Clinical Policy: Glycerol Phenylbutyrate (Ravicti)

Reference Number: ERX.SPA.20
Effective Date: 07.01.16
Last Review Date: 02.22
Line of Business: Commercial, 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 the 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 treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.
- Safety and efficacy for 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 of the following, confirmed by enzymatic, biochemical, or genetic analysis:
   a. Carbamyl phosphate synthetase I (CPSI) deficiency;
   b. Ornithine transcarbamylase (OTC) deficiency;
   c. Argininosuccinate synthetase (ASS) 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 CPSI, OTC, or ASS deficiency: Inadequate response to sodium phenylbutyrate, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 17.5 mL (19 g) per day.

Approval duration: 6 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 17.5 mL (19 g) per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ASL: argininosuccinate lyase
ASS: argininosuccinate synthetase
CPSI: carbamyl phosphate synthetase I
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®)	Weight ≥ 20 kg: 9.9 to 13 g/m^2/day PO in equally divided doses with each meal or feeding Children < 20 kg: 450 to 600 mg/kg/day PO in equally divided doses with each meal or feeding	20 g/day

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 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)
- 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.ravicti.com. Accessed September 27, 2021.
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
1Q18 annual review: Removed dietary protein restriction requirements as this cannot be confirmed. Added therapeutic alternatives dosing information for sodium phenylbutyrate.	11.15.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.25.18	02.19
Policy updated by removing age limitation of 2 months or older based on December, 2018, FDA approval for use in children less than 2 months of age.	01.23.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.20.19	02.20
1Q 2021 annual review: no significant changes; 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

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.