



Independent licensees of the Blue Cross and Blue Shield Association

**Medication Policy Manual**

**Policy No:** dru312

**Topic:** Ravicti®, glycerol phenylbutyrate

**Date of Origin:** July 12, 2013

**Committee Approval Date:** July 14, 2017

**Next Review Date:** July 2018

**Effective Date:** August 1, 2017

**IMPORTANT REMINDER**

This Medication 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 Medication Policy is to provide a guide to coverage. Medication 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**

Glycerol phenylbutyrate (Ravicti) is an oral medication used for the chronic management of urea cycle disorders.

## Policy/Criteria

I. Most contracts require prior authorization approval of glycerol phenylbutyrate (Ravicti) prior to coverage. Glycerol phenylbutyrate (Ravicti) may be considered medically necessary in patients when criteria A and B below are met.

A. Documentation of a urea cycle disorder diagnosis with a history of hyperammonemia.

### AND

B. Treatment with sodium phenylbutyrate (Buphenyl®) was ineffective, not tolerated, or is contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers glycerol phenylbutyrate (Ravicti) to be a self-administered medication.

B. When prior authorization is approved, glycerol phenylbutyrate (Ravicti) may be authorized in quantities not to exceed 17.5 mL 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. Glycerol 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.
- Glycerol phenylbutyrate (Ravicti) is an oral liquid reformulation of sodium phenylbutyrate (Buphenyl), which is available as oral tablets and powder.
- Among these nitrogen-scavenging medications, sodium phenylbutyrate (Buphenyl) is the best value for members and has the longest track record of clinical experience.
- The safety and effectiveness of glycerol phenylbutyrate (Ravicti) 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 dietary protein restriction alone fails to prevent hyperammonemia. [1]
- Phenylbutyrate is a pro-drug of phenylacetate, which binds glutamine and provides an alternative pathway for nitrogen elimination. Pancreatic enzymes are required to remove the glycerol component of glycerol phenylbutyrate (Ravicti) and release the phenylbutyrate. [18]
- 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]
- 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]
  - \* 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.
- There is insufficient evidence that glycerol phenylbutyrate (Ravicti) is more efficacious than sodium phenylbutyrate (Buphenyl).
  - \* Pooled data from the pivotal trial and additional phase II studies suggest that glycerol phenylbutyrate (Ravicti) may be superior to sodium phenylbutyrate (Buphenyl) in the control of ammonia levels. This data, however, is considered preliminary due to the small number of subjects included. [4]

Long-term studies in pediatric patients suggest glycerol phenylbutyrate (Ravicti) may improve neurocognitive function as defined by the BRIEF (Behavior Rating Inventory of Executive Function) score. This data, however, is considered exploratory and hypothesis-generating due to lack of a control group and no prespecified endpoints related to neurocognitive function. [4, 5]

## INVESTIGATIONAL CONDITIONS

- Cancer
  - \* Although not evaluated with glycerol phenylbutyrate (Ravicti), 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 glycerol or sodium phenylbutyrate is safe and effective for this use. Larger, randomized, controlled studies are needed to determine the potential role of glycerol or sodium phenylbutyrate in these populations.
- Cirrhosis and Hepatic Encephalopathy
  - \* 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 phenylbutyrate in this population. [12]
- Other Uses
  - \* Although not evaluated with glycerol phenylbutyrate (Ravicti), 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]. There is no evidence that glycerol phenylbutyrate (Ravicti) is safe and effective for these uses.

There is interest in using glycerol phenylbutyrate (Ravicti) 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 glycerol phenylbutyrate (Ravicti) reported with an incidence of at least 10% include: diarrhea, flatulence, and headache. [18]
- 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]
- Pancreatic enzymes are required to hydrolyze glycerol phenylbutyrate (Ravicti) and release phenylbutyrate. Low or absent pancreatic enzymes or intestinal fat malabsorption may result in reduced or absent digestion of glycerol phenylbutyrate (Ravicti) and subsequent reduced ammonia control. Ammonia levels should be monitored closely in these patients. [18]
- There is no evidence that glycerol phenylbutyrate (Ravicti) is safer than sodium phenylbutyrate (Buphenyl).

## Dosing

- Glycerol phenylbutyrate (Ravicti) is administered in three equally divided dosages, each rounded to the nearest 0.5 mL. The recommended initial dose is as follows: [18]
  - \* Phenylbutyrate-naïve: 4.5 to 11.2 mL/m<sup>2</sup>/day
  - \* Switching from sodium phenylbutyrate (Buphenyl):  
daily dose (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.8
  - \* The maximum daily dosage of glycerol phenylbutyrate (Ravicti) is 17.5 mL.
- Dosage adjustment may be made based upon plasma ammonia, urinary phenylacetylglutamine, and/or plasma phenylacetate. [18]
- The safety and effectiveness of higher doses have not been established.
- Glycerol phenylbutyrate (Ravicti) provides increased adherence potential due to its improved palatability and decreased dosage burden; however, it is unclear if this potential additional benefit justifies the substantial increase in cost.

