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PHARMACY POLICY – 5.01.611

Pharmacologic Treatment of Urea Cycle Disorders

Effective Date: **May 1, 2026***	RELATED MEDICAL POLICIES:
Last Revised: April 13, 2026	None
Replaces: N/A	
*This policy has been revised. Click here to view the changes effective February 5, 2027.	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

When protein is eaten, the body breaks it down into amino acids, which helps carry out bodily functions. Whatever is not needed by the body is then broken down by the liver and turned into waste products that are cleared out of the body through urine. One of these waste products is ammonia. Too much ammonia in the body is toxic. The liver changes ammonia into a non-toxic substance called urea using a series of specific protein molecules (enzymes). This process is called the urea cycle. Urea cycle disorders are inherited and occur when the body can't make one or more of the enzymes it needs to turn ammonia into urea. Ammonia builds up in the body and can lead to brain damage, coma, and even death. Urea cycle disorders most often affect infants, though they can affect children and adults. Treatment of urea cycle disorders is meant to reduce the amount of ammonia in the blood to safe levels. This policy describes when drugs used to treat urea cycle disorders may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Carbamoyl Phosphate Synthetase 1 Activator • **Carbaglu (carglumic acid)**	**Carbaglu (carglumic acid) may be considered medically necessary for the treatment of acute or chronic hyperammonemia in individuals diagnosed with N-acetylglutamate synthase (NAGS) deficiency when the following criteria are met:** • Carbaglu is used for the treatment of acute or chronic hyperammonemia due to NAGS deficiency **AND** • Documented by genetic testing deficiency of the hepatic enzyme NAGS **AND** • The individual has tried generic carglumic acid first and has an inadequate response or intolerance to generic carglumic acid (documentation required) **Carbaglu (carglumic acid) may be considered medically necessary as adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA) when the following criteria are met:** • Carbaglu is used for the treatment of acute hyperammonemia due to PA or MMA **AND** • The individual has tried generic carglumic acid first and has an inadequate response or intolerance to generic carglumic acid (documentation required)
Carbamoyl Phosphate Synthetase 1 Activator • **Generic carglumic acid**	**Generic carglumic acid may be considered medically necessary for treatment of acute or chronic hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency when:** • Documented by genetic testing deficiency of the hepatic enzyme NAGS

Drug	Medical Necessity
	Generic carglumic acid may be considered medically necessary as adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA).
Nitrogen Binding Agent • **Generic glycerol phenylbutyrate** • **Ravicti (glycerol phenylbutyrate)**	**Generic glycerol phenylbutyrate and Ravicti (glycerol phenylbutyrate) may be considered medically necessary when the following criteria are met:** • Medication is used as adjunctive therapy for the chronic management of individuals with urea cycle disorders **AND** • The individual has tried and failed generic sodium phenylbutyrate unless there is a contraindication to use of generic sodium phenylbutyrate **AND** • Has a documented dietary protein restriction plan in place
Urea Cycle Pathway Alternative • **Buphenyl (sodium phenylbutyrate)** • **Olpruva (sodium phenylbutyrate)**	**Buphenyl (sodium phenylbutyrate) and Olpruva (sodium phenylbutyrate) may be considered medically necessary when the following criteria are met:** • Olpruva and Buphenyl are used as adjunctive therapy for the chronic management of individuals with urea cycle disorders **AND** • Documented by genetic testing deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) **AND** • The individual has tried generic sodium phenylbutyrate first and had an inadequate response or intolerance to generic sodium phenylbutyrate (documentation required) **AND** • Has a documented dietary protein restriction plan in place
Urea Cycle Pathway Alternative • **Pheburane (sodium phenylbutyrate)**	**Pheburane (sodium phenylbutyrate) may be considered medically necessary when the following criteria are met:** • Pheburane is used as adjunctive therapy for the chronic management of individuals with urea cycle disorders **AND**

Drug	Medical Necessity
	• Documented by genetic testing deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) **AND** • The individual has tried generic sodium phenylbutyrate first and has an inadequate response or intolerance to generic sodium phenylbutyrate (documentation required) **AND** • Has a documented dietary protein restriction plan in place
Urea Cycle Pathway Alternative • **Generic sodium phenylbutyrate**	**Generic sodium phenylbutyrate may be considered medically necessary when the following criteria are met:** • Generic sodium phenylbutyrate is used as adjunctive therapy for the chronic management of individuals with urea cycle disorders **AND** • Documented by genetic testing deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) **AND** • Documented dietary protein restriction plan is in place

