

FDA Advisory Committee Votes in Favor of Earlier Use of Phosphate Binders in Stage 4 Kidney Disease Patients With Hyperphosphatemia

PHILADELPHIA, Oct. 16 /PRNewswire/ -- At the U.S. Food and Drug Administration's (FDA's) Cardiovascular and Renal Drugs Advisory Committee meeting today, the majority of members voted to recommend the use of phosphate binders, including Shire Pharmaceuticals' non-calcium FOSRENOL(R) (lanthanum carbonate), to treat hyperphosphatemia (elevated levels of phosphorus in the blood) in chronic kidney disease (CKD) Stage 4 patients. Currently, FOSRENOL is indicated to reduce serum phosphate in patients with end stage renal disease (ESRD).

The Committee did not reach consensus on which additional studies may be required, and Shire will work closely with the FDA to agree upon the pathway forward. The FDA Advisory Committee's recommendation is not binding on the FDA, and no time has been set by which the FDA will decide whether to follow this recommendation.

CKD is divided into five stages based on the level of kidney function, with higher stages of disease representing lower kidney filtration rates. In the United States, approximately 20 million adults have some form of CKD, of whom 500,000 have developed ESRD (or CKD Stage 5). An additional 400,000 individuals have significant loss of kidney function and are classified as having CKD Stage 4. Worldwide, almost 1.5 million people with CKD are on dialysis.

"As the Committee heard today, CKD patients are at an increased risk of death. In fact, a 30-year-old dialysis patient has the same risk of death as that of a 90-year-old with normal kidney function," said Keith Hruska, M.D., Professor of Pediatrics, Medicine and Cell Biology, Director, Division of Pediatric Nephrology, Washington University School of Medicine. "These patients that progress to dialysis represent the 'survivors.' That's why it's important to help kidney patients stay as healthy as possible from the early stages of their disease."

As a result of ongoing dialogue with the FDA, Shire had requested that an Advisory Committee Meeting be convened to provide guidance on the studies needed to expand the use of phosphate binders. Following these discussions, the FDA formally invited all three sponsors who presented at today's meeting to collaborate on demonstrating their case for treating CKD Stage 4 and 5 patients who have hyperphosphatemia with phosphate binders.

"Shire is committed to offering its effective phosphate binder, FOSRENOL, to kidney patients who need protection from the complications of elevated serum phosphorus," said Joseph Schlitz, vice president, U.S. Renal Business, Shire Pharmaceuticals. "The high affinity of FOSRENOL for phosphate provides effective monotherapy in a simple dosing regimen, which is one tablet per meal for most patients. Along with its well-established safety profile, FOSRENOL offers an attractive solution for both patients and their healthcare providers. Shire is therefore confident that FOSRENOL is well suited to be a first-line, non-calcium treatment of choice for CKD Stage 4 patients."

While the normal adult range for serum phosphorus is 2.5 to 4.5 milligrams per deciliter (mg/dL), the serum phosphorus levels of many patients on dialysis often exceed 6.5 mg/dL. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that monitoring for hyperphosphatemia should begin in patients with CKD Stage 3, and that serum phosphorus should be maintained within the

target range of 2.7 to 4.6 mg/dL in patients with CKD Stages 3 and 4, or 3.5 to 5.5 mg/dL for CKD Stage 5.

"Based on data in dialysis patients, it is reasonable to expect that treating pre-dialysis patients for secondary conditions, such as hyperphosphatemia, may slow the progression of their bone and cardiovascular disease," said Hartmut H. Malluche, M.D., chief, Nephrology, Bone and Mineral Metabolism, Department of Internal Medicine, University of Kentucky College of Medicine. "Studies have shown that FOSRENOL also is associated with a trend toward positive bone health -- a treatment attribute that also may be of benefit to CKD Stage 4 patients."

Most CKD Stage 4 and 5 patients will develop chronic kidney disease-mineral and bone disorder (CKD-MBD) -- a systemic disorder of mineral and bone metabolism due to CKD. CKD-MBD often manifests as hyperphosphatemia, which causes bone disease characterized by bone pain, brittle bones, skeletal deformities and fractures, and vascular or other soft tissue calcification. Evidence also shows that hyperphosphatemia contributes to cardiovascular disease, which accounts for almost half of all deaths among dialysis patients.

