Subject: Ravicti (glycerol phenylbutyrate)	Original Effective Date: 03/16/15
Policy Number: MCP-242	Revision Date(s):
Review Date(s): 12/15/2016; 6/22/2017	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Ravicti (glycerol phenylbutyrate)** for the treatment of chronic management of urea cycle disorders when appropriate criteria are met.

- **PREFERRRED:** Sodium Phenylbutyrate (Buphenyl)
  - Glycerol phenylbutyrate and sodium phenylbutyrate are similar drugs used for the chronic management of adult and pediatric patients with Urea Cycle Disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. The active metabolite for both drugs is Phenylacetate (PAA).
  - Buphenyl (available as oral tablets and as a powder for oral, nasogastric, or gastrostomy tube administration) may be administered to pediatric patients over 20 kg; Ravicti (available in an oral liquid) is indicated for patients 2 years and older with UCDs and contraindicated in patients younger than 2 months.
  - Notable difference of Buphenyl is the unpleasant smell/taste profile and a higher daily sodium load than the recommended daily allowance (2,400 mg vs 2,300 mg/day) than Ravicti. Ravicti has no sodium and has a mild smell/taste profile compared to Buphenyl. However, there is no evidence that Ravicti is safer or more efficacious than Buphenyl. Furthermore, Buphenyl has a longer track record of clinical experience.
  - There is insufficient evidence that Ravicti is more efficacious than Buphenyl:
    - The major study supporting Ravicti's safety and efficacy involved 44 adults who were randomly assigned to receive Buphenyl or Ravicti for two weeks before being switched to the other product for two weeks. Blood testing showed Ravicti was as effective as Buphenyl in controlling ammonia levels.
    - Pooled data from the pivotal trial and additional phase II studies suggest that Ravicti may be superior to Buphenyl in the control of ammonia levels. This data, however, is considered preliminary due to the small number of subjects included. [12]
    - Long-term studies in pediatric patients suggest Ravicti may improve neurocognitive function as defined by the BRIEF (Behavior Rating Inventory of Executive Function) score. This data, however, is considered exploratory and hypothesis-generating due to lack of a control group and no prespecified endpoints related to neurocognitive function.[12,g]

- Treatment guidelines for urea cycle disorders recommend chronic treatment with nitrogen-scavenging medications, specifically sodium phenylbutyrate (Buphenyl), three to four times daily.[A]

- Glycerol phenylbutyrate (Ravicti) is comparable to sodium phenylbutyrate (Buphenyl) in the chronic management of urea cycle disorders; however, there is insufficient evidence that one is more efficacious than the other.
  - Treatment with glycerol phenylbutyrate was non-inferior compared with sodium phenylbutyrate in adult patients with UCDs during a 4-week, randomized, double-blind, active-controlled, crossover study (n=44).[1,12]
  - Patients in the trial were on stable therapy with sodium phenylbutyrate (Buphenyl) at the time of enrollment. The dose of glycerol phenylbutyrate (Ravicti) was calculated to provide the same amount of phenylbutyrate.
  - The primary endpoint, 24-hour ammonia exposure, is a clinically relevant surrogate endpoint for the morbidity and mortality associated with urea cycle disorders.

CLASSIFICATION: Metabolic Agents; Hyperammonemia Agent; Nitrogen-Binding Agent

FDA INDICATIONS

Urea cycle disorders: For long-term management of patients 2 years and older with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

Limitations of Use:
- Ravicti is not indicated for the treatment of acute hyperammonemia in patients with UCD 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.

Available as: 1.1 g/mL glycerol phenylbutyrate oral solution (delivers 1.02g/ml of phenylbutyrate) in a multi-use, 25 ml glass bottle

FDA Approved: February 1, 2013**.** Ravicti was granted an orphan drug designation by the FDA. Orphan status is granted to drugs that treat conditions or diseases that affect fewer than 200,000 people in the United States.

Black Box Warnings: *None at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Ravicti (glycerol phenylbutyrate) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [BOTH]

- ❒ Prescribed by, or in consultation with, a board-certified geneticist/metabolic specialist or physician experienced in the management of urea cycle disorder. Submit consultation notes if applicable.

