**Original Effective Date: 03/01/2015**
**Current Effective Date: 09/29/2024**
**Last P&T Approval/Version: 07/31/2024**
**Next Review Due By:07/2025**
**Policy Number: C7041-A**

# Ravicti (glycerol phenylbutyrate)

## PRODUCTS AFFECTED

Ravicti (glycerol phenylbutyrate)

## COVERAGE POLICY

*Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.*

***Documentation Requirements:***
*Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.*

**DIAGNOSIS:**
Chronic hyperammonemia

**REQUIRED MEDICAL INFORMATION:**
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. CHRONIC HYPERAMMONEMIA:
1. Documentation of a diagnosis of chronic hyperammonemia due to urea cycle disorder (UCD) AND

2. Documentation diagnosis has been confirmed with enzymatic and/or genetic testing. Documentation of enzymatic, biochemical, or genetic testing confirmation required. (Refer to Appendix) [DOCUMENTATION REQUIRED]
   AND
3. Documentation of baseline plasma ammonia level at diagnosis for monitoring of efficacy [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests that member does NOT have acute hyperammonemia
   AND
5. Prescriber attests that member's condition has failed to be managed with dietary protein restriction and/or amino acid supplementation alone (i.e., essential amino acids, arginine, citrulline, protein-free calorie supplements)
   AND
6. Documented trial (15 days) and failure or ineffectiveness, contraindications, or serious side effects to ALL of the following: sodium phenylbutyrate powder (Buphenyl) AND sodium phenylbutyrate (Buphenyl) tablet AND Pheburane (sodium phenylbutyrate pellets)
   AND
7. Prescriber attests that Ravicti (glycerol phenylbutyrate) therapy will be used concomitantly with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements)

**CONTINUATION OF THERAPY:**

A. CHRONIC HYPERAMMONEMIA:

1. Documentation of stabilization or improvement due to Ravicti therapy as evidenced by decreased fasting plasma ammonia levels which are indicative of efficacy. Submit current plasma ammonia level (within 60 days of request date). [DOCUMENTATION REQUIRED]
   *NOTE: Per package insert, normal ranges and therapeutic target levels for plasma ammonia depend upon the assay method used by the individual laboratory. During treatment with Ravicti, refer to the assay-specific normal ranges and to the therapeutic target ranges for plasma ammonia.*
   AND
2. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

**DURATION OF APPROVAL:**

Initial authorization: 3 months, Continuation of therapy: 12 months

**PRESCRIBER REQUIREMENTS:**

Prescribed by, or in consultation with, a board-certified geneticist/metabolic specialist or physician experienced in the management of urea cycle disorder. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

**AGE RESTRICTIONS:**

No restriction

**QUANTITY:**

Recommended dosage range is 4.5 to 11.2 mL/m2/day in divided equal portions three times daily

**Maximum Quantity Limits –** 17.5mL/day (19 g)

**PLACE OF ADMINISTRATION:**

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and

patient self-administered.

## DRUG INFORMATION

**ROUTE OF ADMINISTRATION:**
Oral

**DRUG CLASS:**
Urea Cycle Disorder - Agents

**FDA-APPROVED USES:**
Indicated for use as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

*Limitations of Use: Ravicti is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels. The safety and efficacy of Ravicti for the treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.*

**COMPENDIAL APPROVED OFF-LABELED USES:**
None

## APPENDIX

**APPENDIX:**
*Appendix 1: Urea Cycle Disorders*. UCDs are caused by a deficiency in any of the below enzymes in the pathway that transforms nitrogen to urea:

- Carbamyl phosphate synthetase I (CPSI) deficiency
- Ornithine transcarbamylase (OTC) deficiency
- Argininosuccinate synthetase (ASS) deficiency (also known as classic citrullinemia or type I citrullinemia,CTLN1)
- Argininosuccinate lyase (ASL) deficiency (also known as argininosuccinic aciduria)
- Arginase deficiency
- N-acetyl glutamate synthetase (NAGS) deficiency**--**The safety and efficacy of Ravicti for the treatment of NAGS deficiency has not been established.

