Hyperammonemia Agents  
Drug Class Monograph

**Line of Business:** Medi-Cal  
**Effective Date:** May 17, 2017  
**Revision Date:** May 17, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutic Subcommittee.

**Drugs:** Buphenyl (sodium phenylbutyrate), Ravicti (glycerol phenylbutyrate), Sodium Phenylbutyrate

**Policy/Criteria:**

**A. Buphenyl (sodium phenylbutyrate)**

**Eligibility Criteria:** Check CCS eligibility for age less than 21 years

**Diagnosis:**
  a. Hyperammonemia for the chronic management of urea cycle disorders

**Specialist:** No restriction

**Criteria:**
  a. Documented concurrent conservative treatment (dietary protein restriction) with or without amino acid supplementation (i.e. Cyclinex, EAA, UCD I&II).

**B. Ravicti (glycerol phenylbutyrate)**

**Eligibility Criteria:** Check CCS eligibility for age less than 21 years

**Diagnosis:**
  a. Hyperammonemia for the chronic management of urea cycle disorders

**Specialists:** No restriction

**Criteria:**
  a. Documented concurrent conservative treatment (dietary protein restriction) with or without amino acid supplementation (i.e. Cyclinex, EAA, UCD I&II).
Clinical Justification:

Clinical Trials:

- **Non-inferiority Study in Adult Patients with Urea Cycle Disorders**
  - A randomized, double-blind, active-controlled, crossover, non-inferiority study (n=45) compared Ravicti to sodium phenylbutyrate by evaluating venous ammonia level in patients with UCDs who had been on sodium phenylbutyrate prior to enrollment for control of their UCD.
  - Patients were required to have a confirmed diagnosis of UCD via enzymatic, biochemical or genetic testing.
  - Patients had to have no clinical evidence of hyperammonemia at enrollment and were not allowed to receive drugs known to increase ammonia levels.
  - Ravicti was non-inferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia at day 14 and 28 when the drugs were expected to be at steady state.

- **Glycerol phenylbutyrate treatment in children with urea cycle disorders: pooled analysis of short and long-term ammonia control and outcomes.**
  - This trial was a short term, open labeled crossover study which compared the ammonia exposure and glutamine levels.
  - 26 patients, between the ages of 2 months to 17 years old, with UCD were treated with glycerol phenylbutyrate (GPB) and sodium phenylbutyrate (NaPBA).
  - In addition, they conducted another a open label extension study which included those 26 patients and additional 23 patients
    - For 12 months, they received glycerol phenylbutyrate to look at the ammonia control, hyperammonemic crisis, amino acid levels, and patient growth.
  - Overall, mean ammonia levels for 12 months were within the normal range.
  - Mean ammonia exposure from GPB treatment was concluded to be non inferior to NaPBA in each individual cross over study.
  - However, in a pooled analysis, mean exposure from GPB was statistically lower (p: 0.008) when compared to NaPBA.
    - In addition, long term use of GPB was associated with normal ranges of glutamine, amino acids and growth.
<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th><strong>Buphenyl (sodium phenylbutyrate)</strong></th>
<th><strong>Ravicti (glycerol phenylbutyrate)</strong></th>
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<td>• Adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) • Neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life) • 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</td>
<td>• Nitrogen-binding agent for chronic management of patients 2 years of age and older 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)</td>
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<th><strong>MOA</strong></th>
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<td>Sodium phenylbutyrate is a prodrug and is rapidly metabolized to phenylacetate, the active form. Phenylacetate conjugates with glutamine via acetylation to form phenylacetylglutamine, which provides a different vehicle for nitrogen waste excretion by the kidneys. Thus, sodium phenylbutyrate decreases elevated plasma ammonia glutamine concentrations in patients with urea cycle disorders</td>
<td>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</td>
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<th><strong>Usual Dosing</strong></th>
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<th><strong>Ravicti (glycerol phenylbutyrate)</strong></th>
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<td><strong>Disorder of the urea cycle metabolism; Adjunct</strong></td>
<td>9.9 to 13 gram/m(2)/DAY ORALLY equally divided with each meal or feeding 3 to 6 times daily</td>
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<td><strong>Disorder of the urea cycle metabolism, Chronic management</strong></td>
<td>• Treatment-naive: Consider residual urea synthetic capacity, dietary protein requirements, and diet adherence in determining initial dosage • Phenylbutyrate-naive: Initial, 4.5 to 11.2 mL/m(2)/day (5 to 12.4 g/m(2)/day) orally given in 3 equally divided doses rounded up to nearest 0.5 mL; MAX dose, 17.5 mL (19 g) per day • Phenylbutyrate-naive with residual enzyme activity: Initial, 4.5 mL/m(2)/day orally given in 3 equally divided doses rounded up to nearest 0.5 mL; MAX dose, 17.5 mL (19 g) per day • Switching from sodium phenylbutyrate tablets: Total daily dose of sodium phenylbutyrate tablets (g) multiplied by 0.86 equals total daily dose of glycerol phenylbutyrate (mL); take orally in 3 equally divided doses rounded up to nearest 0.5 mL; MAX dose, 17.5 mL (19 g) per day • Switching from sodium phenylbutyrate powder: Total daily dose of sodium phenylbutyrate powder (g) multiplied by 0.81 equals the total daily dose of glycerol</td>
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phenylbutyrate (mL); take orally in 3 equally divided doses rounded up to nearest 0.5 mL; MAX dose, 17.5 mL (19 g) per day
• Maintenance dosage: Based on plasma ammonia, plasma phenylacetate, and urinary phenylacetylglutamine levels

