Clinical Policy Title:	glycerol phenylbutyrate
Policy Number:	RxA.261
Drug(s) Applied:	Ravicti®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of Business

Background

Ravicti® is a nitrogen-binding agent. It 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
glycerol phenylbutyrate (Ravicti®)	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

Dosage Forms

- Oral liquid: 1.1 g/mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Urea Cycle Disorder (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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 Weight <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 to glycerol phenylbutyrate or any component of the formulation.

- Boxed Warning(s):
  - None reported

APPENDIX D: General Information

- 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

References

1. Ravicti® Prescribing Information. Lake Forest, IL: Horizon Pharma USA, Inc.; November 2019. Available at https://www.ravicti.com. Accessed February 24, 2021.
2. Nicholas Ah Mew, Kara L Simpson, Andrea L Gropman, et al. Urea Cycle Disorders Overview. June 22, 2017. Available at https://www.ncbi.nlm.nih.gov/books/NBK1217/. Accessed February 24, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Line of Business Policy Applies to was update to all lines of business. 3. Continued Therapy criteria II.A.1 was	07/02/2020	09/14/2020

rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 4. Initial Approval Criteria: Commercial approval duration was updated from length of benefit to 6 months. 5. Continued Therapy Approval criteria: Commercial approval duration was updated from length of benefit to 12 month. 6. Updated APPENDIX C: Contraindications. 7. References were updated.		
Policy was reviewed: 1. Last Review Date was updated. 2. Clinical policy verbiage was updated to “The provision of provider samples does not guarantee….”. 3. APPENDIX B: Therapeutic Alternatives verbiage was updated to "Below are suggested therapeutic alternatives based on clinical guidance...." 4. References were reviewed and updated.	02/24/2021	06/10/2021