**Medication Policy Manual**

**Policy No:** dru323  
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**Topic:** Buphenyl®, sodium phenylbutyrate

**Committee Approval Date:** July 10, 2015

**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

**Benefit determinations should be based in all cases on the applicable contract language.** To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Sodium phenylbutyrate (Buphenyl) is an oral medication used for the chronic management of urea cycle disorders.
Policy/Criteria

I. Most contracts require prior authorization approval of sodium phenylbutyrate (Buphenyl) prior to coverage. Sodium phenylbutyrate (Buphenyl) may be considered medically necessary in patients with documentation of a urea cycle disorder diagnosis.

II. Administration, Quantity Limitations, and Authorization Period
   A. OmedaRx considers sodium phenylbutyrate (Buphenyl) to be a self-administered medication.
   B. When prior authorization is approved, sodium phenylbutyrate (Buphenyl) may be authorized in quantities not to exceed 20 grams (40 tablets) daily.
   C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Sodium phenylbutyrate is considered investigational when used for all other conditions, including, but not limited to:
   A. Amyotrophic lateral sclerosis (ALS)
   B. Anemia, including sickle cell anemia
   C. Progressive familial intrahepatic cholestasis (a.k.a. Byler disease)
   D. Cancer
   E. Cirrhosis and hepatic encephalopathy
   F. Cystic Fibrosis
   G. Homozygous beta thalassemia

Position Statement

Summary
- Phenylbutyrate is a nitrogen-scavenging medication used for the chronic management of urea cycle disorders, a rare genetic disease characterized by accumulation of nitrogen which can result in life-threatening ammonia levels and neurologic injury.
- Sodium phenylbutyrate (Buphenyl) is available as oral tablets and powder.
- The safety and effectiveness of sodium phenylbutyrate (Buphenyl) in conditions other than urea cycle disorders have not been established.

Background
- The urea cycle is responsible for the elimination of nitrogen formed by the breakdown of proteins. Patients with a urea cycle disorder have a rare genetic defect in one or more of the enzymes utilized in the cycle, which cause accumulation of nitrogen and can result in life-threatening ammonia levels and neurologic injury. [1]
The nitrogen-scavenging medications aid in the elimination of excess nitrogen and are utilized for chronic management when diet protein restriction alone fails to prevent hyperammonemia. [1]

Phenylbutyrate in a pro-drug of phenylacetate, which binds glutamine and provides an alternative pathway for nitrogen elimination.

Treatment guidelines for urea cycle disorders recommend chronic treatment with nitrogen-scavenging medications, specifically sodium phenylbutyrate (Buphenyl), three to four times daily. [2,19]

Clinical Efficacy

UREA CYCLE DISORDERS

Although evidence is based on case series and small trials, the standard of care for the chronic management of urea cycle disorders is the administration of oral nitrogen-scavenger medications, such as sodium phenylbutyrate (Buphenyl), in patients refractory to dietary protein restriction. [1, 3]

* Dietary protein is chronically restricted through specialized formulas to prevent excess nitrogen accumulation.

* Once a specific urea cycle disorder diagnosis is made, additional treatment is tailored to the specific enzyme deficiency utilizing specific treatments such as carglumic acid (Carbaglu®).

Glycerol phenylbutyrate (Ravicti) is comparable to sodium phenylbutyrate (Buphenyl) in the chronic management of urea cycle disorders; however, there is insufficient evidence that one is more efficacious than the other.

* A randomized, active-controlled, crossover trial reported glycerol phenylbutyrate (Ravicti) was non-inferior to sodium phenylbutyrate (Buphenyl) in the chronic management of ammonia levels in 46 patients with a urea cycle disorder. [4, 5]

* Patients in the trial were on stable therapy with sodium phenylbutyrate (Buphenyl) at the time of enrollment. The dose of glycerol phenylbutyrate (Ravicti) was calculated to provide the same amount of phenylbutyrate.

* The primary endpoint, 24-hour ammonia exposure, is a clinically relevant surrogate endpoint for the morbidity and mortality associated with urea cycle disorders.

INVESTIGATIONAL CONDITIONS

- Cancer

* Several small-scale trials have evaluated sodium phenylbutyrate (Buphenyl) in cancer, including acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) [6, 7], colorectal cancer [8], brain tumors [8, 9], and solid tumors [10, 11]. There is no evidence that sodium phenylbutyrate (Buphenyl) is safe and effective for this use. Larger, randomized, controlled studies are needed to determine the potential role of sodium phenylbutyrate (Buphenyl)
in these populations.

- **Cirrhosis and Hepatic Encephalopathy**
  
  * Although not evaluated with sodium phenylbutyrate (Buphenyl), a small (N=178), phase II trial evaluating the safety and efficacy of glycerol phenylbutyrate (Ravicti) in patients with cirrhosis demonstrated it potentially decreases hepatic encephalopathic events. Larger, randomized, controlled studies are needed to determine the potential role of glycerol or sodium phenylbutyrate in this population. [12]

- **Other Uses**
  
  * Several small-scale trials have evaluated sodium phenylbutyrate (Buphenyl) in other uses, including amyotrophic lateral sclerosis (ALS) [13], anemia [14], sickle cell anemia [15], and homozygous beta thalassemia [16]. Larger, randomized, controlled studies are needed to determine the potential role of sodium phenylbutyrate (Buphenyl) in these populations.
  
  * There is interest in using glycerol phenylbutyrate (Ravicti), the liquid formulation of sodium phenylbutyrate (Buphenyl), for the treatment of cystic fibrosis and progressive familial intrahepatic cholestasis (a.k.a. Byler disease); however, clinical trials have yet to be conducted to evaluate the efficacy and safety of glycerol phenylbutyrate (Ravicti) for these conditions. [8]

**Safety**

- The most common adverse reactions of sodium phenylbutyrate (Buphenyl) include: dysmenorrhea, decreased appetite, body odor, and taste aversion. [17]

- The active moiety of both glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl), phenylacetate, is associated with neurotoxicity. If symptoms of neurotoxicity are present in the absence of hyperammonemia, the dose of these agents should be reduced. [17, 18]

**Dosing**

- Sodium phenylbutyrate (Buphenyl) is administered in three to six equally divided dosages. The recommended dose is as follows: [17]
  
  * Patients weighing < 20 kg: 450 to 600 mg/kg/day
  * Patients weighing > 20 kg: 9.9 to 13 g/m²/day
  * The maximum daily dosage of sodium phenylbutyrate (Buphenyl) is 20 grams (40 tablets)

- The safety and effectiveness of higher doses have not been established.
References


5. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Medical Review NDA 203-284; Glycerol phenylbutyrate (Ravicti). [cited 6/10/2013]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000TOC.cfm