"Shire recently completed a multicenter, placebo-controlled study in patients with CKD Stages 3 and 4 with hyperphosphatemia. The results showed that FOSRENOL-treated patients had statistically significant reductions in serum phosphate levels compared to placebo after eight weeks of treatment. This study provided valuable insights into controlling hyperphosphatemia in CKD Stages 3 and 4 patients," said Ray Pratt, M.D., vice president, scientific leader, Renal Business Unit, Research and Development, Shire Pharmaceuticals. "We are committed to offering all patients the most effective phosphate binder therapy and will continue to invest in a clinical program that includes the development of additional FOSRENOL formulation options aimed at further simplifying treatment for all CKD patients."

Managing Hyperphosphatemia

Phosphorus, an element found in nearly all foods, is absorbed from the gastrointestinal tract into the bloodstream. When the kidneys fail, they no longer effectively remove phosphorus. While the normal adult range for phosphorus is 2.5 to 4.5 mg/dL, the blood phosphorus levels of many patients on dialysis often exceed 6.5 mg/dL. Such levels have been linked to a significantly higher morbidity and mortality risk for patients who have undergone at least one year of dialysis. Research has shown that for each mg/dL increase in mean serum phosphorus, the relative risk of death increases by six percent.

Hyperphosphatemia is managed with a combination of dialysis, diet restriction, and phosphorus-binding agents, because diet and dialysis alone generally cannot adequately control phosphorus levels. Such binders "soak up" phosphorus in the gastrointestinal tract, before it can be absorbed into the blood, and aid patients in maintaining acceptable levels of mean serum phosphorus.

FOSRENOL

FOSRENOL is indicated to reduce serum phosphate in patients with ESRD.

FOSRENOL is an effective, non-calcium, phosphate binder that reduces high phosphorus levels in ESRD patients. FOSRENOL is formulated as an easy-to-use, unflavored, chewable tablet that can be taken without water, an important consideration for ESRD patients who must restrict their fluid intake.

FOSRENOL is available in a broad range of dosage strengths comprised of

500-milligram (mg), 750-mg, and 1-g tablets. Patients taking FOSRENOL can achieve serum phosphorus target levels with as few as three tablets per day. (Dosing based on three meals per day. Number of meals per day may vary. To achieve certain doses, additional tablets may be required.)

FOSRENOL has a high affinity for phosphate and works by binding to dietary phosphorus in the gastrointestinal tract. Once bound, the FOSRENOL/phosphorus complex cannot pass into the bloodstream and is eliminated from the body, thereby decreasing mean serum phosphorus levels.

To date, FOSRENOL has been clinically tested in more than 5,200 patients globally, with nearly 1,000 of these patients having been followed for more than one year. In addition, more than 87,000 patients have been prescribed FOSRENOL in the U.S. alone. FOSRENOL has the most extensive long-term safety data package of any phosphate binder and is generally well tolerated. Trials involving patients treated with FOSRENOL showed sustained serum phosphorus reduction in a majority of patients, with some patients being followed over a six-year duration.

FOSRENOL is now available in 23 countries, including Canada, France, Germany, Italy, and the UK, and continues to be launched in new markets around the world.

Important Safety Information

The most common adverse events were gastrointestinal, such as nausea and vomiting, and generally abated over time with continued dosing. The most common side effects leading to discontinuation in clinical trials were gastrointestinal events (nausea, vomiting, and diarrhea). Other side effects reported in trials included dialysis graft complications, headache, abdominal pain, and hypotension. Although studies were not designed to detect differences in risk of fracture and mortality, there were no differences demonstrated in patients treated with FOSRENOL compared to alternative therapy for up to three years. The duration of treatment exposure and time of observation in the clinical program were too short to conclude that FOSRENOL does not affect the risk of fracture or mortality beyond three years. While lanthanum has been shown to accumulate in the GI tract, liver, and bone in animals, the clinical significance in humans is unknown. Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease, or bowel obstruction were not included in FOSRENOL clinical studies. Caution should be used in patients with these conditions. FOSRENOL should not be taken by patients who are nursing or pregnant. FOSRENOL should not be taken by patients who are under 18 years of age.

For Full Prescribing Information on FOSRENOL, please visit <http://www.fosrenol.com>.

SHIRE PLC

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe. Shire believes that a carefully selected portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

For further information on Shire, please visit the Company's website: <http://www.shire.com>.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's Attention Deficit and Hyperactivity Disorder (ADHD) franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval date of SPD503 (guanfacine extended release) (ADHD); Shire's ability to secure new products for commercialization and/or development; Shire's ability to benefit from its acquisition of New River Pharmaceuticals Inc.; the successful development of JUVISTA and other risks and uncertainties detailed from time to time in Shire plc's filings with the Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2006.

SOURCE Shire plc