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Horizon Pharma plc Announces FDA Approval to Expand the Age Range for RAVICTI® (glycerol phenylbutyrate) Oral Liquid to People with Urea Cycle Disorders Two Months of Age and Older

DUBLIN, Ireland, May 01, 2017 (GLOBE NEWSWIRE) -- Horizon Pharma plc (NASDAQ:HZNP), a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs, today announced the U.S. Food and Drug Administration (FDA) has approved its supplemental New Drug Application (sNDA) to expand the age range for RAVICTI® (glycerol phenylbutyrate) Oral Liquid to people two months of age and older who have urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI initially was approved by the FDA in 2013 for adults and children as young as two years of age.

"Through our ongoing collaboration with physicians and parents of children living with UCDs, we understand the devastating effects of hyperammonemic events early in a child's life," said Jeffrey W. Sherman, M.D., FACP, executive vice president, research and development and chief medical officer, Horizon Pharma plc. "The approval by the FDA of our sNDA to expand RAVICTI to children as young as two months is an important step in helping young children with UCDs. We will continue to invest in RAVICTI to address the unmet needs of those with UCDs, as well as help their caregivers and family members more confidently tackle the challenges of the disease."

The approval is based on three studies that assessed monthly ammonia control and hyperammonemic crises (HACs) in pediatric patients with UCDs two months to two years of age. Patients were treated with RAVICTI for an average of eight months, and received RAVICTI either at study initiation or by enrolling on stable doses of sodium phenylbutyrate or sodium benzoate then switching to equivalent doses of RAVICTI. Results found RAVICTI to be safe and effective in the pediatric patients studied, with RAVICTI-treated patients maintaining stable ammonia levels relative to their pre-study enrollment.

"This approval represents a significant advance for very young children with UCDs, one of the most vulnerable patient populations, as more severe cases of the disease tend to present earlier in life and can lead to serious long-term impairments if not diagnosed and treated early," said Susan Berry, M.D., professor and division director for genetics and metabolism, department of pediatrics, University of Minnesota and primary investigator for the RAVICTI studies leading to the sNDA approval.

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.

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. 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 a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. The Company markets 11 medicines through its orphan, rheumatology and primary care business units. For more information, please visit www.horizonpharma.com. Follow @HZNPplc on Twitter or view careers on our LinkedIn page.

Forward-Looking Statements
This press release contains forward-looking statements, including statements regarding the potential of RAVICTI to treat UCD patients 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 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.

Contacts:

Tina Ventura

Senior Vice President, Investor Relations

Investor-relations@horizonpharma.com

U.S. Media Contact:

Matt Flesch

Executive Director, Product Communications

media@horizonpharma.com

Ireland Media Contact:

Ray Gordon

Gordon MRM

ray@gordonmrm.ie


Primary Logo

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