Urea Cycle Disorder Pharmacologic Agents (Buphenyl®, Ravicti®, generics)

Policy # 00632
Original Effective Date: 01/01/2019
Current Effective Date: 09/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider sodium phenylbutyrate (Buphenyl®)‡ and glycerol phenylbutyrate (Ravicti®)‡ for the treatment of urea cycle disorders to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for sodium phenylbutyrate (Buphenyl) and glycerol phenylbutyrate (Ravicti) will be considered when the requested drug's criteria are met:

- Ravicti:
  Initial:
  - Patient has a diagnosis of Urea Cycle Disorder; AND
  - Patient can NOT be managed by dietary protein restriction and/or amino acid supplementation alone; AND
  - Ravicti is NOT being used to treat N-acetylglutamate synthase (NAGS) deficiency or acute hyperammonemia; AND
  - Ravicti is used in combination with dietary protein restriction and, in some cases, dietary supplements; AND
  - Patient has tried and failed (e.g. intolerance or inadequate response) GENERIC sodium phenylbutyrate unless there is clinical evidence or patient history that suggests the use of GENERIC sodium phenylbutyrate will be ineffective or cause an adverse reaction to the patient (e.g. congestive heart failure, severe renal insufficiency, or a clinical state where there is sodium retention with edema).

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

Continuation:

- Initial criteria have been met; AND
- There is clinical documentation indicating that there is disease stability or improvement (e.g. normalized plasma ammonia levels).
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

- Buphenyl, sodium phenylbutyrate:

Initial:

- Patient has a diagnosis of Urea Cycle Disorder; AND
- Patient can NOT be managed by dietary protein restriction and/or amino acid supplementation alone; AND
- The requested drug is used with dietary protein restriction and, in some cases, dietary supplements; AND
- The requested drug is NOT being used for acute hyperammonemia; AND
- If the request is for branded Buphenyl: the patient has tried and failed (e.g. intolerance or inadequate response) GENERIC sodium phenylbutyrate unless there is clinical evidence or patient history that suggests the use of GENERIC sodium phenylbutyrate will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

Continuation:

- Initial criteria have been met; AND
- There is clinical documentation indicating that there is disease stability or improvement (e.g. normalized plasma ammonia levels)
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the continued use of sodium phenylbutyrate (Buphenyl) or glycerol phenylbutyrate (Ravicti) when there is no documentation that the patient has experienced an improvement or disease stability to be **not medically necessary.****

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Based on review of available data, the Company considers the use of branded sodium phenylbutyrate (Buphenyl) and branded glycerol phenylbutyrate (Ravicti) when there is no documentation that the patient has tried and failed (e.g. intolerance or inadequate response) GENERIC sodium phenylbutyrate to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sodium phenylbutyrate (Buphenyl) and glycerol phenylbutyrate (Ravicti) when the patient selection criteria are not met to be **investigational*** (with the exception of the criteria denoted above as **not medically necessary**).**

Background/Overview

Ravicti is a nitrogen-binding agent indicated for chronic management of patients with urea cycle disorders 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. Ravicti is not indicated for treatment of acute hyperammonemia in patients with urea cycle disorders. Recommended dosage range is 4.5 to 11.2 mL/m^2/day. Ravicti is available as an oral liquid containing 1.1 grams per mL. The maximum total daily dosage is 17.5 mL (19 gm).

Buphenyl has a generic equivalent available, therefore any reference to Buphenyl in this section also refers to its generic. Buphenyl is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. Buphenyl is available in both 500 mg tablets and 250 gm containers of powdered drug. The use of Buphenyl tablets is indicated for children weighing more than 20 kg and for adults. The usual total daily dose of Buphenyl tablets and powder for patients with urea cycle disorders is 450–600 mg/kg/day in patients

weighing less than 20 kg, or 9.9–13.0 g/m^2/day in larger patients. The safety or efficacy of doses in excess of 20 grams (40 tablets) per day has not been established.

Urea Cycle Disorders
Urea cycle disorders are caused by lack of an enzyme in the urea cycle metabolic pathway, which transforms nitrogen to urea for excretion from the body. The typical presentation in newborns is within 24 to 48 hours of age. Features include somnolence and poor feeding, lethargy, vomiting, coma, central hyperventilation, hyperammonemia, and seizures. The initial approaches to therapy include rehydration, removing nitrogen (ammonia) from the body using medications and/or hemodialysis, stopping protein intake and minimizing catabolism, and stimulating anabolism and the uptake of nitrogen precursors by muscle. Drugs FDA approved for use in the chronic management of urea cycle disorders include Ravicti and Buphenyl. Due to Buphenyl's generic availability, it offers an equally efficacious and more cost effective method for treatment over Ravicti, however the use of Ravicti would be preferred over Buphenyl in patients with congestive heart failure, severe renal insufficiency, or a clinical state where there is sodium retention with edema due to the sodium content in Buphenyl.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Both Ravicti and Buphenyl (and its generic) are approved for the treatment of urea cycle disorders.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Ravicti for the treatment of urea cycle disorders was established in one study in adult patients and two open label studies in pediatric patients. All of the studies were switchover, non-inferiority studies with Buphenyl or Ravicti. In all three studies, Ravicti was found to be non-inferior to Buphenyl with regards to blood ammonia control. The ammonia area under the curve over 24

hours (NH_3-AUC_{0-24}) was 866 mmol/L*hour in the Ravicti group vs. 977 mmol/L*hour in the Buphenyl group for the adult trial. In study 2, the NH_3-AUC_{0-24} was 647.63 mmol/L*hour in the Ravicti group vs. 914.43 mmol/L*hour in the Buphenyl group. In study 3. the NH_3-AUC_{0-24} was 604 mmol/L*hour in the Ravicti group vs. 815 mmol/L*hour in the Buphenyl group.

References

1. Ravicti [package insert]. Horizon Therapeutics. Lake Forest, Illinois. Updated April 2017.
2. Buphenl [package insert]. Ucyclyd Pharma. Scottsdale, Arizona. Updated April 2008.
3. Ravicti Drug Evaluation. Express Scripts. Updated February 2013.

Policy History

Original Effective Date: 01/01/2019
Current Effective Date: 09/14/2020
08/09/2018 Medical Policy Committee review
08/15/2018 Medical Policy Implementation Committee approval. New policy.
08/01/2019 Medical Policy Committee review
08/14/2019 Medical Policy Implementation Committee approval. No change to coverage.
08/06/2020 Medical Policy Committee review
08/12/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 08/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.