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| • Powder may be mixed with solid food, liquid food, or water; give orally via mouth, gastrostomy, or nasogastric tube only; shake lightly before use  
• Once mixed with food, give immediately; if mixed with water, may be stored at room temperature or refrigerated and given within 1 week | • Take with food  
Instillation, gastrostomy tube  
• Withdraw dose using an oral syringe and administer directly into gastrostomy/nasogastric tube  
• Flush tube once with 30 mL water and allow to drain; flush a second time with additional 30 mL water to clear tube  
Nasogastric  
• Withdraw dose using an oral syringe and administer directly into gastrostomy/nasogastric tube  
• Flush tube once with 30 mL water and allow to drain; flush a second time with additional 30 mL water to clear tube  
Oral  
• Administer directly into the mouth using oral syringe or dosing cup |

| PK/PD | Absorption  
• Phenylacetate (active metabolite), Tmax, Oral (tablets and powder): 3.55 to 3.74 hours  
• Phenylacetate (active metabolite), Tmax, IV: 30 to 60 minutes  
Distribution  
• phenylbutyrate (prodrug) and phenylacetylglutamine (metabolite), Vd: 0.2 L/kg [3]  
• phenylacetate (active metabolite), Vd: 0.3 L/kg  
Metabolism  
• Hepatic and renal: rapid and extensive  
Phenylacetate: active metabolite  
Excretion  
• Renal: 80 to 100% as phenylacetylglutamine  
• Total body clearance: 18 mg/hour/kg  
Elimination Half Life  
• Phenylacetate (active metabolite): 1.15 to 1.29 hours  
• Sodium phenylbutyrate (prodrug): 0.76 to 0.77 hours |
| Absorption  
• Tmax, Oral: 8 hours (phenylbutyrate (PBA)); 12 hours (phenylacetate (PAA)); 10 hours (phenylacetylglutamine (PAGN))  
Distribution  
• Protein binding, phenylbutyrate (PBA): 80.6% to 98%  
• Protein binding, phenylacetate (PAA): 37.1% to 65.6%  
• Protein binding, phenylacetylglutamine (PAGN): 7% to 12%  
Metabolism  
• GI tract, extensive  
Excretion  
• Renal: 68.9% |

| Drug-drug interaction | No | Corticosteroids, valproic acid, haloperidol, probenecid |
| Common Side effects | Acidosis, Hypoalbuminemia, Anemia, Amenorrhea, Irregular periods | Rash, Decrease in appetite, Diarrhea, Flatulence, Upper abdominal pain, Dizziness, Headache, Fatigue |
| Pregnancy | C | C |
| Lactation | Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks |
before prescribing this drug during breastfeeding.

**Storage and stability**

Store at room temperature between 15 and 30 degrees C (59 and 86 degrees F). After opening, keep containers tightly closed.

When dissolved in water, the powder for oral, nasogastric, or gastrostomy tube administration has been shown to be stable at room temperature or refrigerated for up to 1 week.

Store between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F).

**How supplied**

<table>
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<tr>
<th>Generic</th>
<th>Ravicti</th>
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<tr>
<td>• Oral Powder: 3 GM/1 Dose</td>
<td>• Oral Solution: 1.1 GM/1 ML</td>
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<tr>
<td>Buphenyl</td>
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<td>• Oral Powder: 3 GM/1 Dose</td>
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<td>• Oral Tablet: 500 MG</td>
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**References:**


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<td>05/17/2017</td>
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