Drug	Investigational
• **Buphenyl (sodium phenylbutyrate),** • **Carbaglu (carglumic acid),** • **Generic carglumic acid** • **Olpruva (sodium phenylbutyrate),** • **Pheburane (sodium phenylbutyrate),** • **Ravicti (glycerol phenylbutyrate)** • **Generic glycerol phenylbutyrate**	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of Buphenyl (sodium phenylbutyrate), Carbaglu (carglumic acid), generic carglumic acid, Olpruva (sodium phenylbutyrate), Pheburane (sodium phenylbutyrate), Ravicti (glycerol phenylbutyrate), generic glycerol phenylbutyrate, and generic sodium phenylbutyrate for conditions not outlined in this policy are considered investigational.**

Drug	Investigational
• **Generic sodium phenylbutyrate**	

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews and all other reviews for all drugs listed in this policy may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews for all drugs listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **All other reviews for all drugs listed in this policy may be approved up to 3 years as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

N/A

Related Information

Consideration of Age

The ages stated in this policy for which generic sodium phenylbutyrate, Buphenyl (sodium phenylbutyrate), Olpruva (sodium phenylbutyrate), Pheburane (sodium phenylbutyrate), Carbaglu (carglumic acid), Ravicti (glycerol phenylbutyrate), and glycerol phenylbutyrate are considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

This policy is managed through the pharmacy benefit.

Evidence Review

Background

Urea Cycle Disorders (UCDs) result from inherited deficiencies of enzymes or transporters including: N-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate acid synthetase (AS), argininosuccinate acid lyase (ASL), or arginase (ARG). OTC is the most common enzyme deficiency of these disorders. These enzymes are responsible for the synthesis of urea from ammonia (NH3, NH4+). UCDs are rare genetic disorders, and its clinical manifestations are characterized by hyperammonemia and life-threatening hyperammonemic crises. Hyperammonemia-related neurologic injury ranges from lethal cerebral edema to mild cognitive impairment among individuals with milder genetic defects. The goal of management is to control ammonia levels and avoid hyperammonemic crisis. Treatments are directed towards reducing ureagenesis through dietary protein restriction, arginine, or citrilline supplementation, and administration of nitrogen-scavenging drugs.

The deficiency of the enzymes or transporters involved in UCDs varies from individual to individual, and some individuals have a total or near total absence of activity of the first four enzymes of the urea cycle (OTC, CPS, AS, and ALS). These deficiencies lead to accumulation of ammonia and other precursor metabolites during the first few days of life. Some individuals may have partial absence of the enzymes of the urea cycle, leading to a milder form of the disease. Individuals may present with clinical manifestations across the lifespan, including as newborn/infants and in early childhood.

Most individuals are diagnosed after presenting symptoms of hyperammonemia. If an elevated blood ammonia level is confirmed, and the results of other routine lab tests are consistent with a UCD diagnosis (normal anion gap, normal blood glucose, absence of liver disease), amino acid levels are tested to establish a specific diagnosis. The laboratory hallmark of a urea cycle disorder (UCD) is an elevated plasma ammonia concentration (>100 to 150 micromol/L).

The initial management of UCDs is to rehydrate and maintain good urine output without overhydrating. The next step is to remove nitrogen (ammonia) from the body using medications and/or hemodialysis. It is important to stop protein intake and minimize catabolism, as well as stimulate anabolism and uptake of nitrogen precursors by muscle. For chronic management of urea cycle disorders, if dietary protein restriction and/or amino acid supplementation cannot manage the disorder alone, then Buphenyl (sodium phenylbutyrate) is the next option.

Summary of Evidence

Buphenyl (sodium phenylbutyrate)

Previously, neonatal-onset disease was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their nitrogen-free analogs. However, with hemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate, and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in newborns diagnosed after birth but within the first month of life is almost 80%. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy.

Individuals with neonatal-onset disease have a high incidence of mental retardation. Those who had IQ tests administered had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100% (14/14 individuals tested); argininosuccinic acid synthetase deficiency, 88% (15/17 individuals tested); and carbamylphosphate synthetase deficiency, 57% (4/7 individuals tested). Retardation was severe in the majority of individuals. In individuals diagnosed during gestation and treated prior to any episode of hyperammonemic encephalopathy, survival is 100%, but even in these individuals, most subsequently demonstrate cognitive impairment or other neurologic deficits. In late-onset deficiency individuals, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98%. The two deaths in this group of individuals occurred during episodes of hyperammonemic encephalopathy. However, compliance with the therapeutic regimen has not been adequately documented to allow

evaluation of the potential for sodium phenylbutyrate and dietary protein restriction to prevent mental deterioration and recurrence of hyperammonemic encephalopathy if carefully adhered to. The majority of these individuals tested (30/46 or 65%) have IQ's in the average to low average/borderline mentally retarded range. Reversal of preexisting neurologic impairment is not likely to occur with treatment and neurologic deterioration may continue in some individuals. Even on therapy, acute hyperammonemic encephalopathy recurred in the majority of individuals for whom the drug is indicated.

