Medical Policy

BlueCross BlueShield of Kansas
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Title: Urea Cycle Disorders

- **Prime Therapeutics will review Prior Authorization requests**

  Prior Authorization Form:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6299KS-URCD.pdf

  Link to Drug List (Formulary):
  https://www.bcbsks.com/drugs/

Professional
Original Effective Date: January 1, 2016
Revision Date(s): January 1, 2016; February 1, 2017; January 1, 2018
Current Effective Date: January 1, 2018

Institutional
Original Effective Date: January 1, 2016
Revision Date(s): January 1, 2016; February 1, 2017; January 1, 2018
Current Effective Date: January 1, 2018

DESCRIPTION

The intent of the Urea Cycle Disorders Prior Authorization (PA) program is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines-as well as to encourage use of generic sodium phenylbutyrate before the use of Buphenyl. The PA criteria consider these agents appropriate for use in patients who have been diagnosed with any of the following urea

cycle disorders (UCD): carbamylphosphate synthetase I deficiency [CPSID], ornithine transcarbamylase deficiency [OTCD], argininosuccinic acid synthetase deficiency [ASSD], argininosuccinic acid lyase deficiency [ASLD], or arginase deficiency [ARGD]. The use of these agents in N-acetyl glutamate synthetase deficiency [NAGS] has not been evaluated. The agents may not be used in the acute setting. Patients must be unable to maintain a plasma ammonia level within the normal range with the use of dietary protein restriction and, if clinically appropriate, with essential amino acid supplementation. The patient may not have any FDA labeled contraindications to therapy with the requested agent and the dose must be within the FDA labeled dosing. The program allows use of Buphenyl when the patient has had a trial and failure, documented intolerance, FDA labeled contraindication, or hypersensitivity to generic sodium phenylbutyrate. Requests will be reviewed when patient-specific documentation is provided.

Target Drugs

- [a]**Buphenyl** (sodium phenylbutyrate)
- **Ravicti** (glycerol phenylbutyrate)

[a]-generic available, targeted in criteria

FDA Approved Indications and Dosage[1,4]

Agent(s)	Indication(s)	Dosing
[a]**Buphenyl** (sodium phenylbutyrate)	▪ Adjunctive therapy in the chronic management of patients with urea cycle disorders (UCD) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). ▪ All patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life) ▪ All patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. ▪ Buphenyl must be combined with dietary protein restriction, and, in some cases, essential amino acid supplementation.	▪ Usual total daily dose in patients with UCD: 450-600 mg/kg/day in patients <20kg or 9.9-13.0 g/m^2/day in larger patients in equally divided doses with each meal or feeding. ▪ The powder is to be mixed with food for immediate use and is designed for oral use only (mouth, gastrostomy, or nasogastric tube). ▪ The safety and/or efficacy of doses >20 grams (40 tablets) per day has not been established.

Agent(s)	Indication(s)	Dosing
Ravicti (glycerol phenylbutyrate)^	-Chronic management of adult and pediatric patients ≥2 months of age with urea cycle disorders that cannot be managed by dietary protein restriction and in some cases, amino acid supplementation alone. -Ravicti must be used with dietary protein restriction and/or dietary supplements (e.g. essential amino acids, arginine, citrulline, protein-free calorie supplements).	Initial dose in phenylbutyrate naïve patients: 4.5 to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day) ▪ Switching from sodium phenylbutyrate tablets: daily dosage of sodium phenylbutyrate (g) X 0.86. ▪ Switching from sodium phenylbutyrate powder: daily dosage of sodium phenylbutyrate (g) x 0.81. ▪ For patients with some enzyme activity who are not adequately controlled with dietary restriction, the recommended starting dose is 4.5 mL/m^2/day. ▪ For patients ≥2 years old: Give Ravicti in 3 equally divided doses, each rounded up to the nearest 0.5 mL. ▪ For patients 2 months to <2 years old: Give Ravicti in 3 or more equally divided doses, each rounded up to the nearest 0.1 mL. ▪ Maximum daily dosage is 17.5 mL.

^ Limitations of use: not indicated for the treatment of acute hyperammonemia; efficacy in N-acetylglutamate synthase (NAGS) deficiency has not been established; contraindicated in patients <2 months of age or with known hypersensitivity to phenylbutryrate.
a-generic is available, targeted in criteria

POLICY

Prior Authorization Criteria for Approval

Initial Evaluation

Buphenyl OR Ravicti will be approved for use when ALL of the following are met:

1. ALL of the following:
   a. The patient has a plasma ammonia level of 150 µmol/L (>260 µg/dL) or higher if a neonate or > 100 µmol/L (>175 µg/ dL) if an older child or adult
      AND
   b. The patient has a normal anion gap
      AND
   c. The patient has a normal blood glucose level
   AND

2. The patient has a diagnosis of ONE of the following urea cycle disorders:
   a. carbamylphosphate synthetase I deficiency [CPSID]
   b. ornithine transcarbamylase deficiency [OTCD]
   c. argininosuccinic acid synthetase deficiency [ASSD]
   d. argininosuccinic acid lyase deficiency [ASLD]
   e. arginase deficiency [ARGD]