- ❒ Prescribed with active involvement of a nutritionist to maximize caloric intake with neutral nitrogen balance

2. Diagnosis/Indication [ALL]

Clinical documented diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*):

- ❒ Diagnosis of **chronic** hyperammonemia with enzymatic and or genetic diagnosis.
  NOTE: DNA mutation analysis is the method of choice in confirming the diagnosis of UCD as it is clinically available for all genes of the urea cycle.[8]

- ❒ Member does <u>not</u> have acute hyperammonemia
  - ➢ *Not for treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are required to reduce plasma ammonia levels*

- ❒ At least ONE (1) of the following urea cycle enzyme deficiency: [ONE]
  - ❍ Ornithine transcarbamylase (OTC)
  - ❍ Argininosuccinate synthetase (ASS) or citrullinemia I
  - ❍ Argininosuccinate lyase (ASL) or argininosuccinic aciduria
  - ❍ Carbamyl phosphate synthase (CPS1)
  - ❍ Arginase (ARG) or hyperargininemia
  - ❍ Ornithine translocase (0RNT1); also called hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
  - ❍ Citrin (aspartate glutamate translocase)

  NOTE: Safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency, another type of UCD, has not been established.[a]

3. Age/Gender/Other restrictions [ALL]

- ❒ 2 years of age or older
  - ➢ *The safety and efficacy for use in children under 2 years of age have not been established. PK and ammonia control were studied in 4 patients between the ages of 2 months and <2 years of age, but there was insufficient data to establish a safe and effective dose for this age range. The use in those <2 months of age is contraindicated.*

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❑ Member's condition has failed to be managed with dietary protein restriction and/or amino acid supplementation alone (i.e. essential amino acids, arginine, citrulline, protein-free calorie supplements). Documentation required.
  - ➢ *Treatment must be used in conjunction with dietary protein restriction; and with dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements) in some cases*

- ❑ Therapeutic failure or ineffectiveness, contraindications, or clinical intolerance to both of the following. Documentation required: [BOTH]
  - ❍ sodium phenylbutyrate powder or Buphenyl powder **AND**
  - ❍ Buphenyl tablet

  NOTE: Prescriber must submit clinical documentation and rationale for Medical Director Review stating the reason(s) that the preferred product, sodium phenylbutyrate (Buphenyl®) powder, is not appropriate for the member. Additional documentation may be required as deemed appropriate by Medical Director.

- ❑ Ravicti (glycerol phenylbutyrate) therapy will be used **concomitantly** with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).[a] Documentation required.

5. Contraindications/Exclusions/Discontinuations

Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to phenylbutyrate or any of its components
  - ➢ *Signs of hypersensitivity include wheezing, shortness of breath, coughing, low blood pressure, flushing, nausea and rash.*
- ❒ Less than 2 years of age
- ❒ Concurrent therapy with: [ANY]
  - ❍ Corticosteroids, valproic acid (Depakene, and others), and haloperidol (Haldol, and generics): May increase plasma concentrations of ammonia.
  - ❍ Probenecid: Concomitant use of probenecid may decrease excretion of phenylacetate and phenylacetylglutamine.

<u>Exclusions</u> [ANY]

- ❒ Prescribed for the management of *acute* hyperammonemia
- ❒ Prescribed for the treatment of N-acetylglutamate synthase (NAGS) deficiency

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

CONTINUATION OF THERAPY

Ravicti (glycerol phenylbutyrate) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

2. Compliance

- ❑ History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Documentation of **stabilization or improvement** to Ravicti therapy as evaluated by a board-certified geneticist/metabolic specialist or physician experienced in the management of urea cycle disorder, including decreased fasting plasma ammonia levels which are indicative of efficacy.

- ❒ Member is actively on dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to phenylbutyrate or any of its components
  - ❍ Less than 2 years of age
  - ❍ Concurrent therapy with: [ANY]
    - Corticosteroids, valproic acid (Depakene, and others), and haloperidol (Haldol, and generics): May increase plasma concentrations of ammonia.
    - Probenecid: Concomitant use of probenecid may decrease excretion of phenylacetate and phenylacetylglutamine.
- ❒ Exclusions [ANY]
  - ❍ Prescribed for the management of *acute* hyperammonemia
  - ❍ Prescribed for the treatment of N-acetylglutamate synthase (NAGS) deficiency

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

Glycerol phenylbutyrate (Ravicti) is administered in three equally divided dosages, each rounded to the nearest 0.5 mL. The recommended initial dose is as follows:[a]

