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Medication Policy Manual **Policy No:** dru312

Topic: Medications for Urea Cycle Disorders **Date of Origin:** July 12, 2013

- Olpruva, sodium phenylbutyrate
- Glycerol phenylbutyrate (generic, Ravicti)

Committee Approval Date: April 2, 2026 **Next Review Date:** 2027

Effective Date: June 1, 2026

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

Medications included in this policy are oral medications used for the chronic management of urea cycle disorders.

Policy/Criteria

Most contracts require pre-authorization approval of medications for urea cycle disorders prior to coverage.

I. Continuation of therapy (COT): Medications for urea cycle disorders may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for urea cycle disorders may be considered medically necessary in patients when there is clinical documentation (such as chart notes) confirming that criteria A, B, and C below are met.

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

AND

B. Treatment with both of the following products (1 and 2) was ineffective, not tolerated, or contraindicated:

1. Buphenyl (sodium phenylbutyrate).

AND

2. Pheburane (sodium phenylbutyrate).

AND

C. **For use of brand Ravicti (glycerol phenylbutyrate)**: There is an intolerance or contraindication to an inactive ingredient in the generic glycerol phenylbutyrate.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers medications for urea cycle disorders coverable only under the pharmacy benefit (as a self-administered medication).

B. When pre-authorization is approved, medications for urea cycle disorders (as listed in *Table 1*) will be authorized as follows:

TABLE 1.

Product	Quantity Limit
Glycerol phenylbutyrate (generic, Ravicti)	Not to exceed 17.5 mL daily
Olpruva (sodium phenylbutyrate)	Not to exceed 20 grams daily

C. Authorization **shall** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that all of the following are met:

1. Current medical necessity criteria are met.

2. Buphenyl (sodium phenylbutyrate) and Pheburane (sodium phenylbutyrate) are not treatment options.

3. Ongoing clinical benefit, such as disease stability or improvement.

IV. Medications for urea cycle disorders are 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.

H. Maple syrup urine disease.

Position Statement

Summary

- Medications for urea cycle disorders contain phenylbutyrate, a nitrogen-scavenging medication used for the chronic management of urea cycle disorders, which is a rare genetic disease characterized by accumulation of nitrogen which can result in life-threatening ammonia levels and neurologic injury.
- This policy limits use of medications for urea cycle disorders to patients with a diagnosis of a urea cycle disorder, with a history of hyperammonemia, and who have previously tried Buphenyl AND Pheburane (sodium phenylbutyrate), up to the doses known to be safe and effective.
    * Coverage of brand Ravicti (glycerol phenylbutyrate) is limited to use only when an inactive ingredient in generic glycerol phenylbutyrate is contraindicated or not tolerated.
- Glycerol phenylbutyrate (generic, Ravicti) is an oral liquid reformulation of Buphenyl (sodium phenylbutyrate), which is available as oral tablets and powder.
- Pheburane (sodium phenylbutyrate) is an oral pellet formulation.
- Olpruva (sodium phenylbutyrate) is an oral pellet formulation that must be reconstituted into a suspension.
- Among these nitrogen-scavenging medications, Buphenyl (sodium phenylbutyrate) and Pheburane (sodium phenyl butyrate) offer the best value for members and are available without prior authorization.

- The safety and effectiveness of medications included in this policy for 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 in 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 (generic, Ravicti) and release the phenylbutyrate. [18]
- Treatment guidelines for urea cycle disorders recommend chronic treatment with nitrogen-scavenging medications, specifically sodium phenylbutyrate, 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, in patients refractory to dietary protein restriction. [1, 3]
- Glycerol phenylbutyrate (generic, Ravicti) is comparable to sodium phenylbutyrate in the chronic management of urea cycle disorders; however, there is insufficient evidence that one medication for urea cycle disorders is more efficacious than the other.
    * A randomized, active-controlled, crossover trial reported glycerol phenylbutyrate (generic, Ravicti) was non-inferior to sodium phenylbutyrate 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 at the time of enrollment. The dose of glycerol phenylbutyrate (generic, 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 (generic, Ravicti) is more effective than sodium phenylbutyrate.
    * Pooled data from the pivotal trial and additional phase II studies suggest that glycerol phenylbutyrate (generic, Ravicti) may be superior to sodium phenylbutyrate 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 (generic, 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 medications for urea cycle disorders, several small-scale trials have evaluated sodium phenylbutyrate 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 (generic, 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 medications for urea cycle disorders, several small-scale trials have evaluated sodium phenylbutyrate in other uses, including amyotrophic lateral sclerosis (ALS), anemia, sickle cell anemia, homozygous beta thalassemia, and maple syrup urine disease [13-16,19]. There is no evidence that medications for urea cycle disorders are safe and effective for these uses.
  * There is interest in using medications for urea cycle disorders 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 medications for urea cycle disorders for these conditions. [8]

Safety

- The most common adverse reactions of glycerol phenylbutyrate (generic, Ravicti) reported with an incidence of at least 10% include: diarrhea, flatulence, and headache. [18]
- The most common adverse reactions of Olpruva (sodium phenylbutyrate) reported with an incidence of at least 3% include: menstrual dysfunction, decreased appetite, body odor, and taste aversion. [20]
- The active moiety of medications for urea cycle disorders, 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 (generic, Ravicti) and release phenylbutyrate. Low or absent pancreatic enzymes or intestinal fat

malabsorption may result in reduced or absent digestion of glycerol phenylbutyrate (generic, Ravicti) and subsequent reduced ammonia control. Ammonia levels should be monitored closely in these patients. [18]

- There is no evidence that glycerol phenylbutyrate (generic, Ravicti) is safer than the other versions of sodium phenylbutyrate.

Dosing

- Glycerol phenylbutyrate (generic, 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^2/day
    - Switching from sodium phenylbutyrate: daily dose (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.8
    - The maximum daily dosage of glycerol phenylbutyrate (generic 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 (generic, 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.
- Olpruva (sodium phenylbutyrate) is administered at 9.9 to 13 g/m^2/ day in three to six equally divided doses, rounding each dose to the nearest available strength, with 20 grams per day being the maximum dosage.[20]
- Olpruva is an oral pellet formulation that must be reconstituted with water to form an oral suspension. [20]

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Revision History

Revision Date	Revision Summary
4/2/2026	• Glycerol phenylbutyrate (generic) added to policy. • Added step therapy through generic glycerol phenylbutyrate for coverage of brand Ravicti (glycerol phenylbutyrate),
4/3/2025	No changes to coverage criteria with this annual review.
6/20/2024	No changes to coverage criteria with this annual review.
9/14/2023	• Renamed policy to "Medications for urea cycle disorders." • Added newly FDA-approved drug Olpruva (sodium phenylbutyrate) with same intent/criteria as Ravicti (glycerol phenylbutyrate).
6/15/2023	No changes to coverage criteria with this annual update.
3/16/2023	Effective 6/1/2023: • Added additional step therapy requirement with Pheburane (sodium phenylbutyrate). • Updated reauthorization criteria now requires annual review and confirmation that lower cost alternatives are not a treatment option.
6/17/2022	No changes to coverage criteria with this annual update.
7/16/2021	No changes to coverage criteria with this annual update.
7/24/2020	Added continuation of therapy criteria (no change to intent of policy).
10/23/2019	No changes to coverage criteria with this annual update.
7/20/2018	• Updated investigational uses to include maple syrup urine disease. • Updated criteria with standard policy language (no changes to intent).
7/14/2017	No changes to coverage criteria with this annual update.
7/15/2016	No changes to coverage criteria with this annual update.

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