Safety

The assessment of clinical adverse events came from 206 individuals treated with sodium phenylbutyrate. Adverse events (both clinical and laboratory) were not collected systematically in these individuals but were obtained from individual-visit reports by the 65 co-investigators. Causality of adverse effects is sometimes difficult to determine in this individual population because they may result from either the underlying disease, the individual's restricted diet, intercurrent illness, or sodium phenylbutyrate. Furthermore, the rates may be underestimated because they were reported primarily by parent or guardian and not the individual.

In female individuals, the most common clinical adverse event reported was amenorrhea/menstrual dysfunction (irregular menstrual cycles), which occurred in 23% of the menstruating individuals. Decreased appetite occurred in 4% of all individuals. Body odor (probably caused by the metabolite, phenylacetate) and bad taste or taste aversion were each reported in 3% of individuals.

Carbaglu (carglumic acid)

Acute and Chronic Hyperammonemia due to NAGS Deficiency

The efficacy of carglumic acid in the treatment of hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency individuals who received carglumic acid treatment for a median of 7.9 years (range 0.6 to 20.8 years). Treatment with carglumic acid was divided in two regimens. For acute treatment, individuals received a total daily dose of 100 to 250 mg/kg per day primarily administered in 2 to 4 divided doses for the first few days of treatment. For maintenance treatment, the dosage was reduced over time based upon biochemical and clinical responses. The clinical observations in the 23 individual case series were retrospective, unblinded and uncontrolled and preclude any meaningful formal statistical analyses of the data. However,

short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3. Persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Of the 23 NAGS deficiency individuals who received treatment with carglumic acid, a subset of 13 individuals who had both well documented plasma ammonia levels prior to carglumic acid treatment and after long-term treatment with carglumic acid were selected for analysis.

All 13 individuals had abnormal ammonia levels at baseline. The overall mean baseline plasma ammonia level was 271 micromol/L. By day 3, normal plasma ammonia levels were attained in individuals for whom data were available. Long-term efficacy was measured using the last reported plasma ammonia level for each of the 13 individuals analyzed (median length of treatment was 6 years; range 1 to 16 years). The mean and median ammonia levels were 23 micromol/L and 24 micromol/L, respectively, after a mean treatment duration of 8 years.

Acute Hyperammonemia due to Propionic Acidemia and Methylmalonic Acidemia

A randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the efficacy of Carbaglu in the treatment of hyperammonemia in individuals with propionic acidemia (PA) or methylmalonic acidemia (MMA) (NCT01599286). Eligible hyperammonemic episodes, defined as an admission to the hospital with a plasma ammonia level ≥ 70 micromol/L, were randomized 1:1 to receive either Carbaglu or placebo for 7 days or until hospital discharge, whichever occurred earlier. All individuals received standard of care, including a combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine; the use of alternative pathway medications (e.g., sodium benzoate and medications with phenylacetate as an active metabolite) was prohibited. Carbaglu was dosed at 150 mg/kg/day for individuals ≤ 15 kg or 3.3 g/m2/day for individuals > 15 kg and was divided into 2 equal doses administered 12 hours apart by NG tube, G-tube, or oral syringe. Plasma ammonia testing was performed at pre-randomization and at post-dosing intervals of every 6 -12 hours for the first 48 hours and every day thereafter if the ammonia level was ≥ 50 micromol/L.

The efficacy evaluation was based on 90 hyperammonemic episodes (42 treated with Carbaglu and 48 with placebo) in 24 individuals (12 male and 12 female) with PA (n = 15) or MMA (n = 9). The median individual age was 8 years (range 4 days to 29 years). The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level ≤ 50 micromol/L (normal range) or hospital discharge. The median time to reach the primary endpoint was 1.5 days in the Carbaglu group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% confidence interval: -1.2, 0.1), driven exclusively by an effect on plasma ammonia normalization.

Throughout the first three days of treatment, a higher proportion of Carbaglu-treated episodes reached the primary endpoint compared to placebo-treated episodes.

Safety

Adverse reactions occurring in 2 or more individuals treated with carglumic acid in the retrospective case series (≥ 10%) were vomiting (26%), abdominal pain (17%), pyrexia (17%), tonsillitis (17%), anemia (13%), diarrhea (13%), ear infection (13%), infections (13%), nasopharyngitis (13%) and hemoglobin decreased (13%).

