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Urea Cycle Disorders Prior Authorization Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1,2]

Agent	Indication	Dosage
Buphenyl® (sodium phenylbutyrate)[a] Oral tablet Powder for oral, nasogastric, or gastrostomy tube administration	• Adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamoylphosphate 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 is 450-600 mg/kg/day in patients < 20 kg, or 9.9-13.0 g/m^2/day in larger patients, in equally divided doses with each meal or feeding (i.e., 3-6x/day). The powder is to be mixed with food (solid or liquid) for immediate use and is designed for oral use only (mouth, gastrostomy, or nasogastric tube). When mixed with water, powder is stable up to one week. The safety or efficacy of doses > 20 grams (40 tablets) per day has not been established.
Ravicti® (glycerol phenylbutyrate) Oral liquid	• 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). <u>Limitations of Use:</u> • Not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly-acting interventions are essential to reduce plasma ammonia levels. • Safety and efficacy for the treatment of *N*-acetylglutamate synthase (NAGS) deficiency has not been established.	Initial dose in phenylbutyrate naïve patients: 4.5-11.2 mL/m^2/day (5 to 12.4 g/m^2/day). Switching from sodium phenylbutyrate: • total daily dosage of sodium phenylbutyrate *tablets* (g) x 0.86 • total daily dosage of sodium phenylbutyrate *powder* (g) x 0.81 Total daily dose is typically in 3 equally divided dosages. Maximum total daily dosage is 17.5 mL (19 g).

a – generic equivalent available

CLINICAL RATIONALE

Urea cycle disorders (UCDs) are rare genetically inherited metabolic deficiencies that result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency, or total absence, of any of the enzymes in the urea cycle (carbamoyl phosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG1]) or the cofactor producer (N-acetyl glutamate synthetase [NAGS]) results in the accumulation of ammonia (hyperammonemia) 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.[3-5]

The most important diagnostic step in UCDs is clinical suspicion of hyperammonemia. Laboratory data useful in the diagnosis of UCD includes, but is not limited to, plasma ammonia, anion gap, and plasma glucose. A normal anion gap and normal blood 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. The diagnosis of a specific UCD can be confirmed by genetic testing. Specifically, NAGS, OTC, and CPSI deficiencies can be confirmed by liver biopsy.[3-5]

Pharmacologic therapy for acute hyperammonemia consists of initial IV administration of a combination preparation of sodium phenylacetate and sodium benzoate, ideally while the dialysis is being arranged and the diagnostic workup is under way. If chronic therapy is warranted, the patient can then be switched to nitrogen scavengers such as sodium phenylbutyrate, glycerol phenylbutyrate, and carglumic acid.[4-6] Sodium phenylbutyrate (Buphenyl) and glycerol phenylbutyrate (Ravicti) are metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine to form phenylacetylglutamine, which is then excreted by the kidneys. On a molar basis it is comparable to urea, which makes it an alternate vehicle for excreting waste nitrogen.[1,2]

Long term management options to prevent hyperammonemia includes dietary modification and nutritional oversight (e.g., protein restriction, limitation of alcohol intake, essential amino acid supplementation if clinically appropriate).[4-6] Not all adult patients who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered since many of these patients can become more brittle as time goes on.[4,5]

SAFETY

Sodium phenylbutyrate (Buphenyl) is contraindicated for management of acute hyperammonemia, which is a medical emergency.[2]

Glycerol phenylbutyrate (Ravicti) is contraindicated in patients with known hypersensitivity to phenylbutyrate.[1]

REFERENCES

1. Ravicti prescribing information. Horizon Therapeutics USA, Inc. November 2019.
2. Buphenyl prescribing information. Horizon Therapeutics USA, Inc. February 2020.
3. Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. April 2003 [Updated June 2017]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1217/.
4. Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. Available at: https://www.rarediseasesnetwork.org/cms/ucdc/Healthcare-Professionals/Urea-Cycle-Treatment-Guidelines. Accessed June 2020.

5. Summar M. Urea Cycle Disorders. National Organization for Rare Disorders (NORD). Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/. Accessed June 2020.
6. 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):1041-1230.

Urea Cycle Disorders Prior Authorization

TARGET AGENT(S)
Buphenyl® (sodium phenylbutyrate)[a]
Ravicti® (glycerol phenylbutyrate)
a – generic equivalent available

Brand (generic)	GPI	Multisource Code
Buphenyl (sodium phenylbutyrate)[a]		
250 gm powder	30908060002950	M, N, O, or Y
500 mg tablet	30908060000320	M, N, O, or Y
Ravicti (glycerol phenylbutyrate)		
1.1 g/mL	30908030000920	M, N, O, or Y

a – generic equivalent available

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) 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 enzyme analysis OR genetic testing:
    a. carbamoyl phosphate synthetase I deficiency [CPSID]
    b. ornithine transcarbamylase deficiency [OTCD]
    c. argininosuccinic acid synthetase deficiency [ASSD]
    d. argininosuccinic acid lyase deficiency [ASLD]
    e. arginase deficiency [ARG1D]

    AND
3. The requested agent will NOT be used as treatment of 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, when 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 request is for a generic equivalent
        OR
        ii. The request is for a brand agent AND ONE of the following:
            1. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent
            OR
            2. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent

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 an intolerance or hypersensitivity to generic sodium phenylbutyrate
    OR
    iii. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate

AND

7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders) 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 the requested agent
AND
9. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication

Length of Approval: 12 months

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's 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 requested agent will NOT be used as treatment of 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 the area of the patient's diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
7. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication

Length of Approval: 12 months