



December 22, 2016

## **Horizon Pharma plc Announces the U.S. Patent and Trademark Office Issuance of an Additional Notice of Allowance With Claims Covering RAVICTI® (glycerol phenylbutyrate) Oral Liquid**

### **Will Represent Seventh U.S. Patent to be Listed in the Orange Book for RAVICTI**

DUBLIN, Ireland, Dec. 22, 2016 (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 that it has received a Notice of Allowance from the United States Patent and Trademark Office for U.S. patent application number 13/610,580, entitled "Methods of Therapeutic Monitoring of Phenylacetic Acid Prodrugs" that covers Horizon's U.S. approved medicine RAVICTI (glycerol phenylbutyrate) Oral Liquid.

This Notice of Allowance concludes the substantive examination of the patent application and will result in the issuance of a U.S. patent after administrative processes are completed. The U.S. patent scheduled to issue from this application will expire on September 22, 2030. After issuance, Horizon plans to list the U.S. patent in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, or Orange Book.

#### **About RAVICTI®**

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients  $\geq 2$  years of age 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 and protein-free calorie supplements). RAVICTI is indicated for use in all 28 Member States of the European Union and 3 Member States of the European Economic Area as a nitrogen-binding agent for chronic management of adult and pediatric patients two months of age and older with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI is indicated for use in Canada as an adjunctive therapy for chronic management of adult and pediatric patients two years of age and older with UCDs.

#### **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:**

- | In patients less than 2 months of age
- | In patients who develop or have known hypersensitivity to phenylbutyrate

##### **WARNINGS AND PRECAUTIONS:**

- | Phenylacetate (PAA), the major metabolite of RAVICTI, may be toxic at levels  $\geq 500$   $\mu\text{g/mL}$ . 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.
- | 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.
- | RAVICTI should be used with caution in patients who are pregnant or planning to become pregnant. Based on animal data it 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](http://www.ucdregistry.com) or call 1-855-823-2592.

- 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  $\geq 10\%$  of adult patients during short-term treatment (n=44, 4 weeks) with RAVICTI were diarrhea, flatulence, and headache.
- Adverse reactions occurring in  $\geq 10\%$  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 events occurring in  $\geq 10\%$  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.

#### **About Urea Cycle Disorders (UCDs)**

Urea Cycle Disorders or UCDs are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes where they get symptoms from the ammonia in their blood being excessively high - called hyperammonemic crises - which may result in 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 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](http://www.horizonpharma.com). Follow [@HZNPplc](https://twitter.com/HZNPplc) on Twitter or view careers on our [LinkedIn](#) page.

#### **Forward-Looking Statements**

This press release contains forward-looking statements, including statements regarding the issuance of a patent based on the Notice of Allowance from the U.S. Patent and Trademark Office, the expected term of the patent, if issued, potential patent protection for RAVICTI and plans to list newly issued patents in the FDA's Orange Book. 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 risks regarding whether the administrative processes required for the issuance of a patent as indicated in the Notice of Allowance will be completed in a timely matter or at all, whether the patent, if issued as indicated in the Notice of Allowance, will provide sufficient protection and market exclusivity for RAVICTI, whether any patents covering RAVICTI may be challenged, invalidated, infringed or circumvented by third parties and other factors 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.

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