Urea Cycle Disorder
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO034

Description
Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane) are orally administered nitrogen-binding agents used in the treatment of urea cycle disorder (UCD).

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
sodium phenylbutyrate (generic Buphenyl)	Urea Cycle Disorder	500mg tablets	1200 tablets/30 days[~]
		3g/tsp powder (250g bottle)	600 grams/30 days[~]
sodium phenylbutyrate (Buphenyl)		500mg tablets	1200 tablets/30 days[~]
		3g/tsp powder (250g bottle)	600 grams/30 days[~]
sodium phenylbutyrate (Pheburane)		Oral pellets (84g bottle)	600 grams/30 days[~]
glycerol phenylbutyrate (Ravicti)		1.1g/mL (25mL bottle)	525 mL (570g)/30 days*

*Glycerol phenylbutyrate (Ravicti) max dose of 17.5ml/day (no more than 19 g/day)
[~]Sodium phenylbutyrate (Buphenyl, Pheburane) max dose of 20g/day

Initial Evaluation

I. **Sodium phenylbutyrate (Buphenyl, Pheburane)** may be considered medically necessary when the following criteria below are met:
   A. Member is diagnosed with **Urea Cycle Disorder (UCD)** when the following are met:
      1. Management by dietary protein restriction and amino acid supplementation alone has been ineffective; **AND**
      2. Member will continue dietary protein restriction and, if needed, amino acid supplementation; **AND**

3. Documentation of baseline ammonia level indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age); **OR**
    i. Member is transitioning from IV amino acid infusion (sodium phenylacetate/sodium benzoate) to oral therapy; **AND**

B. Treatment with generic sodium phenylbutyrate has been ineffective, contraindicated, or not tolerated; **AND**

C. Member must demonstrate a medical reason they are unable to utilize generic sodium phenylbutyrate. Convenience of administration route or palatability preference does not equate to medical necessity (documentation required); **AND**

1. For brand sodium phenylbutyrate (Buphenyl) tablets:
    i. Member weighs at least 20 kg (44 lbs.)

II. **Glycerol phenylbutyrate (Ravicti)** may be considered medically necessary when the following criteria below are met:

A. Member meets criteria IA-IB; **AND**

B. Member must demonstrate a medical reason they are unable to utilize sodium phenylbutyrate products (Buphenyl, Pheburane). Convenience of administration route or palatability preference does not equate to medical necessity (documentation required).

III. Glycerol phenylbutyrate (Ravicti), sodium phenylbutyrate (Buphenyl, Pheburane) are considered investigational when used for all other conditions, including but not limited to:

A. Amyotrophic lateral sclerosis (ALS)

B. Acute hyperammonemia

C. N-acetylglutamate synthase (NAGS) deficiency

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation member will be continuing dietary protein restriction and, if needed, amino acid supplementation; **AND**

IV. Member has exhibited a reduction from baseline in plasma ammonia levels; **OR**
   A. Member has maintained a plasma ammonia level within normal range for member's age (see supporting evidence for normal ranges)

Supporting Evidence

I. Urea cycle disorders (UCD) are rare genetic metabolic deficiencies caused by missing enzymes in the urea cycle, the most common being ornithine transcarbamylase (OTC) deficiency. All of the following are known UCDs: carbamylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG], and N-acetyl glutamate synthetase [NAGS]. In UCD, the body is unable to convert the excess amino acids from food breakdown into uric acid that is secreted from the body resulting in high levels of ammonia in the body. In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals may not exhibit hyperammonemia or symptoms until later during infancy, childhood, or even adulthood due to a partial enzyme deficiency. It is important that the diagnosis and treatment be started early to improve survival.

II. An elevated plasma ammonia level of 150 µmol/L (>260 µg/dl), or higher, in neonates and > 100 µmol/l (175 µg/dl) in older children and adults, is a strong indication for the presence of a urea cycle disorder. Hyperammonemia can be the first symptom in patients without a known family history of UCD or without knowing the patient's genetics. Normalization of ammonia levels is critical to prevent neurologic abnormalities and impaired cognitive function in hyperammonemia. Acute management includes hemodialysis, fluid management, and IV infusion of sodium phenylacetate-sodium benzoate. Once patients are stabilized (ammonia level <100 mmol/L and mental status returns to baseline), patients can transition to oral therapy (sodium phenylbutyrate or glycerol phenylbutyrate). Per Orphanet Guidelines for Rare Diseases, not all patients who recover from an episode of hyperammonemia require chronic nitrogen-scavenging agents, but they should be considered if the patient cannot manage the disease with dietary treatment alone.