- ❒ Phenylbutyrate-naïve: Recommended dose range, based on body surface area (BSA) is 4.5 to 11.2 mL/m2/day (5 to 12.4 g/m2/day)
- ❒ Patients switching from sodium phenylbutyrate (Buphenyl) to Ravicti: should receive the dosage of Ravicti that contains the same amount of phenylbutyrate. The conversion is as follows: total daily dosage of Ravicti (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.8
- ❒ Maximum dose: Adults and children 2 years and older: 19 g/day according to the prescribing information.
  - ➢ *The dose should be adjusted to produce a fasting plasma ammonia level that is less than ½ the upper limit of normal (ULN) per age. Urinary phenylacetylglutamine (U-PAGN) and plasma phenylacetate (PAA) measurements may be helpful to guiding Ravicti dose adjustments.*

2. Authorization Limit [ALL]

- ❒ Quantity limit: 525 mL/30 days [maximum total daily dose is 17.5 mL (19 g)]
  - ➢ *The safety and effectiveness of higher doses have not been established.*
- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time
- ❒ Duration of initial authorization: 3 months
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every 6 months to determine continued need based on documented positive clinical response
  - ➢ *Continued treatment for up to 12 months appears to maintain control of blood ammonia levels.*
- ❒ Duration of continuation of treatment: May be authorized up to **SIX (6) months** at a time.

3. Route of Administration [ALL]

- ❒ Ravicti (glycerol phenylbutyrate oral liquid) is considered a **self-administered** medication. May be administered directly into a nasogastric tube or gastrostomy tube using an oral syringe
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

Ravicti (glycerol phenylbutyrate oral liquid) is considered **experimental and investigational** for all other indications. Therefore, all other uses of Ravicti that are not an FDA-approved indication or included in 'Coverage Criteria' section above are considered experimental/investigational and is not a covered benefit.

SUMMARY OF EVIDENCE/POSITION STATEMENTS

Urea Cycle Disorders (UCDs) is a genetic disorder comprised of several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia. The urea cycle is responsible for the elimination of nitrogen formed by the breakdown of proteins. Patients with a urea cycle disorder have a rare genetic defect in one or more of the enzymes utilized in the cycle, which cause accumulation of nitrogen and can result in life-threatening ammonia levels and neurologic injury.[11] These enzymes are found in the liver, where they process nitrogen-containing waste products (such as ammonia) into urea. The six enzymes in the urea cycle are ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASD), arginase (ARG), arginosuccinase acid lyase (ALD), carbamyl phosphate synthetase (CPS), and N-acetylglutamate synthetase (NAGS). Deficiencies in any of these enzymes can lead to urea cycle disorders.

The main function of the urea cycle is the detoxification of ammonia and the synthesis of arginine. The urea cycle is a process that takes place primarily in the liver in which nitrogen waste (ammonia, NH_3) is removed from the body. After consumption, proteins are broken down into amino acids. Ammonia is produced from leftover amino acids and must be eliminated. The liver produces several enzymes that convert ammonia into urea, which is excreted in the urine. If this process is disturbed, ammonia levels begin to rise.

UCDs result in the accumulation of toxic levels of ammonia in the blood and brain of affected patients and can present in the neonatal period or later in life depending on the severity and type of defect. UCDs can cause an accumulation of glutamine in the astrocytes, hyperammonemia, encephalopathy, mental status changes, brain edema, seizures, coma, and death if inadequately treated. Hyperammonemia is the major cause of morbidity and mortality in UCD patients, and outcome during hyperammonemic crises correlates with blood ammonia levels. Survivors of the metabolic decompensation frequently have severe neurologic injury. Control of blood ammonia levels is the main objective of both acute and chronic management of UCD patients.[1,2]

UCDs are estimated to affect about 1 in 14,000 births.[13,14,15] The therapeutic aims in patients with hyperammonemia are to correct the biochemical abnormalities and ensure adequate nutritional intake. Treatment involves compounds that increase the removal of nitrogen waste.

