Horizon Pharma plc Submits Supplemental New Drug Application for RAVICTI® (glycerol phenylbutyrate) Oral Liquid to Expand Age Range to Include Newborns

February 27, 2018

DUBLIN, Ireland, Feb. 27, 2018 (GLOBE NEWSWIRE) -- Horizon Pharma plc (NASDAQ:HZNP) today announced that it has submitted a supplemental New Drug Application (sNDA) with the U.S. Food and Drug Administration (FDA) to expand the approved indication for RAVICTI® (glycerol phenylbutyrate) Oral Liquid to include infants younger than two months of age living with urea cycle disorders (UCDs).

Currently, RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients greater than two months of age with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI is not indicated for treatment of acute hyperammonemia in patients with UCDs, and the safety and efficacy of RAVICTI for the treatment of n-acetylglutamate synthase (NAGS) deficiency has not been established. The sNDA seeks to expand RAVICTI's indication to include an age range down to birth, and is based on an open-label clinical study evaluating 16 patients with UCDs less than two months of age. The FDA is expected to complete their review during the second half of 2018.

"Urea cycle disorders are typically most severe when the onset of symptoms begin early in life, and symptoms that begin right after birth are particularly challenging," said Shao-Lee Lin, M.D., Ph.D., executive vice president, head of research and development and chief scientific officer, Horizon Pharma plc. "As part of Horizon's ongoing effort to reinvest in our medicines, this sNDA submission brings us closer to achieving our mission to make RAVICTI available for the majority of those living with a UCD, including newborns."

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
RAVICTI was first approved in the U.S. in February 2013 for the chronic management of adult and pediatric patients ?2 years of age with UCDs that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. In April 2017, the indication for RAVICTI was expanded to include children as young as two months of age. RAVICTI is not indicated for treatment of acute hyperammonemia in patients with UCDs, and the safety and efficacy of RAVICTI for the treatment of n-acetylglutamate synthase (NAGS) deficiency has not been established. Click here for more information about RAVICTI.

RAVICTI® (glycerol phenylbutyrate) Oral Liquid

INDICATIONS AND USAGE
RAVICTI is a nitrogen-binding agent indicated for chronic management of patients 2 months 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).

LIMITATIONS OF USE

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

DETAILED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- *Patients less than 2 months of age*: Children less than 2 months of age may have immature pancreatic exocrine function, which could impair hydrolysis of RAVICTI, leading to impaired absorption of phenylbutyrate and hyperammonemia.
- *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 µg/mL or greater. Reduce RAVICTI dosage if symptoms of neurotoxicity, including vomiting, nausea, headache, somnolence or confusion, are present in the absence of high ammonia or other intercurrent illnesses.
- *Reduced phenylbutyrate absorption in 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.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Limited available data with RAVICTI use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. 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.
- *Nursing mothers:* 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.

ADVERSE REACTIONS

- In ?10% of adult patients: diarrhea, flatulence, and headache occurred during 4-week treatment (n=44) with RAVICTI; nausea, vomiting, diarrhea, decreased appetite, dizziness, headache and fatigue occurred during 12-month treatment (n=51) with RAVICTI.
- In ?10% of 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.
- In ?10% of 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=6) 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 (e.g., alfentanil, quinidine, cyclosporine): RAVICTI may decrease exposure to the concomitant drug.
- Midazolam: Use of RAVICTI decreased exposure of midazolam with concomitant use.

Click here to download a copy of the RAVICTI 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 @HZNPplc on Twitter, like us on Facebook or explore career opportunities on LinkedIn.

Forward-Looking Statements
This press release contains forward-looking statements, including statements regarding the potential of RAVICTI to treat UCD patients, the potential outcome of the sNDA submission and Horizon Pharma's plans to continue investing in RAVICTI. 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 whether the FDA approves the sNDA filing for RAVICTI, Horizon Pharma's ability to successfully market RAVICTI, the availability of reimbursement and payor coverage for RAVICTI and demands on Horizon Pharma's cash and other resources, as well as those described in Horizon'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 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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