Drug Monograph

Drug/Drug Class:	**Ravicti® (glycerol phenylbutyrate) Liquid / Urea Cycle Disorder Treatment Agent**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Ravicti® is available as a 1.1 g/mL liquid (which delivers 1.02 g/mL of phenylbutyrate). Lyne Laboratories Inc. Brockton, MA 02310 Hyperion Therapeutics Inc. 601 Gateway Blvd. South San Francisco, CA 94080
Summary of Findings:	Ravicti is a nitrogen-binding agent that has demonstrated efficacy for the chronic management of patients with urea cycle disorders.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Fiscal Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☒ No PA Required ☐ Appropriate Indications ☐ 15 Day First Fill Fiscal Edit

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Urea cycle disorders (UCDs) are genetic disorders that involve deficiencies of specific enzymes involved in the urea cycle, a series of biochemical steps normally required to remove ammonia from the blood. Excess ammonia levels may cause CNS damage, coma, or death.

Dosage Form(s) [1]

Ravicti® is available as a 1.1 g/mL liquid (which delivers 1.02 g/mL of phenylbutyrate).

Manufacturer

Lyne Laboratories Inc. Brockton, MA 02310

Hyperion Therapeutics Inc. 601 Gateway Blvd. South San Francisco, CA 94080

Indication(s) [1]

Ravicti is approved for use as a nitrogen-binding agent for chronic management of adult and pediatric patients >= 2 years of age with urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

Clinical Efficacy[1-7] (mechanism of action/pharmacology, comparative efficacy)

PHARMACOLOGY (1,2)

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

PHARMACOKINETICS (1,2,7)

Ravicti varies in it's protein binding: PBA (81% to 98%); PAA (37% to 66%); PAGN (7% to 12%). It is hydrolyzed to PBA; PBA undergoes beta-oxidation to PAA; PAA is conjugated with glutamine to PAGN which is renally eliminated.

EFFICACY (1,3-6)

SUMMARY

The approval of Ravicti was primarily based upon a randomized, double-blind, active-controlled, crossover, noninferiority study that compared Ravicti to sodium phenylbutyrate. The study evaluated ammonia levels in 45 adult patients with UCDs who had been on sodium

phenylbutyrate. The results indicated that Ravicti was noninferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Three additional studies in children and adults also provided evidence supporting the long-term safety and effectiveness of Ravicti in patients 2 years of age and older.

CONCLUSION (1)
Ravicti is effective for the treatment of urea cycle disorders.
Urea Cycle Disorders

STUDY DESIGN	Randomized, double-blind, active-controlled, crossover, noninferiority clinical trial (n=45).
INCLUSION CRITERIA	Adult patients with a UCD who had been on sodium phenylbutyrate. Patients were required to have a confirmed diagnosis of a UCD involving deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS), confirmed 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 (eg, valproate), increase protein catabolism (eg, corticosteroids), or significantly affect renal clearance (eg, probenecid).
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Forty-five patients were randomized 1:1 to receive either 2 weeks of sodium phenylbutyrate followed by Ravicti for 2 weeks, or 2 weeks of Ravicti followed by sodium phenylbutyrate for 2 weeks. Each regimen was given 3 times a day with meals, and the dose of Ravicti was calculated to deliver the same amount of PBA as the previous sodium phenylbutyrate dose at study entry. Forty-four patients received at least 1 dose of Ravicti in the trial. Patients adhered to a low protein diet and received amino acid supplements. After 2 weeks, at which time steady-state was achieved for each treatment, the patients had 24 hours of ammonia measurements.
RESULTS	Ravicti was noninferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Forty-four patients were evaluated in the analysis. The mean 24-hour AUC for venous ammonia during steady-state dosing was 866 mcmol/L x hour and 977 mcmol/L x hour for Ravicti and sodium phenylbutyrate, respectively. The ratio of geometric means was 0.91 (95% CI, 0.8 to 1.04).
SAFETY	The most common adverse reactions were diarrhea, flatulence, and headaches.

Contraindications[1]

- Patients younger than 2 months of age.
- Known hypersensitivity to phenylbutyrate.

Warnings and Precautions[1]

- Neurotoxicity has been reported (eg, somnolence, fatigue, dysgeusia, hypoacusis, disorientation, impaired memory, neuropathy); monitor and reduce dose if necessary.
- Pancreatic enzyme insufficiency or intestinal fat malabsorption may reduce oral absorption; monitor ammonia levels in patients with these conditions.

Adverse Effects[1]

Most common, >= 2%	Ravicti (n=44)	Sodium Phenylbutyrate (n=45)
Diarrhea	16%	7%
Flatulence	14%	2%
Headache	14%	9%
Abdominal pain	7%	4%
Decreased appetite	7%	4%
Fatigue	7%	2%
Vomiting	7%	4%
Ammonia increased	5%	2%
Dyspepsia	5%	7%
Nausea	2%	7%
Abdominal discomfort	0	7%
Dizziness	0	9%

Drug Interactions[1]

- Corticosteroids
- Haloperidol
- Probenecid
- Valproic acid

Dosage and Administration[1]

The recommended oral dose range is 4.5 to 11.2 mL/m(2)/day (5 to 12.4 g/m(2)/day) rounded up to the nearest 0.5 mL and divided in 3 equal doses; use an oral syringe or dosing cup and take with food. The maximum daily dose is 17.5 mL (19 g). The patient must maintain dietary protein restrictions. Dose modification is necessary for hepatic impairment.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE/ DAY**	COST/ DAY
Glycerol phenylbutyrate oral solution	Ravicti	Hyperion	1.1 g/mL, 25 mL/bottle	5 mL	$ 93.75
Sodium phenylbutyrate	Buphenyl	Ucyclyd	500 mg tablets	7 grams	$ 145.46
			3 g powder/ teaspoon, 250 g/bottle	7 grams	$145.46

*Wholesale Acquisition Cost (WAC)

Conclusion

Ravicti is a nitrogen-binding agent that has demonstrated efficacy for the chronic management of patients with urea cycle disorders. UCDs are genetic disorders that involve deficiencies of specific enzymes involved in the urea cycle, a series of biochemical steps normally required to remove ammonia from the blood. Excess ammonia levels may cause CNS damage, coma, or death. Ravicti was reviewed under the fast track program at the US Food and Drug Administration, and was granted orphan product designation since it will be used to treat a rare disease.

Recommendation

The Division recommends Open Access status for this product.

References

1. Product Information: Ravicti™, glycerol phenylbutyrate oral liquid. Hyperion Therapeutics, Inc., South San Francisco, CA, 01/2013.

2. McGuire BM, Zupanets IA, Lowe ME et al: Pharmacology and safety of glycerol phenylbutyrate in healthy adults and adults with cirrhosis. Hepatology 2010; 51(6):2077-2085.

3. Smith W, Diaz GA, Lichter-Konecki U 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 Jan 13 (Epub ahead of print).

4. Diaz GA, Krivitzky LS, Mokhtarani M et al: Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatology 2012 Sep 7 (Epub ahead of print).

5. Lichter-Konecki U, Diaz GA, Merritt JL 2nd 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(4):323-329.

6. 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; 100(3):221-228.

7. Mokhtarani M, Diaz GA, Rhead W et al: Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders. Mol Genet Metab 2012; 107(3):308-314.

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