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Horizon Pharma plc to Present Data on RAVICTI® (glycerol phenylbutyrate) Oral Liquid for Urea Cycle Disorder Patients Aged Two Months to Two Years

DUBLIN, Ireland, March 22, 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 presentation of new data on the use of RAVICTI® (glycerol phenylbutyrate) Oral Liquid in children living with urea cycle disorders (UCD) two months to two years of age. These data will be presented on Thursday, March 23 at the American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting in Phoenix, Arizona.

The study results are from two clinical trials that enrolled children with UCDs aged two months to less than two years. Study participants were predominantly on relatively stable doses of sodium phenylbutyrate and switched to equivalent doses of RAVICTI. The primary outcomes measured in the study were targeted mean normalized plasma ammonia of less than 100 µmol/L, hyperammonemic crises (HACs) and adverse events (AEs). Safety and efficacy was also evaluated after patients transitioned to RAVICTI.

"The RAVICTI development program is part of our overall approach to reinvest in our medicines for people living with rare diseases," said Jeffrey W. Sherman, M.D., FACP, executive vice president, research and development and chief medical officer, Horizon Pharma plc. "While UCDs are very rare and can be devastating, continued advancements in diagnosis and ongoing studies evaluating management options are helping improve the long-term outcome of people living with the disorder."

RAVICTI is currently indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients two years of age or greater with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI is not indicated for patients less than two years of age. In June 2016, Horizon submitted a supplemental New Drug Applications (sNDA) with the U.S. Food and Drug Administration (FDA) seeking to expand the approved age range for RAVICTI to include children as young as two months of age.

The poster presentation (abstract #2873; poster #71), entitled "Safety and Efficacy of Glycerol Phenylbutyrate for Management of Urea Cycle Disorders in Patients Aged 2 Months to 2 Years," will be presented on Thursday, March 23, 2017 from 10:00 a.m. - 11:30 a.m. at the ACMG Annual Meeting.

About Urea Cycle Disorders

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 where it can 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

In the U.S., RAVICTI was approved in February 2013 and is indicated for the chronic management of adult and pediatric patients ≥2 years of age with 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).

Important Safety Information

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.
- The use of RAVICTI in patients < 2 months of age is contraindicated.

CONTRAINDICATIONS:
RAVICTI is contraindicated in patients:

- Less than 2 months of age. Children < 2 months of age may have immature pancreatic exocrine function, which could impair hydrolysis of RAVICTI, leading to impaired absorption of phenylbutyrate and hyperammonemia.
- With known hypersensitivity to phenylbutyrate. Signs of hypersensitivity 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 ≥500 µg/mL. Reduce RAVICTI dosage if symptoms of neurotoxicity, including vomiting, nausea, headache, somnolence, confusion, or sleepiness, 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:* 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 will include evaluation of pregnancy outcomes in patients with UCDs. For more information regarding the registry program, visit www.ucdregistry.com or call 1-855-823-2595.
- *Nursing Mothers:* Caution should be exercised when administering RAVICTI to nursing mothers, as breastfeeding is not recommended with maternal use of RAVICTI. It is not known whether RAVICTI or its metabolites are present in breast milk.

ADVERSE REACTIONS

- Adverse reactions occurring in ≥10% of adult patients during short-term treatment (n=44, 4 weeks) with RAVICTI were diarrhea, flatulence, and headache.
- Adverse reactions occurring in ≥10% of adult patients during long-term treatment (n=51, 12 months) with RAVICTI were nausea, vomiting, diarrhea, decreased appetite, hyperammonemia, dizziness, headache, and fatigue.
- Adverse reactions occurring in ≥10% of pediatric patients during long-term treatment (n=26, 12 months) with RAVICTI were upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, hyperammonemia, and headache.

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 PAGN and PAA.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the Full Prescribing Information and Medication Guide for RAVICTI.

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.

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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