The main goal of treatment is to avoid hyperammonemia in order to prevent neurological sequelae. Treatment for UCDs includes a protein-restrictive diet, arginine or citrulline supplementation, and the use of nitrogen-scavenging drugs.[a]

The treatment of UCDs consists of dietary protein management to limit ammonia production in conjunction with medications and/or supplements which provide alternative pathways for the removal of ammonia from the bloodstream.[8-10] Long-term management of the disorder typically includes a protein-restricted diet, dietary supplements to aid in the formation or activation of the deficient enzymes, and sodium phenylbutyrate (Buphenyl).

Pharmacotherapy
Medications used in the treatment of hyperammonemia include the following:

- Urea cycle disorder treatment agents (e.g., sodium phenylbutyrate, carglumic acid, sodium phenylacetate, and sodium benzoate)
- Antiemetic agents (e.g., ondansetron, granisetron, palonosetron, dolasetron)

Other treatments
Other management approaches for hyperammonemia include the following:

- Cessation of protein and/or nitrogen intake
- Hemodialysis
- Supportive care with parenteral intake of calories

Phenylbutyrate is a nitrogen-scavenging medication used for the chronic management of urea cycle disorders characterized by accumulation of nitrogen which can result in life-threatening ammonia levels and neurologic injury. The nitrogen-scavenging medications assist in the elimination of excess nitrogen and are utilized for chronic management when diet alone fails to prevent hyperammonemia.[11] Phenylbutyrate is a pro-drug of phenylacetate, which binds glutamine and provides an alternative pathway for nitrogen elimination. Pancreatic enzymes are required to remove the glycerol component of glycerol phenylbutyrate (Ravicti) and release the phenylbutyrate. [a]

- Drug therapy has been focused on enhancing the loss of waste nitrogen.[3-7] The nitrogen-binding agents approved for chronic management of UCDs include glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl).[a,f] Both are "ammonia scavengers", providing alternative pathways for removal of ammonia from the bloodstream and helping to prevent hyperammonemia.
- The nitrogen-binding agents approved for the chronic management of patients with urea cycle disorders include glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl).

Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl) are similar drugs used for the chronic management of adult and pediatric patients (2 years and older) with UCDs that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. The active metabolite for both drugs is Phenylacetate (PAA). These medications are administered three to four times per day in order to ensure continual removal of toxic ammonia from the bloodstream. Ravicti is an oral liquid reformulation of Buphenyl, which is available as oral tablets and powder.

Glycerol phenylbutyrate, a triglyceride containing 3 phenylbutyrate (PBA) molecules, is released from the glycerol backbone by lipases in the gastrointestinal tract and hydrolyzed to phenylbutyrate (PBA), which is converted by beta-oxidation to form the active moiety, phenylacetate (PAA). PAA conjugates with glutamine (providing 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN). Two moles of nitrogen on PAGN provide an alternative to urea for nitrogen waste excretion for patients who cannot synthesize urea due to urea cycle disorders.[1]

When optimal management fails, or in the case of neonatal onset carbamyl phosphate synthetase (CPS) and ornithine transcarbamylase (OTC) deficiency, liver transplant becomes a treatment option.

Hayes
At the time of this writing, there was no Hayes report found regarding urea cycle disorders (UCDs) or pharmacological treatment of UCDs.

Pivotal Trials

The FDA approval of Ravicti was based on separate studies in adults and pediatrics. Two open-label uncontrolled extension trials in adults and children with urea cycle disorders receiving glycerol phenylbutyrate found that mean ammonia values remained below the upper limit of normal (ULN) of 35 micromol/L at each monthly visit over a 12-month period.[12,16,17]

❖ **Clinical Studies in Adults[a,h,12]**

Two Phase 3 trials evaluating glycerol phenylbutyrate in adult patients with UCDs were reviewed for FDA approval (one randomized controlled trial and one uncontrolled, open-label, long-term trial).

A randomized, double-blind, active-controlled, crossover, non-inferiority study enrolled 45 subjects with UCDs who had been on sodium phenylbutyrate prior to enrollment. The trial was designed to compare Ravicti to sodium phenylbutyrate by evaluating venous ammonia levels. The primary endpoint was to establish non-inferiority in the 24-hour AUC (a measure of exposure to ammonia over 24 hours) for venous ammonia on days 14 and 28 when the drugs were expected to be at steady state. The subjects were randomized to Sodium phenylbutyrate for 2 weeks followed by Ravicti for 2 weeks or Ravicti for 2 weeks followed by Sodium phenylbutyrate for 2 weeks. The dose of Ravicti was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dose the patients were taking when they entered the trial. Both treatments were administered three times daily with meals. Forty-four subjects were evaluable for analysis. Ravicti was noninferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Mean 24-hour AUCs for venous ammonia during steady-state dosing were 866 µmol/L hour and 977 µmol/L hour with Ravicti and sodium phenylbutyrate, respectively.