### Cross References

Buphenyl®, sodium phenylbutyrate, Medication Policy Manual dru323

Codes	Number	Description
N/A		

## References

1. Lanpher BC, Gropman A, Chapman KA, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2011 Sep 1]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. [cited 3/18/14]; Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1217/>
2. Urea Cycle Disorders Conference group. Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr. 2001 Jan;138(1 Suppl):S1-5. Review. PubMed PMID: 11148543.
3. Lee B. Urea Cycle Disorders: Management. In: TePas, E (Ed). UpToDate, Waltham, MA, 2014.
4. Diaz GA, Krivitzky LS, Mokhtarani M, et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatology. 2012 Sep 7. doi: 10.1002/hep.26058. [Epub ahead of print] PubMed PMID: 22961727.
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](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000TOC.cfm)
6. Maslak P, Chanel S, Camacho LH, et al. Pilot study of combination transcriptional modulation therapy with sodium phenylbutyrate and 5-azacytidine in patients with

- acute myeloid leukemia or myelodysplastic syndrome. *Leukemia*. 2006 Feb;20(2):212-7. PubMed PMID: 16357841.
7. Gore SD, Weng LJ, Figg WD, et al. Impact of prolonged infusions of the putative differentiating agent sodium phenylbutyrate on myelodysplastic syndromes and acute myeloid leukemia. *Clin Cancer Res*. 2002 Apr;8(4):963-70. PubMed PMID: 11948101.
  8. National Institutes of Health, Clinicaltrials.gov. [cited 6/22/15]; Available from: <http://www.clinicaltrials.gov>
  9. Phuphanich S, Baker SD, Grossman SA, et al. Oral sodium phenylbutyrate in patients with recurrent malignant gliomas: a dose escalation and pharmacologic study. *Neuro Oncol*. 2005 Apr;7(2):177-82. PubMed PMID: 15831235; PubMed Central PMCID: PMC1871887.
  10. Lin J, Gilbert J, Rudek MA, Zwiebel JA, et al. A phase I dose-finding study of 5-azacytidine in combination with sodium phenylbutyrate in patients with refractory solid tumors. *Clin Cancer Res*. 2009 Oct 1;15(19):6241-9. doi: 10.1158/1078-0432.CCR-09-0567. Epub 2009 Sep 29. PubMed PMID: 19789320; PubMed Central PMCID: PMC2845396.
  11. Camacho LH, Olson J, Tong WP, et al. Phase I dose escalation clinical trial of phenylbutyrate sodium administered twice daily to patients with advanced solid tumors. *Invest New Drugs*. 2007 Apr;25(2):131-8. Epub 2006 Oct 20. PubMed PMID: 17053987.
  12. Rockey DC, Vierling JM, et al; HALT-HE Study Group. Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. *Hepatology*. 2014 Mar;59(3):1073-83. doi: 10.1002/hep.26611. PubMed PMID: 23847109.
  13. Cudkowicz ME, Andres PL, Macdonald SA, et al; Northeast ALS and National VA ALS Research Consortiums. Phase 2 study of sodium phenylbutyrate in ALS. *Amyotroph Lateral Scler*. 2009 Apr;10(2):99-106. doi: 10.1080/17482960802320487. PubMed PMID: 18688762.
  14. Micromedex® Healthcare Series [Internet database]. Greenwood Village, CO: Truven Health Analytics. Updated periodically.
  15. Resar LM, Segal JB, Fitzpatrick LK, et al. Induction of fetal hemoglobin synthesis in children with sickle cell anemia on low-dose oral sodium phenylbutyrate therapy. *J Pediatr Hematol Oncol*. 2002 Dec;24(9):737-41. PubMed PMID: 12468915.
  16. Collins AF, Pearson HA, Giardina P, et al: Oral sodium phenylbutyrate therapy in homozygous beta thalassemia: a clinical trial. *Blood* 1995; 85:43-49.
  17. Buphenyl [package insert]. South San Francisco, CA: Hyperion Therapeutics, Inc.; April 2009.
  18. Ravicti [package insert]. South San Francisco, CA: Hyperion Therapeutics, Inc.; June 2015.
  19. Haberle, J, Boddaert, N, Burlina, A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012;7:32. PMID: 22642880

### Revision History

Revision Date	Revision Summary
07/14/17	No criteria changes with this annual update
07/15/16	No criteria changes with this annual update