09-J1000-98

Original Effective Date: 07/15/13

Reviewed: 05/10/23

Revised: 07/01/23

Subject: Glycerol Phenylbutyrate (Ravicti®)

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DESCRIPTION:

Glycerol phenylbutyrate (Ravicti®) is a triglyceride containing 3 molecules of phenylbutyrate (PBA). Phenylacetate (PAA), the major metabolite of PBA, is the active moiety of glycerol phenylbutyrate. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN), which is excreted by the kidneys. On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

Glycerol phenylbutyrate is used as adjunctive therapy for the chronic management of hyperammonemia in subjects with urea cycle disorders (UCDs), including deficiencies in carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (ASS) enzymes.

UCDs are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH3, NH4+). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected individuals.

POSITION STATEMENT:

Initiation of glycerol phenylbutyrate (Ravicti®) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

Urea Cycle Disorders (UCDs)

1. The member has a diagnosis of urea cycle disorders (UCD) involving known or proven deficiencies of **ANY** of the following- documentation must be submitted:
    a. carbamylphosphate synthetase (CPS)

b. ornithine transcarbamylase (OTC)

c. argininosuccinic acid synthetase (AS)

2. The member has documentation of a protein restrictive diet
3. The drug is not being used to manage acute hyperammonemia or N-acetylglutamate synthase (NAGS) deficiency
4. The member has tried and had intolerable adverse effects to an adequate trial of sodium phenylbutyrate **AND** Pheburane and **ALL** of the following must be submitted:
    a. The specific intolerance(s) and rationale for using Ravicti must be specified
    b. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
    c. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
5. Dosage does not exceed 17.5 mL (19 grams) daily

Continuation of glycerol phenylbutyrate therapy **meets the definition of medical necessity** for the treatment of urea cycle disorders when **ALL** the following criteria are met:

1. Member has a beneficial response to glycerol phenylbutyrate for the treatment of urea cycle disorders (does not include use of samples)
2. Member has been previously approved for glycerol phenylbutyrate by Florida Blue or another health plan in the past 2 years, or the member has previously met all indication-specific initiation criteria for coverage
3. Dosage does not exceed 17.5 mL (19 grams) daily

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Glycerol phenylbutyrate (Ravicti) is a nitrogen-binding agent indicated for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. The product must be used with dietary protein restriction and, in some cases, dietary supplements. Glycerol phenylbutyrate is not indicated for treatment of acute hyperammonemia in patients with UCDs. The safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.

Glycerol phenylbutyrate oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles.

Glycerol phenylbutyrate should be taken with food, administered directly into the mouth via oral syringe or dosing cup.

Switching From Sodium Phenylbutyrate to Glycerol Phenylbutrate

Individuals switching from sodium phenylbutyrate to glycerol phenylbutyrate should receive the dosage of glycerol phenylbutyrate that contains the same amount of phenylbutyric acid. The conversion is as follows:

Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.86

Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate powder(g) x 0.81

Initial Dosage in Phenylbutyrate-Naïve Individuals:

The recommended dosage range, based upon body surface area, in individuals naïve to phenylbutyrate (PBA) is 4.5

to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day).

For individuals with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m^2/day. See prescribing information for an estimation of 24 hr dosing based on the total grams of dietary protein ingested. Follow plasma ammonia levels to determine the need for dose titration.

The total daily dosage should not exceed 17.5 mL (19 grams).

Dose Adjustments

- Hepatic impairment: start dosage at lower end of range.

Drug Availability

- Glycerol phenylbutyrate oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles. The bottles are supplied in the following configurations:
    - Single 25-mL bottle per carton
    - Four 25-mL bottles per carton

PRECAUTIONS:

Contraindication:

Known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

Warnings:

The major metabolite of glycerol phenylbutyrate is phenylacetate (PAA) which is associated with neurotoxicity. Signs and symptoms of PAA neurotoxicity include somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting neuropathy.

If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or other intercurrent illnesses, reduce the glycerol phenylbutyrate dosage.

Monitor ammonia levels closely in individuals with pancreatic insufficiency or intestinal malabsorption. Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels. Monitor ammonia levels closely when corticosteroids and glycerol phenylbutyrate are used concomitantly.

Hyperammonemia may be induced by haloperidol and by valproic acid. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in UCD individuals.

See prescribing information for additional drug interactions.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

E72.20	Disorder of urea cycle metabolism, unspecified
E72.22	Arginosuccinic aciduria
E72.29	Other disorders of urea cycle metabolism
E72.4	Disorders of ornithine metabolism

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Urea Cycle Disorder: a genetic disorder caused by a mutation which results in a deficiency of one of the six enzymes in the urea cycle. These enzymes are responsible for removing ammonia from the blood stream.

RELATED GUIDELINES:

Sodium Phenylbutyrate (Buphenyl®), 09-J1000-97

OTHER:

None

REFERENCES:

1. Clinical Pharmacology. Copyright© 2020 Elsevier. Accessed 10/08/20.
2. Ingenix HCPCS Level II, Expert 2013.
3. Ingenix ICD-9-CM for Physicians-Volumes 1 & 2, Expert 2013.
4. Micromedex® 2.0, ©2020 Truven Health Analytics Inc. Accessed 10/08/20.
5. National Urea Cycle Disorders Foundation. Copyright© 2005-2013. Available at http://www.nucdf.org/ucd.htm. Accessed 05/21/13.
6. Ravicti® Prescribing Information. Horizon Therapeutics USA, Inc. Lake Forest (IL). Revised 11/2019.
7. 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. Accessed 05/20/13.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/10/23.

GUIDELINE UPDATE INFORMATION:

07/15/13	New Medical Coverage Guideline.
01/15/15	Review and revision to guideline; consisting of position statement, references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/20	Review and revision to guideline; consisting of updating the position statement and references.
07/01/23	Review and revision to guideline; consisting of updating the position statement to include a step through generic sodium phenylbutyrate and Pheburane.