Clinical Policy: Glycerol Phenylbutyrate (Ravicti)

Reference Number: CP.PHAR.207
Effective Date: 05.01.16
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Glycerol phenylbutyrate (Ravicti®) is a nitrogen-binding agent.

FDA Approved Indication(s)

Ravicti is indicated 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).

Limitation(s) 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Ravicti is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Urea Cycle Disorder (must meet all)**:**

1. Diagnosis of a UCD caused by one or more of the following, confirmed by enzymatic, biochemical, or genetic analysis:
   a. Carbamyl phosphate synthetase 1 (CPS1) deficiency;
   b. Ornithine transcarbamylase (OTC) deficiency;
   c. Argininosuccinate synthetase (AS) deficiency (also known as classic citrullinemia or type I citrullinemia, CTLN1);
   d. Argininosuccinate lyase (ASL) deficiency (also known as argininosuccinic aciduria);
   e. Arginase deficiency;
2. Prescribed by or in consultation with a physician experienced in treating metabolic disorders;

3. For members with UCD caused by CPS1, OTC, or AS deficiency: Both of the following (a and b):
   a. Member must use generic sodium phenylbutyrate, unless contraindicated or clinically significant adverse events are experienced;
   b. If member has intolerance or contraindication to generic sodium phenylbutyrate, member must use Pheburane®, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 17.5 mL (19 g) per day.

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Urea Cycle Disorder (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. For members with UCD caused by CPS1, OTC, or AS deficiency: Both of the following (a and b):
   a. Member must use generic sodium phenylbutyrate, unless contraindicated or clinically significant adverse events are experienced;
   b. If member has intolerance or contraindication to generic sodium phenylbutyrate, member must use Pheburane, unless contraindicated or clinically significant adverse effects are experienced;
3. Member is responding positively to therapy;

4. If request is for a dose increase, new dose does not exceed 17.5 mL (19 g) per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ASL: argininosuccinate lyase
AS: argininosuccinate synthetase
CPS1: carbamyl phosphate synthetase 1
CTLN1: type I citrullinemia
FDA: Food and Drug Administration
NAGS: N-acetyl glutamate synthetase
OTC: ornithine transcarbamylase
UCD: urea cycle disorder

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sodium phenylbutyrate (Buphenyl®, Pheburane®)	**UCD caused by CPS1, OTC, or ASS deficiency:** Weight ≥ 20 kg: 9.9 to 13 g/m^2/day PO in equally divided doses with each meal or feeding	20 g/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Weight < 20 kg: 450 to 600 mg/kg/day PO in equally divided doses with each meal or feeding	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity
- Boxed warning(s): none reported

Appendix D: 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 1 (CPS1) deficiency
- Ornithine transcarbamylase (OTC) deficiency
- Argininosuccinate synthetase (AS) deficiency (also known as classic citrullinemia or type I citrullinemia, CTLN1)
- Argininosuccinate lyase (ASL) deficiency (also known as argininosuccinic aciduria)
- N-acetyl glutamate synthetase (NAGS) deficiency
- Arginase deficiency

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
UCD	Total daily dosage given in 3 equally divided doses up to nearest 0.5 mL (age ≥ 2 years) or 0.1 mL (age < 2 years): • In phenylbutyrate-naïve patients, the Ravicti dosage is 4.5-11.2 mL/m^2/day • In patients switching from sodium phenylbutyrate, the total daily dosage of Ravicti (mL) equals the daily dosage of sodium phenylbutyrate (g) x 0.81 (powder) or x 0.86 (tablets)	17.5 mL/day

VI. Product Availability

Oral liquid: 1.1 g/mL

VII. References

1. Ravicti Prescribing Information. Lake Forest, IL: Horizon Pharma USA, Inc.; September 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203284Orig1s012lbl.pdf. Accessed November 12, 2024.
2. Haberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J Inherit Metab Dis.* 2019;42(6):1192-1230. doi:10.1002/jimd.12100.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.28.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.27.21	02.22
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less.	04.26.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
1Q 2023 annual review: no significant changes; updated "CPSI" with "CPS1" to clarify the enzyme name; references reviewed and updated.	11.10.22	02.23
Per August SDC: modified redirection to be stepwise, first requiring generic sodium phenylbutyrate, then if member has intolerance or contraindication to generic sodium phenylbutyrate member must use Pheburane.	08.22.23	11.23
Revised stepwise redirection language per SDC request from an 'or' to 'and' statement.	01.10.24	
1Q 2024 annual review: no significant changes; references reviewed and updated.	11.12.23	02.24
Per ad hoc SDC request: added redirection to generic sodium phenylbutyrate followed by redirection to Pheburane for requests for continuation of therapy.	11.07.24	12.24
1Q 2025 annual review: no significant changes; references reviewed and updated.	11.12.24	02.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering

benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.