lake Forest, IL: Horizon Pharma; November 2018.
2. Ravicti [prescribing information]. Lake Forest, IL: Horizon Pharma; December 2018.
3. 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.

4. Hereditary urea cycle abnormality. Medline Plus. A service of the U.S. National Library of Science, National Instituties of Health (NIH). Updated January 28, 2019. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000372.htm. Accessed on February 16, 2019.
5. Summar M. Urea cycle disorders. National Organization of Rare Disorders [Web site]. Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/. Accessed on February 11, 2019.
6. National Organization for Rare Disorders (NORD). Urea cycle disorders. Accessed on February 22, 2019. Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	03/13/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committe.