## BACKGROUND AND OTHER CONSIDERATIONS

**BACKGROUND:**
Ravicti is indicated for the management of urea cycle disorders in members 2 months of age and older who cannot be managed solely by dietary protein restriction and/or amino acid supplementation.
Ravicti is a nitrogen-binding agent.
Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).
Ravicti is not indicated for treatment of acute hyperammonemia in members with UCDs.

**CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:**
All other uses of Ravicti (glycerol phenylbutyrate oral liquid) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Ravicti (glycerol phenylbutyrate oral liquid) include: Hypersensitivity to sodium phenylbutyrate or any component of the formulation; management of acute hyperammonemia.

**OTHER SPECIAL CONSIDERATIONS:**

*PREFERRED: Sodium Phenylbutyrate*

- Glycerol phenylbutyrate and sodium phenylbutyrate are similar drugs used for the chronic management of adult and pediatric members with Urea Cycle Disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. The active metabolite for both drugs is Phenylacetate (PAA).
- Buphenyl (available as oral tablets and as a powder for oral, nasogastric, or gastrostomy tube administration) may be administered to pediatric members over 20 kg; Ravicti (available in an oral liquid) is indicated for members 2 years and older with UCDs and contraindicated in members younger than 2 months.
- Notable difference of Buphenyl is the unpleasant smell/taste profile and a higher daily sodium load than the recommended daily allowance (2,400 mg vs 2,300 mg/day) than Ravicti. Ravicti has no sodium and has a mild smell/taste profile compared to Buphenyl. However, there is no evidence that Ravicti is safer or more efficacious than Buphenyl. Furthermore, Buphenyl has a longer track record of clinical experience. Pheburane has taste-masking properties that make it more palatable than Buphenyl products.
- There is insufficient evidence that Ravicti is more efficacious than Buphenyl. The major study supporting Ravicti's safety and efficacy involved 44 adults who were randomly assigned to receive Buphenyl or Ravicti for two weeks before being switched to the other product for two weeks. Blood testing showed Ravicti was as effective as Buphenyl in controlling ammonia levels. Pooled data from the pivotal trial and additional phase II studies suggest that Ravicti may be superior to Buphenyl in the control of ammonia levels. This data, however, is considered preliminary due to the small number of subjects included.

Long-term studies in pediatric members suggest 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.

## CODING/BILLING INFORMATION

*Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement*

| HCPCS CODE | DESCRIPTION |
|---|---|
| NA | |

**AVAILABLE DOSAGE FORMS**:

Ravicti LIQD 1.1GM/ML (25ml bottle)

## REFERENCES


1. Ravicti (glycerol phenylbutyrate) [prescribing information]. Lake Forest, IL: Horizon Pharma USA, Inc; September 2021.
2. Buphenyl (sodium phenylbutyrate) [prescribing information]. Deerfield, IL: Horizon Pharma; March 2023.
3. 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
4. Ravicti (glycerol phenylbutyrate) FDA Clinical Review available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000MedR.pdf
5. GA Diaz et al. Ammonia control and neurocognitive outcome among urea cycle disorder members

treated with glycerol phenylbutyrate. Hepatology 2013; 57:2171.
6. U Lichter-Konecki et al. Ammonia control in children with urea cycle disorders (UCDs); phase2 comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Mol Genet Metab 2011; 103:323.
7. Smith W, Diaz GA, Lichter-Konecki U, et al. Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. J Pediatr 2013; 162:1228.
8. Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. National Institutes of Health, Rare Diseases Clinical Research Network. Available at https://rarediseases.org/organizations/urea-cycle-disorders- consortium/Accessed May 2020.
9. Gene Reviews: Urea Cycle Disorders Overview. http://www.ncbi.nlm.nih.gov/books/NBK1217/ Accessed on May 2020.

| SUMMARY OF REVIEW/REVISIONS | DATE |
|---|---|
| REVISION- Notable revisions:<br>Diagnosis<br>Required Medical Information<br>Other Special Considerations<br>References | Q3 2024 |
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>Prescriber Requirements<br>Contraindications/Exclusions/<br>Discontinuation | Q2 2023 |
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>Quantity<br>Contraindications/Exclusions/Discontinuation<br>References | Q3 2022 |
| Q2 2022 Established tracking in new format | Historical changes on file |