Glycerol Phenylbutyrate (RAVICTI™)
National Drug Monograph
Abbreviated Review
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section of the PBM INTRAnet (http://vaww.pbm.va.gov).

Introduction[1-6]

Glycerol phenylbutyrate (RAVICTI™), a nitrogen-binding agent, was approved by the U.S. Food and Drug Administration (FDA) February 1, 2013 for use in chronic management of adult and pediatric (≥ 2 years of age) patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. The prescribing information states that glycerol phenylbutyrate must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free caloric supplements). Glycerol phenylbutyrate is not indicated for the treatment of acute hyperammonemia in patients with UCDs as other more acute interventions should be used to reduce plasma ammonia levels.[1]

The urea cycle disorders are a result of an inherited defect in the urea cycle enzymes including carbamoylphosphate synthetase I (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase I, as well as deficiencies in N-acetylglutamate synthase (NAGS), or membrane transporters necessary for the management of nitrogen waste excretion and the synthesis of urea from ammonia, and are reported to have a prevalence of 1:8,000 to 1:44,000. Neonates with severe deficiencies will present with hyperammonemic coma within the first few days after being born, with approximately a 50% mortality rate. Patients with partial enzyme deficiencies may remain undiagnosed for months or years, presenting with signs and symptoms which may be gastrointestinal, neurologic, or psychiatric, that may be precipitated by catabolic events, increased protein intake, or medications (e.g., valproic acid).[2-5]

Chronic management of UCDs includes restriction of dietary protein intake and dietary and amino acid supplementation.[2-4] In addition, the nitrate scavenging agents approved for chronic management of UCDs include glycerol phenylbutyrate and sodium phenylbutyrate.[1,6] Glycerol phenylbutyrate contains three molecules of phenylbutyrate, which is hydrolyzed by pancreatic lipases to release phenylbutyrate (PBA). Phenylbutyrate is oxidized to phenylacetate (PAA), which conjugates with glutamine (that contains 2 molecules of nitrogen) to form phenylacetylglutamine (PAGN) that is excreted by the kidneys, providing for an alternate method for excretion of waste nitrogen.[1] Sodium phenylbutyrate (BUPHENYL®) is available in a tablet and powder formulation and is also metabolized to PAA, and is indicated as adjunctive therapy in the chronic management of patients with UCDs (product information specifies for patients with deficiencies of CPS, OTC, or AS).[6] Sodium phenylbutyrate is available nonformulary in VA.

Summary of Clinical Trial Data[1,7,8]

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).[1,7,8] The trials submitted including only pediatric patients will not be reviewed here.[1,7]

In the randomized, double-blind, active-controlled, cross-over trial, glycerol phenylbutyrate was compared to sodium phenylbutyrate in 44 patients ≥ 18 years of age with a diagnosis of UCD (consisting of CPS, OTC, or ASS deficiencies) on a stable dose of sodium phenylbutyrate with controlled ammonia levels of < 100 micromoles/L without signs or symptoms of hyperammonemia. Patients were to adhere to a low-protein diet and received amino acid supplements during the study. Patients received two weeks of treatment before being crossed-over to the alternate treatment for two weeks. The following conversion dose was used: sodium phenylbutyrate (g) X 0.95/1.1 = total daily dose glycerol phenylbutyrate (ml). The doses were administered orally three times daily with meals. The primary endpoint was the 24-hour area under the curve (AUC_{0-24}) for blood ammonia on days 14 and 28 of treatment to establish non-inferiority of glycerol phenylbutyrate to sodium phenylbutyrate. Baseline demographics

included: mean age 33 years (range 18 to 75); 69% female; 33% adult-onset disease; 89% OTC deficiency, 7% ASS deficiency, 4% CPS deficiency. Glycerol phenylbutyrate was found to be non-inferior to sodium phenylbutyrate (refer to results of the primary endpoint in the table below):[1,7,8]