   AND
3. The patient does not have acute hyperammonemia

   AND
4. The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, if clinically appropriate, essential amino acid supplementation

   AND
5. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction

   AND
6. If the requested agent is Buphenyl, one of the following:
   a. The patient has tried and failed generic sodium phenylbutyrate

      OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to generic sodium phenylbutyrate that is not expected to occur with the requested agent

   AND
7. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis

   AND
8. The patient does not have any FDA labeled contraindications to therapy with the requested agent

   AND
9. The dose is within the FDA-labeled dosing

Length of Approval: 12 months

Renewal Evaluation

Buphenyl or Ravicti will be renewed when the following are met:

1. The patient has been previously approved through the Prime Therapeutics Prior Authorization process
   AND
2. The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, if clinically appropriate, essential amino acid supplementation
   AND
3. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction
   AND
4. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
5. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
6. The dose is within the FDA labeled dosing

Length of Approval: 12 months

Agent	Contraindication
Buphenyl (sodium phenylbutyrate)	-acute hyperammonemia
Ravicti (glycerol phenylbutyrate)	-patients < 2 months of age -known hypersensitivity to phenylbutyrate

RATIONALE[2,3,5]

Urea cycle disorders (UCD) are rare genetically inherited metabolic deficiencies that result from defects in the metabolism of waste nitrogen from the breakdown of protein and nitrogen-containing molecules. UCD is caused by deficiency in the enzymes of the urea cycle: carbamylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG], and N-acetyl glutamate synthetase [NAGS]. Severe deficiency in any of the first four enzymes results in the accumulation of ammonia during the first few days of life. In severe disease, infants rapidly develop cerebral edema and signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma whereas milder disease and the associated accumulation of ammonia may be triggered by illness or stress.

Diagnosis is based upon clinical suspicion and biochemical and genetic testing. A normal anion gap and plasma glucose in the presence of a plasma ammonia concentration of 150 µmol/L (>260 µg/dL) or higher in neonates and > 100 µmol/L (175 µg/dL) in older children and adults is indicative of UCD. Molecular genetic testing is available for all urea cycle defects.

Long term management to prevent hyperammonemia include: dietary restriction of protein, use of specialized formulas, and oral nitrogen-scavenging agents. According to guidelines, not all patients who recover from a hyperammonemic episode require chronic nitrogen scavengers but they should be considered and they appear to be safe at the recommended doses. [SVW1]

SAFETY[1,4]

Buphenyl (sodium phenylbutyrate)
The use of sodium phenylbutyrate is contraindicated for management of acute hyperammonemia, which is a medical emergency.

Ravicti (glycerol phenylbutyrate)
The use of glycerol phenylbutyrate is contraindicated in patients <2 months of age as these patients may have immature pancreatic exocrine function, which could impair hydrolysis of this agent, leading to impaired absorption of phenylbutyrate and hyperammonemia. The use of glycerol phenylbutyrate is also contraindicated in patients with known hypersensitivity to phenylbutyrate.

REVISIONS

01-01-2016	Policy published 11-10-2015. Effective 01-01-2016.
01-01-2016	Policy published 12-22-2015. Effective 01-01-2016.
	Description section updated to include adding generic names of Buphenyl and Ravicti.
	In Policy section: ▪ In Item 1 a add ">" to read "…(>175 µg/dl) if an older child or adult" ▪ In Contraindications chart added "-known hypersensitivity to phenylbutyrate"
	Rationale section updated.
	References updated
02-01-2017	Description section updated
	In Policy section: Initial Evaluation ▪ In Item 1 a added "The patient has a" to read "The patient has a plasma ammonia level of 150 µmol/L…" ▪ In Item 1 a corrected "dl" to "dL"
	Rationale section updated
	References updated
01-01-2018	Description section updated
	In Policy section: Initial Evaluation ▪ In Item 4 added "if clinically appropriate" to read "The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, if clinically appropriate, essential amino acid supplementation" ▪ Added the following criteria: "6. If the requested agent is Buphenyl, one of the following: a. The patient has tried and failed generic sodium phenylbutyrate OR b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to generic sodium phenylbutyrate that is not expected to occur with the requested agent AND 7. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis"

	Renewal Evaluation ▪ In Item 2 added "if clinically appropriate" to read "The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, if clinically appropriate, essential amino acid supplementation" ▪ Added the following criteria: "3. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction AND 4. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis"
	Rationale section updated
	References updated

REFERENCES

1. Ravicti prescribing information. Horizon Pharma, Inc. Accessed April 2017.
2. Mew NA, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1217/. Accessed 9/7/17.
3. Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment guidelines. 2016. Accessed 7/25/16.
4. Buphenyl prescribing information. Horizon Pharma, Inc. April 2016.
5. Haeberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012 May 29;7:32.