<u>Long-term (12-month), uncontrolled, open-label study</u>

During a 12-month, open-label, uncontrolled extension study in adult patients (n=51) with UCDs, mean fasting venous ammonia levels remained within normal limits of 6 to 30 mcmol/L. The study was conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period. A total of 51 adults were in the study and all but 6 had been converted from sodium phenylbutyrate to Ravicti. During the 12 months of the study, the mean blood ammonia levels in the adults were within normal limits with a range of 6 to 30 micromoles/L, with a total of 10 hyperammonemic crises reported in 7 patients (14%).[1]

❖ **Clinical Studies in Pediatrics**

Two fixed-sequence, open-label, sodium phenylbutyrate to Ravicti switchover studies were conducted in pediatrics ages 2 to 17 years. The first study was 7 days in duration and the second study was 10 days in duration. A total of 26 subjects were enrolled. The dose of Ravicti was calculated to deliver the same amount of PBA as the dose of sodium phenylbutyrate patients were taking when they entered the trial. Sodium phenylbutyrate or Ravicti were administered in divided doses with meals and the subjects adhered to a low-protein diet throughout the study. After a dosing period with each treatment, all subjects underwent 24 hours of venous ammonia measurements, as well as blood and urine PK assessments.

Similar 24-hour AUCs (AUC 0-24h) for blood ammonia were observed in pediatric patients (n=22) aged 2 to 17 years with UCDs treated with sodium phenylbutyrate and then switched to glycerol phenylbutyrate during 2 fixed-sequence, open-label studies.[1]

- Study 1: AUC 0-24h in 11 pediatrics 6 to 17 years of age; The ammonia AUC0-24h was 604 µmol•h/L vs. 815 µmol•h/L on Ravicti versus sodium phenylbutyrate.
- Study 2: 11 pediatrics 2 years to 5 years of age; the ammonia AUC0-24h was 632 µmol·h/L vs. 720 µmol·h/L on Ravicto versus sodium phenylbutyrate.

DEFINITIONS

Amino acids: Amino acids combine to form proteins, and when proteins are digested, amino acids remain. Amino acids are either essential (obtained through the diet) or nonessential (made by the body from the essential amino acids).

Ammonia: A waste product of protein digestion that is removed by the urea cycle process.

Deficiency: A lower amount than necessary for functioning.

Hyperammonemia: Elevated levels of ammonia in the blood.

Urea: A product from the breakdown of proteins, excreted in the urine.

Urea cycle: A metabolic process in which waste (nitrogen) from the breakdown of proteins in the body is changed by the liver into urea, which is excreted in the urine.

Reference: http://www.rarediseasesnetwork.org/ucdc/learnmore/links.htm and http://www.ravicti.com/glossary

APPENDIX

Appendix 1: Buphenyl (sodium phenylbutyrate) and Ravicti (glycerol phenylbutyrate)

AGENT	
Buphenyl (sodium phenylbutyrate)	• Sodium Phenylbutyrate (Oral route: Powder, Tablet, Enteric Coated tablet) • Generic Availability: Yes [Oral Powder: 3 g/Dose] • 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. • Powder is to be mixed with food for immediate use and is designed for oral use only (mouth, gastrostomy, or nasogastric tube) • Safety and efficacy of doses > 20 grams per day has not been evaluated. • Contraindications: hyperammonemia, acute; do not use for emergency management; hypersensitivity to sodium phenylbutyrate or any component of the product.
Ravicti (glycerol phenylbutyrate)	• Glycerol Phenylbutyrate (Oral route, Solution, Liquid) • Generic Availability: No • Initial dose in phenylbutyrate naïve patients: 4.5 to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day) to be given in 3 equally divided doses. • Switching from sodium phenylbutyrate: daily dosage of sodium phenylbutyrate (g) X 0.86. • 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. • Round total daily dose up to the nearest 0.5 mL. Maximum daily dosage is 17.5 mL. • Contraindications: hypersensitivity to phenylbutyrate; pediatric patients less than 2 months of age.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
J8499	Prescription drug, oral, nonchemotherapeutic, NOS

