

Press Release

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SHIRE DEMONSTRATES COMMITMENT TO IMPROVING PATIENT ADHERENCE IN END STAGE RENAL DISEASE AS NEW PHOSPHATE-BINDER FOSRENOL[®] LAUNCHES IN EUROPE

New research provides important insights into adherence issue

**Data reveal perceptual and practical barriers including the need for phosphate
binders with simplified dosing**

BASINGSTOKE, UNITED KINGDOM — 25 June 2007 - Shire plc (LSE: SHP, NASDAQ: SHPGY, TSX: SHQ). New data from a patient adherence survey presented on Friday 22nd June at the XLIV ERA-EDTA Congress in Barcelona highlight that over 40% of patients with chronic kidney disease (CKD) forget to take their phosphate-binding medication.¹ Phosphate binders are used to treat hyperphosphataemia (unusually high levels of phosphorous in the blood), which, if not managed successfully, can lead to serious health consequences including increased rates of cardiovascular morbidity and mortality and other complications.²

The research reveals that poor patient adherence to phosphate binders is linked to practical barriers such as the complexity of the dosing regimen and not understanding how to take them, as well as perceptual barriers regarding patient beliefs about their need for medication and concerns about adverse events.¹

Rob Horne, Professor of Behavioural Medicine at the School of Pharmacy, University of London, conducted the research which assessed the behavioural patterns of 221 patients with CKD across 8 centres in the UK.

“CKD can have a devastating impact on patients’ lives. The study shows that adherence to phosphate-binding medication is adversely affected by a number of factors, both practical and perceptual,” said Professor Horne. “On the practical side, daily treatment requires often complex dosing schedules on top of an already difficult treatment regimen. This can include long dialysis sessions, strict fluid and dietary restrictions and a complicated medication schedule involving up to 25 tablets per day. Phosphate binders used to manage hyperphosphataemia can alone add up to 12 tablets per day.”

“On the perceptual side, it is essential to recognise that personal beliefs about the value of medication are important. Our study showed that non adherence was linked to doubts about the need for treatment and concerns about taking phosphate binders. We now need to develop more effective methods for helping patients to get the best from their medicines by facilitating informed choice and improved adherence. This should involve the provision of bespoke information to meet individual needs and address concerns as well as efforts to overcome the practical barriers to adherence by making the regimen as convenient and easy to use as possible.” he added.

The research, using validated questionnaires¹, produced the following findings:

- Over 40% of patients forgot to take their phosphate-binder medication sometimes, often or always;
- 38% forgot to take their medication at mealtimes;
- 23% of patients reported altering their dose;
- 19% decided to miss doses;
- 21% took less medication than instructed.¹

Over 70%³ of the estimated 1.5 million people with CKD on dialysis worldwide⁴ will develop hyperphosphataemia due to their failing kidneys being unable to effectively rid their bodies of the excess phosphate absorbed from food. If not managed successfully, hyperphosphataemia can lead to serious health problems including renal osteodystrophy (a bone disorder resulting in painful, brittle bones that may fracture or lead to deformities) and cardiovascular disease which accounts for almost half of all deaths in dialysis patients.⁵

Despite the availability of existing therapies, effective phosphate management remains a challenge with up to 75% of dialysis patients exceeding the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guidelines for serum phosphate levels less than 1.78 mmol/L (5.5 mg/dL).⁶

“This research highlights that a combination of treatment factors, including tablet burden, can contribute to poor patient adherence which may compromise their ability to meet specified global targets for phosphate levels,” said Professor Horne.

FOSRENOL is a newly introduced treatment option in Europe for the nephrologist to use in the management of hyperphosphataemia in CKD patients on dialysis. It is a non-calcium based binder with a high affinity for phosphate that binds to the phosphate in food to effectively reduce serum phosphorous levels.⁷ FOSRENOL can be used effectively as a monotherapy and is associated with a lower tablet burden than existing phosphate binders with the majority of patients requiring just one chewable tablet during each meal.⁸ This compares to other therapies that are often used in combination and may require up to 12 tablets per day. This simplified dosing regime may remove some of the practical barriers to patient adherence identified in the research.

“Adherence is emerging as a key issue for patients with CKD, with many still having phosphate levels above the recommended global target. Shire is sponsoring Professor Horne’s research as part of its commitment to exploring new ways to improve patient adherence and ultimately better patient outcomes,” said David Milton, Senior Vice President, Shire Renal Business Unit. “FOSRENOL is our effective phosphate binder that offers the added benefit of a reduced pill burden with the majority of CKD patients on dialysis requiring just one tablet during each meal. As part of this commitment, Shire is also developing additional FOSRENOL formulation options aimed at making it even simpler for patients,” he added.

Over 5,000 patients have been treated with FOSRENOL during an extensive clinical development programme⁹, with a small number having been followed up for up to six years.¹⁰ In the US, over 76,000 patients have been prescribed FOSRENOL since it was launched in 2005.¹¹

FOSRENOL is now available in 20 countries, including Canada, France, Germany, Italy, UK and the US and continues to be launched in new markets around the world.