Ravicti (glycerol phenylbutyrate)

Evidence for the efficacy of glycerol phenylbutyrate in treating urea cycle disorder consists of one multicenter, randomized, double-blind, double-dummy, placebo-controlled, cross-over, non-inferiority study. The phase 3 study assessed the non-inferiority of glycerol phenylbutyrate to sodium phenylbutyrate by evaluating blood ammonia levels in adult individuals with UCDs from OTC, CPS, and AS who were being treated with sodium phenylbutyrate for control of their UCD. Adult individuals ≥18 years of age with diagnoses of UCD were enrolled, an each of the individuals had deficiencies including CPS, OTC, or AS, confirmed via enzymatic, biochemical, or genetic testing. They were required to have controlled ammonia levels <100 µmol/L without signs and symptoms of hyperammonemia. The individuals were not allowed to receive drugs known to increase ammonia levels, increase protein catabolism, or significantly affect renal clearance.

The sample size of 46 individuals (only 44 individuals were used in the analysis portion) were randomized equally to received placebo glycerol phenylbutyrate plus active sodium phenylbutyrate, or placebo sodium phenylbutyrate plus active glycerol phenylbutyrate for 14 days and then crossed over to receive the alternative treatment. The dose of glycerol phenylbutyrate was calculated to deliver the same amount of phenylbutyrate as each individual's baseline sodium phenylbutyrate dose.

In both randomized groups, the individuals received the same amount of phenylbutyrate throughout the study and followed a balanced diet in terms of protein and calorie intake. At the end of each treatment period (2 weeks), individuals underwent repeated blood sampling over 24 hours for ammonia plasma and urine levels of metabolites, including phenylbutyrate and phenylacetic acid. The primary efficacy measure was daily ammonia exposure, assessed as 24-hour AUC. Non-inferiority was to be achieved if the upper 95% confidence interval (CI) for the

ratio of the least squares means between glycerol phenylbutyrate and sodium phenylbutyrate was less than or equal to 1.25. The non-inferiority margin of 1.25 is consistent with FDA guidance on bioequivalence studies and corresponds to an absolute difference of approximately 9 umol/L for an individual with an ammonia at the upper limit of normal (35 umol/L), a clinically insignificant change.

When administered at the recommended dose levels sodium phenylbutyrate has been shown from clinical experience to be safe and effective in improving long-term survival in individuals with UCDs (i.e., reducing the incidence of deaths due to hyperammonemic encephalopathy). However, compliance with sodium phenylbutyrate is difficult due to a high pill burden (up to 40 pills or 40 mL of dissolved powder daily for individuals taking 20 g of sodium phenylbutyrate), foul taste, unpleasant odor, and high sodium content (approximately 2,300 mg/day for individuals taking 20 g). All of these factors render sodium phenylbutyrate difficult to take, and compliance is suboptimal even for UCD individuals with the most severe deficiency states, whose alternative is life-threatening hyperammonemia. Consequently, UCDs remains as a rare, serious and life-threatening condition with a not fully met medical need. Ravicti is an alternative therapy to sodium phenylbutyrate in individuals with UCDs as it is expected to provide similar nitrogen-scavenging ability while eliminating the current issues of bad taste, odor, sodium content, and pill burden.

Forty individuals who completed the short-term adult study and 11 individuals who completed the short-term pediatric study enrolled in the long-term protocols; 26 additional, newly-enrolled adult and pediatric individuals were also in the long-term protocol for a total of 77 UCD individuals (51 adult and 26 pediatric individuals ages 6–17, including ARG, ASL, AS, CPS, and OTC subtypes). Mean ammonia values during long term treatment with glycerol phenylbutyrate were similar to the mean fasting values (time 0 or 24h) observed during the short-term controlled studies and well below the upper limit of normal (35 umol/L) for both pediatric and adult individuals at each monthly visit, with monthly means approximately half the upper limit of normal and ranging from 6.3 (Month 9) to 29.6 µmol/L (Month 11).

Safety

The most common adverse events were mild gastrointestinal issues. Adverse events were reported by 61% and 51% of individuals during glycerol phenylbutyrate and sodium phenylbutyrate treatment, respectively. The gastrointestinal disorders included diarrhea, flatulence, abdominal discomfort, dyspepsia, nausea, and oral discomfort. No clinically significant lab or ECG changes were observed. Headache, somnolence, lightheadedness, and confusion are all possible adverse reactions of glycerol phenylbutyrate. Phenylacetic acid

exposure is associated with neurological toxicity at dose-dependent increases manifested by dysgeusia, hypoacusis, disorientation, and impaired memory. One individual experienced a hyperammonemic crisis and one individual withdrew early because of high ammonia and headache; both during sodium phenylbutyrate treatment. One individual had a serious adverse event including gastroenteritis on glycerol phenylbutyrate. There were no deaths during the study.