III. The goal of long-term management of UCD are to prevent hyperammonemia and includes dietary restrictions of protein, use of specialized formulas (in infants and young children), and oral nitrogen-scavenging agents. Sodium phenylbutyrate (Buphenyl, Pheburane) and glycerol phenylbutyrate (Ravicti) and are nitrogen-binding agents used in the chronic management of patients with UCD involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS), that cannot be managed by dietary protein restriction and/or dietary supplementation alone. Treatment must be combined with dietary protein restriction and, in some cases, dietary/amino acid supplementation (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements). Poor adherence with prescribed diets may increase the patient's protein intake, which may necessitate a dosage

increase; therefore, attestation of continuing dietary protein restriction and/or, amino acid supplementation is required.

IV. Sodium phenylbutyrate (Buphenyl, Pheburane) has more real-world data due to the time on the market as sodium phenylbutyrate was approved in 1996 and glycerol phenylbutyrate (Ravicti) was not approved until 2013. Sodium phenylbutyrate (Pheburane) was approved via 505(b)(2) pathway in 2022 and shares the same indication as Buphenyl. There have been several head-to-head non-inferiority studies in both adults and pediatrics, that showed glycerol phenylbutyrate (Ravicti) is as effective as sodium phenylbutyrate (Buphenyl, Pheburane) in treating UCD and has a slightly improved tolerability overall (no salty taste and odorless). Although, there is more data in the use of sodium phenylbutyrate (Buphenyl, Pheburane) and because it is specifically indicated in ornithine transcarbamylase (OTC) therapy, the most common UCD; sodium phenylbutyrate (Buphenyl, Pheburane) is typically started if UCD is suspected, and a genetic profile has not yet been completed. Additionally, in the absence of a clinically significant difference in efficacy between glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane), generic sodium phenylbutyrate is chosen as the preferred agent in the setting of UCD due to generic availability, cost, and a larger pool of safety and efficacy data.

V. Documentation of medical necessity for glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane) is required, as the recommended dose can be obtained with the generic sodium phenylbutyrate, providing a significant price differential (3 – 10x difference). Acceptable rationale for medical necessity include difficulty swallowing, restricted sodium intake, etc. Convenience of administration route or palatability preference does not equate to medical necessity.

VI. The notable differences between glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl) is the unpleasant smell/taste and the higher than the recommended daily allowance of sodium in sodium phenylbutyrate (Buphenyl, Pheburane). Sodium phenylbutyrate products should be used with caution in patients who have conditions that cause edema and/or must maintain restricted sodium intake (congestive heart failure, severe renal insufficiency, cirrhosis, or nephrosis). It is recommended that patients that develop new onset edema or worsening edema with sodium phenylbutyrate discontinue sodium phenylbutyrate products. Furthermore, generic sodium phenylbutyrate and brand sodium phenylbutyrate (Buphenyl) are both available in tablet and powder formulations and are known to have a distinct, strong salty taste. Glycerol phenylbutyrate (Ravicti) is available as a tasteless/odorless oral solution. Sodium phenylbutyrate (Pheburane) shares the same indication as generic sodium phenylbutyrate and Buphenyl, however is formulated as tasteless/odorless oral pellets. Generic sodium phenylbutyrate powder, Buphenyl powder, and glycerol phenylbutyrate (Ravicti) are able to be administered via nasogastric or gastrostomy tube.

VII. Clinical study results showed ammonia values ranged from 9-35 µmol/L; however, the US UCD management guidelines do not specify a direct chronic ammonia treatment target number. Additionally, the normal value changes from neonates, to pediatrics, to adults and the

consensus would be to focus on keeping the body within the normal range for the patient's age on the lab test used, see below table.

Ammonia Level Range Table	
Age Range	**Normal Ammonia Range**
Adults	7-35 mmol/L
Children	28-57 mmol/L
Newborns	64-107 mmol/L

VIII. The quantity limits noted in the table above reflect the maximum daily dose for each agent as there have not been safety/efficacy data over these doses. If the patient is transitioning from sodium phenylbutyrate (Buphenyl, Pheburane) to glycerol phenylbutyrate (Ravicti), a slight initial dosage change to ensure the patient is receiving the same amount of phenylbutyric acid, is required. See appendix for details.

Investigational or Not Medically Necessary Uses

I. Amyotrophic Lateral Sclerosis (ALS)

A. In a phase 2 clinical study (CENTAUR), 137 patients with ALS were randomized 2:1 to receive sodium phenylbutyrate combined with taurursodiol (PB-TURSO) [N=89] or placebo [N=48], for 6 months. The primary endpoint was the ability to slow the disease progression as measured by changes in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). The ALSFRS-R is the principal functional end point referenced in the latest FDA guidance for ALS trials with each point decrease representing lost capability across a 12 point scale, looking at tasks such as breathing, walking, fine motor skills; a higher score meaning higher normal function and less progressed disease symptoms. The primary endpoint was the only endpoint to reach statistical significance with a p-value of 0.03 and a mean rate of change in the ALSFRS-R scores of -1.24 points per month for PB-TURSO versus -1.66 points in placebo. With an absolute mean difference at week 24 of 2.32 in PB-TURSO versus placebo correlating to preserved functioning ability in those taking the study compound over placebo.

