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Urea Cycle Disorders Prior Authorization Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1,2]

Agent(s)	Indication(s)	Dosing
Buphenyl® (sodium phenylbutyrate)[a] Tablet for oral administration Powder for oral, nasogastric, or gastrostomy tube administration	-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.
Ravicti® (glycerol phenylbutyrate)^ Oral Liquid	-Chronic management of adult and pediatric patients ≥2 months of age with urea cycle disorders that 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,	-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: total daily dosage of sodium phenylbutyrate tablets (g) X 0.86. -Switching from sodium phenylbutyrate powder: total daily dosage of sodium phenylbutyrate powder (g) x 0.81.

	citrulline, protein-free calorie supplements).	-For patients with some enzyme activity who are not adequately controlled with protein 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 phenylbutyrate
a-generic is available, targeted in criteria

CLINICAL RATIONALE
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.[3,4]

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.[4, 5]

Long term management to prevent hyperammonemia includes: 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.[3]

Ravicti Efficacy
Ravicti was evaluated in four clinical trials; two evaluated treatment in adults, while the other two evaluated Ravicti in children 2 to 17 years of age. The first study evaluating Ravicti in adults was a randomized, double blind, active-controlled, crossover, noninferiority trial that compared Ravicti with sodium phenylbutyrate (Buphenyl) in patients with UCDs who had been on sodium phenylbutyrate prior to enrollment. Patients were required to have a diagnosis of UCD involving deficiencies of CPS, OTC, or ASS confirmed by enzymatic, biochemical, or genetic testing. Ravicti was non-inferior to sodium phenylbutyrate with regards to the 24-hour

AUC for ammonia. Another long-term (twelve month), uncontrolled, open-label study evaluated monthly ammonia control and hyperammonemic crisis in adults. Patients were converted from sodium phenylbutyrate to Ravicti. During the study period, mean fasting venous ammonia values were within normal limits and seven patients reported ten hyperammonemic crises overall. The efficacy of Ravicti in pediatric patients was evaluated in two open-label, sodium phenylbutyrate to Ravicti switchover studies. The durations of the studies were seven-days and ten-days. Sodium phenylbutyrate or Ravicti was administered in divided doses to patients with UCD subtypes OTC, ASL, and ASS. The 24-hour AUCs for blood ammonia were similar between the treatment arms.[1]

SAFETY

Buphenyl (sodium phenylbutyrate)

The use of sodium phenylbutyrate is contraindicated for management of acute hyperammonemia, which is a medical emergency.[2]

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.[1]

REFERENCES

1. Ravicti prescribing information. Horizon Pharma, Inc. April 2017.
2. Buphenyl prescribing information. Horizon Pharma, Inc. April 2016.
3. Mew NA, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1217/. Accessed 8/3/18.
4. Lee, Brendan, MD, PhD., et al. Urea Cycle Disorders: Clinical Features and Diagnosis. UpToDate. Last updated September 2017. Literature review current through June 2018.
5. Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment guidelines. 2017. Accessed 8/3/18.

Urea Cycle Disorders Prior Authorization

OBJECTIVE
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 the use of generic sodium phenylbutyrate before the use of Buphenyl or Ravicti. 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 or Ravicti when the patient has had a trial and inadequate response, documented intolerance, FDA labeled contraindication, or hypersensitivity to generic sodium phenylbutyrate. Requests will be reviewed when patient-specific documentation is provided.

TARGET AGENTS
Buphenyl (sodium phenylbutyrate)[a]
Ravicti (glycerol phenylbutyrate)
a_generic available, targeted in criteria

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agents will be approved when ALL of the following are met:

1. The patient has a diagnosis of hyperammonemia AND ALL of the following:
    a. The patient has elevated ammonia levels according to the patient's age [Neonate: plasma ammonia level 150 µmol/L (>260 µg/dL) or higher; Older child or adult: plasma ammonia level >100 µmol/L (>175 µg/dL)]
    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 confirmed by enzymatic OR genetic testing:
    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. ONE of the following:
   a. If the requested agent is Buphenyl, one of the following:
      i. The patient has tried and had an inadequate response to generic sodium phenylbutyrate
         OR
      ii. 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

   OR
   b. If the requested agent is Ravicti, one of the following:
      i. The patient has tried and had an inadequate response to generic sodium phenylbutyrate
         OR
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to generic sodium phenylbutyrate

   AND
7. The prescriber is a specialist in metabolic diseases or the prescriber has consulted with a specialist in metabolic diseases
   AND
8. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
9. The requested dose is within FDA approved labeling for the requested indication

Length of Approval: 12 months

Renewal Evaluation
Target Agents will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent (e.g., plasma ammonia level within the normal range)
   AND
3. The patient does not have acute hyperammonemia
   AND
4. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction
   AND
5. The prescriber is a specialist in metabolic diseases or a geneticist or the prescriber has consulted with a specialist in metabolic diseases or a geneticist
   AND
6. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
7. The requested dose is within FDA approved labeling for the requested indication

Length of Approval: 12 months

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