2020 Update

Reviewed prescribing information for all drugs. Updated Ravicti (glycerol phenylbutyrate) criteria from tried and failed Buphenyl (sodium phenylbutyrate) to tried and failed generic sodium phenylbutyrate to reflect the availability now of generic sodium phenylbutyrate.

2021 Update

Reviewed prescribing information for all drugs. Added a new indication for Carbaglu (carglumic acid) for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA) when used as adjunctive therapy along with standard of care.

2022 Update

Reviewed prescribing information for all drugs. Added Pheburane (sodium phenylbutyrate) for the treatment of urea cycle disorders in adult and pediatric individuals. Medical necessity criteria for Pheburane added to be the same as Buphenyl. Pheburane oral pellets offer a unique formulation of sodium phenylbutyrate (NaPB) to help mask the unpleasant taste of NaPB.

2023 Update

Reviewed prescribing information for all drugs. Added Olpruva (sodium phenylbutyrate) to the same medical necessity criteria as Buphenyl.

2024 Update

Reviewed prescribing information for all drugs. Added generic carglumic acid for the treatment of certain individuals with N-acetylglutamate synthase (NAGS), propionic acidemia (PA) and methylmalonic acidemia (MMA).

2025 Update

Reviewed prescribing information for all drugs. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

2026 Update

Reviewed prescribing information for all drugs. Added generic glycerol phenylbutyrate to the policy with same criteria as Ravicti (glycerol phenylbutyrate).

References

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2. Summar ML, Diagnosis, symptoms, frequency, and mortality of 260 patients with urea cycle disorders from a 21-year, multicenter study of acute hyperammonemic episodes. Acta Paediatrica 2008; 97:1420.
3. Summar, Marshall M. "The Incidence of Urea Cycle Disorders." Molecular Genetics and Metabolism 110.1-2 (2013): 179-80.
4. Buphenyl (sodium phenylbutyrate). Prescribing Information. Horizon Pharma USA, Inc., Lake Forest, IL. Revised July 2022.
5. Carbaglu (carglumic acid). Prescribing Information. Recordati Rare Diseases Inc., Lebanon, NJ. Revised January 2024.
6. Ravicti (glycerol phenylbutyrate). Prescribing Information. Horizon Pharma USA, Inc., Lake Forest, IL. Revised September 2021.
7. Pheburane (sodium phenylbutyrate). Prescribing Information. Medunik Pharma, Bryn Mawr, PA. Revised August 2023.
8. Olpruva (sodium phenylbutyrate). Prescribing Information. Acer Therapeutics Inc., The Woodlands, TX. Revised October 2025.

History

Date	Comments
10/01/19	New policy, approved September 10, 2019. Add to Prescription Drug section. Criteria added for Buphenyl (sodium phenylbutyrate), Carbaglu (carglumic acid), and Ravicti (glycerol phenylbutyrate).
02/01/20	Interim Review, approved January 9, 2020. Added coverage criteria for generic sodium phenylbutyrate and updated coverage criteria for Buphenyl (sodium phenylbutyrate).
01/01/21	Annual Review, approved December 1, 2020. Updated Ravicti (glycerol phenylbutyrate) criteria from tried and failed Buphenyl (sodium phenylbutyrate) to tried and failed generic sodium phenylbutyrate.
11/01/21	Annual Review, approved October 21, 2021. Added a new indication to Carbaglu (carglumic acid) for the treatment of acute hyperammonemia due to propionic acidemia or methylmalonic acidemia.
11/01/22	Annual Review, approved October 24, 2022. Added Pheburane (sodium phenylbutyrate) to policy with the identical coverage criteria as Buphenyl (sodium phenylbutyrate). Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/23	Annual Review, approved March 14, 2023. Added Olpruva (sodium phenylbutyrate) to the same medical necessity criteria as Buphenyl.
08/01/24	Annual Review, approved July 8, 2024. Added generic carglumic acid for the treatment of certain individuals with N-acetylglutamate synthase (NAGS), propionic acidemia (PA) and methylmalonic acidemia (MMA).
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
05/01/26	Annual Review, approved April 13, 2026. Added generic glycerol phenylbutyrate to the policy with same criteria as Ravicti (glycerol phenylbutyrate).

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.