



Horizon Pharma plc Announces FDA Approval to Expand the Age Range for RAVICTI® (glycerol phenylbutyrate) Oral Liquid to Include Newborns

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DUBLIN--(BUSINESS WIRE)--Dec. 27, 2018-- Horizon Pharma plc (NASDAQ: HZNP) today announced the U.S. Food and Drug Administration (FDA) has approved a supplemental new drug application (sNDA) to expand the age range for RAVICTI® (glycerol phenylbutyrate) Oral Liquid to include infants younger than two months of age living with a urea cycle disorder (UCD).

RAVICTI is now FDA-approved for use as a nitrogen-binding agent for chronic management of UCDs in adults and children of all ages 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. RAVICTI is not indicated for treatment of acute hyperammonemia in patients with UCDs, and its safety and efficacy for the treatment of n-acetylglutamate synthase (NAGS) deficiency has not been established.

“The FDA approval of RAVICTI for children younger than two months provides a new alternative for the management of patients with a UCD that is easy to dose and administer to infants given the liquid formulation,” said Nicola Longo, M.D., Ph.D., clinical geneticist at Primary Children’s Hospital and the University of Utah Hospital, and a lead investigator of a clinical study evaluating RAVICTI for newborns. “UCDs are severe and can be life-threatening. We hope that the combination of early diagnosis – through newborn screening or by measurement of ammonia levels – and the availability of novel treatments, such as this one, can help to improve the outcome of affected patients.”

A study was conducted to assess safety, efficacy and pharmacokinetics in pediatric patients with UCDs two months of age and younger (n=16). In the study, 10 patients transitioned to RAVICTI from sodium phenylbutyrate, three transitioned from intravenous sodium benzoate and sodium phenylacetate, and three were treatment naïve. Patients were treated with RAVICTI for an average of 10.7 months. Results demonstrated safety and efficacy in children younger than two months, with RAVICTI-treated patients maintaining stable ammonia levels relative to their pre-study enrollment. In addition, mean ammonia levels were lower during treatment with RAVICTI compared to baseline values.

“As we increase our efforts to develop new investigational medicines for people living with rare and rheumatic diseases, Horizon continues to seek ways to better serve patients with our current medicines,” said Elizabeth Thompson, Ph.D., vice president, clinical development, rare diseases, Horizon Pharma. “The FDA approval of RAVICTI for children under the age of two months is a milestone in our efforts to help people living with UCDs, and we are proud to be bringing a new treatment option to the vulnerable newborn patient population.”

A UCD is a rare genetic disorder that affects approximately 1 in 35,000 live births in the United States. It is caused by an enzyme deficiency in the urea cycle, a process that is responsible for converting excess ammonia from the bloodstream and ultimately removing it from the body. Because of this, people with a UCD experience hyperammonemia, or elevated ammonia levels in their blood, that can then reach the brain and cause irreversible brain damage, coma or death. UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life.¹

About RAVICTI® (glycerol phenylbutyrate) Oral Liquid

INDICATIONS AND USAGE

RAVICTI (glycerol phenylbutyrate) Oral Liquid is indicated for use as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or 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).

LIMITATIONS OF USE

- RAVICTI is not indicated for the treatment of acute hyperammonemia in patients with UCDs 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.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- *Patients with known hypersensitivity to phenylbutyrate:* Reactions include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

WARNINGS AND PRECAUTIONS

- *Neurotoxicity:* Phenylacetate (PAA), the major metabolite of RAVICTI, may be toxic at levels of 500 micrograms/mL or greater. If symptoms of vomiting, nausea, headache, somnolence, or confusion, are present in the absence of high ammonia or other intercurrent illness which explains these symptoms, consider the potential for PAA neurotoxicity which may need reduction in the RAVICTI dosage.

- *Pancreatic Insufficiency or Intestinal Malabsorption:* Low or absent pancreatic enzymes or intestinal disease resulting in fat malabsorption may result in reduced or absent digestion of RAVICTI and/or absorption of phenylbutyrate and reduced control of plasma ammonia. Monitor ammonia levels closely.

ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials (at least 10% of patients) were:

- *Adult patients:* diarrhea, flatulence, and headache occurred during 4-week treatment (n=45) with RAVICTI; nausea, vomiting, diarrhea, decreased appetite, dizziness, headache, and fatigue occurred during 12-month treatment (n=51) with RAVICTI.
- *Pediatric patients ages 2 to 17 years:* upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, and headache occurred during 12-month treatment (n=26) with RAVICTI.
- *Pediatric patients ages 2 months to less than 2 years:* neutropenia, vomiting, diarrhea, pyrexia, hypophagia, cough, nasal congestion, rhinorrhea, rash, and papule occurred during 12-month treatment (n=17) with RAVICTI.
- *Pediatric patients less than 2 months of age:* vomiting, gastroesophageal reflux, increased hepatic enzymes, feeding disorder (decreased appetite, hypophagia), anemia, cough, dehydration, metabolic acidosis, thrombocytosis, thrombocytopenia, neutropenia, lymphocytosis, diarrhea, flatulence, constipation, pyrexia, lethargy, and irritability/agitation occurred during 24-month treatment (n=16) with RAVICTI.

DRUG INTERACTIONS

- Corticosteroids, valproic acid, or haloperidol may increase plasma ammonia level. Monitor ammonia levels closely.
- Probenecid may affect renal excretion of metabolites of RAVICTI, including phenylacetylglutamine (PAGN) and PAA.
- CYP3A4 substrates with narrow therapeutic index (eg, alfentanil, quinidine, cyclosporine): RAVICTI may decrease exposure to the concomitant drug.
- Midazolam: Use of RAVICTI decreased exposure of midazolam with concomitant use.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* RAVICTI should be used with caution in patients who are pregnant or planning to become pregnant. Based on animal data, RAVICTI may cause fetal harm. A voluntary patient registry monitors pregnancy outcomes in women exposed to RAVICTI. For more information regarding the registry program, visit www.ucdregistry.com or call 1-855-823-2595.
- *Lactation:* breastfeeding is not recommended during treatment with RAVICTI. There are no data on the presence of RAVICTI in human milk, the effects on the breastfed infant, nor the effects on milk production.

Please see [Full Prescribing Information](#).

About Horizon Pharma plc

Horizon Pharma plc is focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By fostering a growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, we strive to make a powerful difference for patients, their caregivers and physicians. For us, it's personal: by living up to our own potential, we are helping others live up to theirs. For more information, please visit www.horizonpharma.com, follow us [@HZNPplc](#) on Twitter or like us on [Facebook](#).

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the potential of RAVICTI to treat UCD patients. These forward-looking statements are based on management expectations and assumptions as of the date of this press release, and actual results may differ materially from those in these forward-looking statements as a result of various factors. These factors include Horizon Pharma's ability to successfully market RAVICTI and the availability of reimbursement and payor coverage for RAVICTI, as well as those described in Horizon Pharma's filings with the United States Securities and Exchange Commission, including those factors discussed under the caption "Risk Factors" in those filings. Forward-looking statements speak only as of the date of this press release and Horizon Pharma does not undertake any obligation to update or revise these statements, except as may be required by law.

References:

1. Ah Mew N, Lanpher BC, Gropman A, et al.; Urea Cycle Disorders Consortium. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2015 Apr 9]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1217/>

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