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3. Albaaj F, Hutchison AJ. Lanthanum carbonate for the treatment of hyperphosphataemia in renal failure and dialysis patients. *Expert Opin. Pharmacother* 2005; 6(2): 319-328.
4. Global dialysis. Global dialysis: dialysis standards and statistics. Available at www.globaldialysis.com/stats.asp. Accessed on 18 May 2007.
5. The National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases. U.S. Renal Data System, USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Available at http://www.usrds.org/2005/pdf/06_morb_and_mort_05.pdf. Accessed on 18 May 2007.
6. Kim J *et al.* Achievement of proposed NKF-K/DOQI Bone Metabolism and Disease Guidelines: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 269A.
7. Hutchison AJ, Maes B, Vanwalleghem J *et al.* Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study. *Nephron Clin Pract* 2006;102(2):c61–c71
8. Vemuri N *et al.* Lanthanum carbonate provides serum phosphorus control with a reduced tablet burden. Poster presented at ERA/EDTA, Glasgow, 15-18 July 2006
9. Shire Data on File 08.2644

10. Hutchison A *et al* on behalf of the SPD405-309 Lanthanum Study Group. Evidence for the long-term safety and tolerability of lanthanum carbonate. Poster presented at 38th Annual Meeting of the American Society of Nephrology, Philadelphia, 8-13 November 2005.
 11. Verispan 2007, *Verispan Total Patient Tracker*.
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Notes to editors:

Managing Hyperphosphataemia

Phosphorus, an element found in nearly all foods, is absorbed from the gastrointestinal tract into the blood stream. When the kidneys fail, they no longer effectively filter out phosphates, even with the help of blood-cleansing dialysis machines. While the normal adult range for phosphorus is 2.5 (0.8mmol/L) to 4.5 mg/dL (1.4mmol/L), the blood phosphorus levels of many patients on dialysis exceed 6.5 mg/dL (2.1mmol/L). Such levels have been linked to a significantly higher illness and death risk for patients who have undergone at least one year of dialysisⁱ with over 70 per cent of patients developing hyperphosphataemia.ⁱⁱ

Hyperphosphataemia disrupts the delicate interplay between the body's levels of calcium, parathyroid hormone (PTH) and vitamin D. Over time, hyperphosphataemia can ultimately lead to calcification of the heart, lung and some arteriesⁱⁱⁱ. Accumulating evidence shows that hyperphosphataemia contributes to cardiovascular disease, which accounts for almost half of all deaths among dialysis patients^{iv}. Studies have shown that cardiovascular mortality in dialysis patients aged 25-34 years is more than 5 times greater than that in people aged 65-74 in the general population.^v

Since dialysis and diet restrictions alone generally cannot control phosphate levels, patients traditionally manage hyperphosphataemia by taking phosphate binding agents with every meal and snack. Such binders "soak up" phosphate in the gastrointestinal tract, before it can be absorbed into the blood.

FOSRENOL[®] (lanthanum carbonate)

FOSRENOL[®] works by binding to dietary phosphate in the GI tract; once bound, the lanthanum/phosphate complex cannot pass through the intestinal lining into the blood stream and is eliminated from the body. As a consequence, overall phosphate absorption from the diet is decreased significantly. Shire has conducted an extensive worldwide clinical research programme for FOSRENOL involving over 5000 patients^{vi}, with a small number followed for up to 6 years.^{vii} This programme has demonstrated that FOSRENOL is an effective phosphate binder with a good tolerability profile for long-term use. FOSRENOL was approved by the FDA in October 2004. In March 2005 regulatory authorities in the EU granted marketing authorization for FOSRENOL in sixteen member states, thus completing the first step in securing marketing approval throughout Europe. Later, the European process was completed resulting in recommendation for approval in the remaining 11 member states. FOSRENOL is now available in 20 countries, including Canada, France, Germany, UK and the US and continues to be launched in new markets around the world. The company has out-licensed the rights to develop, market and sell FOSRENOL in Japan to Bayer Yakuin Ltd.

Patients with renal insufficiency may develop hypocalcaemia. Serum calcium levels should therefore be monitored at regular time intervals for this patient population and appropriate supplements given.

No data are available in patients with severe hepatic impairment. Caution should, therefore, be exercised in these patients, as elimination of absorbed lanthanum may be reduced.

FOSRENOL should not be used during pregnancy.

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in clinical studies with Fosrenol.

The most commonly reported Adverse Drug Reactions (ADRs) (>1/100, 1/10) are gastrointestinal reactions such as abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea and vomiting. These are minimized by taking FOSRENOL with food and generally abated with time with continued dosing. Hypocalcaemia was the only other commonly reported adverse reaction.

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 believes that a carefully selected portfolio of products with a strategically aligned and relatively small-scale sales force will deliver strong results.

Shire's focused strategy is to develop and market products for specialty physicians. 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.

For further information on Shire, please visit the Company's website: 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.

ⁱ Block GA *et al.* Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis* 1998; 31: 607-617

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- ii Kim J et al. Achievement of proposed NKF-K/DOQI Bone Metabolism and Disease Guidelines: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; 14: 269A
 - iii Norris KC. Toward a new treatment paradigm for hyperphosphataemia in chronic renal disease. *Dial Transplant* 1998; 27 (12): 767–773
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 - v Foley R *et al.* Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32 (5) Suppl 3:112–119
 - vi Shire Data on File 08.2644
 - vii Hutchison A et al on behalf of the SPD405-309 Lanthanum Study Group. Evidence for the long-term safety and tolerability of lanthanum carbonate. Poster presented at 38th Annual Meeting of the American Society of Nephrology, Philadelphia, 8-13 November 2005