	Glycerol Phenylbutyrate	Sodium Phenylbutyrate	Ratio of Geometric Means
Blood Ammonia* Mean AUC_{0-24} (SD)	866 (661)	977 (865)	0.91 (95% CI 0.8 to 1.04)
Minimum	302	206	
Maximum	4666	3351	

*micromoles·hr/L; SD=standard deviation

In the long-term, uncontrolled, open-label trial of adult and pediatric patients with UCD, 51adults treated with glycerol phenylbutyrate (45 patients had been converted from sodium phenylbutyrate) were evaluated to determine the effect of treatment on monthly ammonia levels and hyperammonemic crisis. 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%).[1,7,8]

Safety[1]

Refer to the manufacturer's prescribing information for complete safety information.[1]

Contraindications: Glycerol phenylbutyrate is contraindicated in patients less than 2 years of age and in patients with known hypersensitivity to phenybutyrate.[1]

Warnings and Precautions: Phenylacetate, the major metabolite of glycerol phenylbutyrate, has been associated with neurotoxicity. If symptoms of neurotoxicity develop while on treatment, the dose of glycerol phenylbutyrate should be reduced. Absorption of phenylbutyrate may be reduced in patients with pancreatic insufficiency or intestinal malabsorption; ammonia levels should be monitored closely in these patients.[1]

Deaths and Other Serious Adverse Events (Sentinel Events): No deaths were reported in two long-term (median treatment exposure 51 weeks) open-label studies with glycerol phenylbutyrate.[1,7] One patient experienced a treatment emergent serious adverse event (acute gastroenteritis) while receiving treatment with glycerol phenylbutyrate during a short-term comparison trial.[7] Treatment emergent serious adverse events were reported to occur in 15 of 77 (19.5%) of patients in long-term, open-label safety extension trials; with hyperammonemia being reported in 11 patients (14 events), and other events including gastroenteritis, aggression, abdominal pain, dizziness, lobar pneumonia, lung infiltration, peripheral neuropathy, psychotic disorder, and pelvic pain.[7]

Adverse Reactions: The following adverse reactions occurred in $\geq$ 10% of adults treated with glycerol phenylbutyrate: nausea, vomiting, diarrhea, decreased appetite, hyperammonemia, dizziness, headache, and fatigue.[1]

The following is a comparison of adverse reactions reported in $\geq$ 2 adults treated with glycerol phenylbutyrate or sodium phenylbutyrate in a randomized, double-blind, cross-over trial.[1]

Adverse Reaction	Glycerol Phenylbutyrate (N=44) N (%)	Sodium Phenylbutyrate (N=45) N (%)
Abdominal discomfort	0	3 (7)
Abdominal pain	3 (7)	2 (4)
Diarrhea	7 (16)	3 (7)
Dyspepsia	2 (5)	3 (7)
Flatulence	6 (14)	1 (2)
Nausea	1 (2)	3 (7)
Vomiting	3 (7)	2 (4)
Fatigue	3 (7)	1 (2)
Increased ammonia	2 (5)	1 (2)
Decreased appetite	3 (7)	2 (4)
Dizziness	0	4 (9)
Headache	6 (14)	4 (9)

Pregnancy and Nursing Mothers: Glycerol phenylbutyrate is pregnancy category C and should only be used in pregnant women if the benefit of treatment outweighs the potential risk to the fetus. It is unknown if glycerol phenylbutyrate is excreted in human milk; therefore, the risk to the nursing infant vs. the benefit of treatment to the mother needs to be taken into consideration.[1]

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Look-alike/Sound-alike (LA/SA) Error Risk Potential

As part of a Joint Commission standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Glycerol phenylbutyrate	None	None	None	Sodium phenylbutyrate Glycerin/mineral oil/phenol (CPRS menu) Glycopyrrolate
RAVICTI™	None	None	None	Rectiv

Dosage and Administration[1]

Glycerol phenylbutyrate is available as an oral liquid of 1.1 g/ml in a multi-use, 25 ml glass bottle. The dosing recommendations for treatment naïve patients and those being switched from sodium phenylbutyrate are as follows:

Treatment Naïve Patients	Patients Switched from Sodium Phenylbutyrate
• Recommended dose range, based on body surface area (BSA) is 4.5 to 11.2 ml/m^2/day (5 to 12.4 g/m^2/day) • For patients with some residual enzyme activity that are not adequately controlled with protein restriction, the recommended starting dose is 4.5 ml/m^2/day • In determining initial dose, consider patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence. Dietary protein is ~ 16% nitrogen by weight; since 47% of dietary nitrogen is excreted as waste and ~ 70% of a phenylbutyrate dose will be converted to urinary phenylacetylglutamine (U-PAGN), an initial estimated dose for a 24 hr period of glycerol phenylbutyrate is 0.6 ml per gram of dietary protein ingested over 24hrs. • Total daily dose (TDD) should not exceed 17.5 ml	• Patients should be converted to a dose of glycerol phenylbutyrate that contains the same amount of phenylbutyric acid as sodium phenylbutyrate using the following conversion dose: TDD glycerol phenylbutyrate (ml) = TDD sodium phenylbutyrate (g) X 0.8

Additional recommendations for administration of glycerol phenylbutyrate include:[1]

- Each dose should be taken with food and administered directly into the mouth using an oral syringe or dosing cup
- If being administered via nasogastric tube or gastrostomy tube, an oral syringe should be used to withdraw the required amount from the bottle, the tip of the syringe should be placed into the tip of the administration tube and the dose administered using the plunger of the syringe, the tube should then be flushed once with 30 ml water and allowed to drain, then flushed a second time with an additional 30 ml water to clear the tube
- Administer in 3 equally divided doses, rounded to the nearest 0.5 ml
- The maximum total daily dose is 17.5 ml (19 g)
- 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

Recommendations for dosage adjustment are as follows:

- Based on plasma ammonia: dose should be adjusted to a fasting plasma ammonia level that is half the upper limit normal based on age
- Based on urinary phenylacetylglutamine (U-PAGN): if available, U-PAGN levels may be used to guide dose adjustments. Each gram of U-PAGN that is excreted over a period of 24 hours covers the waste nitrogen that is generated from 1.4 grams of dietary protein. If the U-PAGN excretion is not enough to cover the daily dietary protein intake and the fasting ammonia is more than half the ULN, the dose of glycerol phenylbutyrate should be increased. The amount of increase should take into consideration the amount of dietary protein that has been covered, as per the 24-hr U-PAGN level and the estimated dose of glycerol phenylbutyrate needed per gram of dietary protein intake and the maximum total daily dose of 17.5 ml.

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- Based on plasma phenylacetate (PAA): if available, plasma PAA may be used to guide dosing in patients with symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness in the absence of high ammonia or intercurrent illness. Ammonia levels should be monitored closely when adjusting doses of glycerol phenylbutyrate. The ratio of PAA to PAGN may also be useful to guide adjustment in doses. In patients with a high PAA to PAGN ratio, a further increase in dose of glycerol phenylbutyrate may not increase PAGN formation, even if PAA concentration are increased, due to saturation of the conjugation reaction. The PAA to PAGN ratio is generally < 1 in patients without significant PAA accumulation.
- Moderate to severe hepatic impairment: starting dose is at the lower end of the range

Acquisition Cost and Utilization

Refer to VA pricing sources for updated information.

Conclusions

The nitrogen-binding agents approved for the chronic management of patients with urea cycle disorders include glycerol phenylbutyrate (available in an oral liquid) and sodium phenylbutyrate (available as oral tablets and as a powder for oral, nasogastric, or gastrostomy tube administration). According to data from one comparison trial in adults, treatment with glycerol phenylbutyrate is non-inferior to sodium phenylbutyrate in maintaining blood ammonia levels in patients with urea cycle disorders on a low-protein diet and receiving amino acid supplements. Continued treatment for up to 12 months appears to maintain control of blood ammonia levels. It would be expected that the prevalence of urea cycle disorders in the Veteran population would be very low. Under these circumstances, it would be anticipated that utilization of nitrogen-binding agents for this condition would be minimal.

References

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