B. An open-label extension (OLE) was allowed for those who completed the CENTAUR trial (97 patients in total between both arms) for up to 30 months. Fifty-six patients on PB-TURSO and 34 on placebo enrolled, all receiving PB-TURSO in the OLE, those originally on placebo were changed over. The risk of key events including death, tracheostomy, first hospitalization and progression-free survival were all evaluated. Median key event-free survival duration was 4.8 months longer in participants originally randomized to PB-TURSO versus placebo, and median tracheostomy/PAV-free survival duration was 7.3 months longer. As of the analysis cut-off, median time to first hospitalization was not yet reached in the group originally randomized to PB-TURSO, compared with 14.1 months in the group originally randomized to placebo.

C. The OLE noted that this added to the previously reported overall functional/survival benefits from the primary phase 2 randomized, blinded trial. On September 7th, a second FDA advisory panel met to discuss the phase 2 and OLE data, as the March panel negatively reviewed this data pushing back the first PDUFA date by several months. On September 7th, the committee was 7-2 favorable, changing their prior decision. Currently, there is a recruiting phase 3 trial (PHOENIX) and a PDUFA date on September 29th. If approved, PB-TURSO would be an add-on agent to those already approved in the treatment of ALS, riluzole, and edaravone. At this time, sodium phenylbutyrate is considered experimental and investigational for the treatment of ALS.

II. Acute hyperammonemia
   A. Neither glycerol phenylbutyrate (Ravicti) nor sodium phenylbutyrate (Buphenyl, Pheburane) are indicated to treat acute hyperammonemia, which is considered a life-threatening emergency. Rapidly acting interventions are essential to reduce plasma ammonia levels. Treatment of acute hyperammonemia includes stopping protein intake, hydration, and initiation of IV arginine hydrochloride, sodium benzoate/sodium phenylacetate (Ammonul), and/or oral citrulline.

III. N-acetylglutamate synthase (NAGS) deficiency
   A. The efficacy and safety of glycerol phenylbutyrate (Ravicti) for the treatment of hyperammonemia due N-acetylglutamate synthase (NAGS) deficiency has not been established.

Appendix

I. The recommended dosages for patients that are treatment naïve or switching from sodium phenylbutyrate (Buphenyl, Pheburane) to phenylbutyrate (Ravicti) are different. A direct conversion of dosing can be calculated for patients already on sodium phenylbutyrate (Buphenyl, Pheburane) to sodium phenylbutyrate (Ravicti):
   a. Total daily dose glycerol phenylbutyrate (mL) = 0.8 x total daily dose of sodium phenylbutyrate (grams)

References

1. Ravicti [Prescribing Information]. South San Francisco, CA: Hyperion Therapeutics Inc.; September 2021.
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3. Pheburane [Prescribing Information]. Lucane Pharma.; June 2022.
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8. Lee B. Urea cycle disorders: management. In: Post TW, ed. UpToDate. UpToDate; 2022. Accessed September 07, 2022. https://www.uptodate.com/contents/urea-cycle-disorders-management.
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10. Paganoni S, Hendrix S, Dickson SP, et al. Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalisation in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial. *J Neurol Neurosurg Psychiatry.* 2022 May 16;93(8):871–5. doi: 10.1136/jnnp-2022-329024. Epub ahead of print. PMID: 35577511.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Carbaglu (carglumic acid)	Acute hyperammonemia due to NAGS deficiency
	Chronic hyperammonemia due to NAGS deficiency
	Acute hyperammonemia due to PA or MMA

Policy Implementation/Update

Action and Summary of Changes	Date
Added new product, sodium phenylbutyrate (Pheburane) to policy. Added generic sodium phenylbutyrate to QL table. Expanded on quantity limits to meet weight-based dosing. Updated formatting to separate generic SPB, Buphenyl, Pheburane, and Ravicti. Removed age requirement. Removed ammonia lab requirement in initial criteria and replaced with documentation of baseline level, allow coverage in members transitioning from IV to oral therapy; added requirement of documentation of medical necessity for branded products; added attestation for continuing amino acid supplementation/diet in renewal, added NAGS to E/I and updated E/I evidence. Updated supporting evidence and references. Added appendix and related policies section.	09/2022
Updated policy name, added second medication to the policy, sodium phenylbutyrate. Expanded on quantity limits to meet weight-based dosing; added clinical criteria for review of sodium phenylbutyrate. Updated renewal criteria. Added ALS as experimental indication. Revised and strengthened the supporting evidence.	12/2021
Criteria update: Included new FDA expanded indication for pediatric patients 2 months and older. Glycerol phenylbutyrate (Ravicti) was originally approved for pediatric patients 2 years and older. Additionally, a question was added to the renewal portion of this policy to assess for toxicity.	01/2019
Previous Reviews	07/2013;

	08/2013