ICD-9	Description **[For dates of service *prior* to 10/01/2015]**
270.6	Disorders of urea cycle metabolism

ICD-10	Description **[For dates of service *on or after* 10/01/2015]**
E72.2	Disorders of urea cycle metabolism

REFERENCES

Package Insert, FDA, Drug Compendia

a. Ravicti (glycerol phenylbutyrate) [prescribing information]. South San Francisco, CA: Hyperion Therapeutics; June 2014.
b. American Hospital Formulary Service (AHFS). Drug Information 2015. [STAT!Ref Web site]. 05/02/14. Available at: http://online.statref.com. [via subscription only].
c. Micromedex Healthcare Series. DrugDex. [Micromedex Web site]. Available at: http://www.thomsonhc.com/micromedex2/librarian [via subscription only].
d. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2015. Available from Wolters Kluwer Health, Inc.
e. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2015. URL: http://www.clinicalpharmacology.com.
f. BUPHENYL (sodium phenylbutyrate) tablets, powder. Scottsdale, AZ: Ucyclyd Pharma, Inc.; Apr 2009.
g. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Medical Review NDA 203-284; Glycerol phenylbutyrate (Ravicti). [cited 6/10/2013]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000TOC.cfm
h. Ravicti (glycerol phenylbutyrate) FDA Clinical Review available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000MedR.pdf

Clinical Trials, Definitions, Peer-Reviewed Publications

1. Lee B, Rhead W, Diaz GA, et al. Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. Mol Genet Metab. 2010 Jul;100(3):221-8.
2. Lee, B. Urea cycle disorders: Clinical features and diagnosis. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Accessed March 2015.
3. Singh RH. Nutritional management of patients with urea cycle disorders. J Inherit Metab Dis. 2007;30(6):880-887. PubMed
4. Gropman AL, Summar M, Leonard JV. Neurological implications of urea cycle disorders. J Inherit Metab Dis. 2007;30(6):865-879. PubMed
5. Braissant O. Current concepts in the pathogenesis of urea cycle disorders. Mol Genet Metab. 2010;100(suppl 1):S3-S12. PubMed
6. Auron A, Brophy PD. Hyperammonemia in review: pathophysiology, diagnosis, and treatment. Pediatr Nephrol. 2012;27(2):207-222. PubMed

7. Adeva MM, Souto G, Blanco N, Donapetry C. Ammonium metabolism in humans. Metabolism. 2012;61(11):1495-1511. PubMed
8. Haeberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders. Orphanet J Rare Dis. May 29 2012;7(1):32.
9. Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. J Pediatr 2001;138:S56-61.
10. Smith W, Kishnani PS, Lee B, et al. Urea cycle disorders: clinical presentation outside the newborn period. Crit Care Clin 2005;21:S9-17.
11. Lee B. Urea Cycle Disorders: Management. In: TePas, E (Ed). UpToDate, Waltham, MA, 2014.
12. GA Diaz et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatology 2013; 57:2171.
13. NUCDF resources page. The National Urea Cycle Disorders Foundation website. Available at: www.nucdf.org. Accessed February 13, 2013
14. UCDC resources page. The NIH-funded UCD Consortium website. Available at: http://rarediseasesnetwork.epi.usf.edu/ucdc/takeaction/index.htm. Accessed February 13, 2013
15. HA Krebs, WA Johnson. "Metabolic of Ketonic Acids in Animal tissues." Biochem J. 1937;31:645-660
16. U Lichter-Konecki et al. Ammonia control in children with urea cycle disorders (UCDs); phase 2 comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Mol Genet Metab 2011; 103:323.
17. W Smith et al. Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. J Pediatr 2013; 162:1228.

Government Agencies, Professional Societies, and Other Authoritative Publications

A. Urea Cycle Disorders Conference group. Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr. 2001 Jan;138(1 Suppl):S1-5. Review. PubMed PMID: 11148543.
B. National Urea Cycle Disorders Foundation. Copyright© 2005-2013. Available at http://www.nucdf.org/ucd.htm.
C. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. National Institutes of Health, Rare Diseases Clinical Research Network. Available at http://rarediseasesnetwork.epi.usf.edu/ucdc/physicians/guidelines-main.htm.