# lanthanum carbonate 500, 750, 1000mg chewable tablets (Fosrenol®) No. (286/06)

## Shire Pharmaceuticals Contract Ltd

7 July 2006 *(Issued March 2007)*

The Scottish Medicines Consortium has completed its assessment of the above product and advises Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**Lanthanum carbonate (Fosrenol®)** is accepted for restricted use within NHS Scotland as a phosphate-binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis.

Lanthanum carbonate is as effective as calcium carbonate in reducing phosphate to target levels. It is restricted to use as a second-line agent in patients where a non-aluminium, non-calcium phosphate binder is required.

Overleaf is the detailed advice on this product.

**Vice Chairman,**
**Scottish Medicines Consortium**

**Lanthanum carbonate 500,750,1000mg tablets (Fosrenol®)**

## Indication

Lanthanum Carbonate is indicated as a phosphate-binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

## Dosing information

750mg – 3000mg daily with or immediately after food, with the daily dose divided between meals. Tablets must be chewed and not swallowed whole.

## UK launch date

September 2006

## Cost of relevant comparators

| Drug | Daily Dose Range* | Annual cost (365 days) (£) |
|---|---|---|
| **Lanthanum carbonate (Fosrenol®)** | **750-3000mg** | **617 - 1963** |
| Sevelamer (Renagel®) | 2.4-12g | 747 - 3734 |
| Calcium carbonate (Calcichew Forte®) | 3 tablets | 240 |
| Calcium acetate (Phosex®) | 3 -12 tablets | 120 - 482 |
| Calcium carbonate (Calcichew®) | 3 - 6 tablets | 102 – 204 |
| Calcium carbonate (Adcal®) | 3 - 6 tablets | 79 – 159 |
| Aluminium hydroxide (Alu-cap®) | 4 - 20 tablets | 46 - 228 |

*Doses given are for comparison only and do not imply therapeutic equivalence, and this is particularly true for these preparations which are titrated according to individual's needs. Costs are from the eVadis database accessed on the 9th May 2006.

## Summary of evidence on comparative efficacy

Hyperphosphataemia is a serious complication that affects most patients with established renal failure (ERF) who require dialysis. Lanthanum is a naturally occurring rare element which when administered as the carbonate salt dissociates in the acid environment of the upper gastrointestinal (GI) tract releasing lanthanum ions. These ions bind with dietary phosphate to form an insoluble complex, which is not absorbed from the GI tract.

The phase lll clinical trial programme comprised two randomised trials to establish efficacy (one double-blind placebo and one open-label, active comparator), followed by open label extensions of these studies to establish safety and tolerability; one long-term safety and tolerability study against standard treatment and one comparative study with calcium carbonate to establish the effects of treatment on renal bone disease.

The two efficacy studies were of a similar three-part design and included similar patient populations (adults ≥ 18 years who had undergone thrice-weekly haemodialysis for at least three consecutive months). The study design included a screening and washout period of one to three weeks during which patients with a serum phosphate level of >1.8 or >1.9mmol/l (5.6-5.9 mg/dl) were entered into a five or six week titration phase, when doses were adjusted weekly until phosphate levels reached the target level (≤1.8mmol/l), and then they were randomised to a maintenance assessment phase. The primary outcome measures

were based on the predialysis, serum phosphate level. Secondary outcome measures included changes in serum calcium, calcium x phosphate product, and intact parathyroid hormone (PTH).

In the active comparator study, after the initial washout phase, 767 patients in the intention to treat population (ITT) were randomised to 20 weeks maintenance treatment with lanthanum (n=510) or calcium carbonate (n=257) during which the dose of phosphate binders could be adjusted on the basis of monthly phosphate assessments. Patients with adequate phosphate control following washout, serum calcium above the upper limit of normal, serum PTH above 1,000ng/l were excluded. The lanthanum carbonate dose ranged from 375-3000mg daily and the calcium carbonate dose from 1500-9000mg daily. Slightly over half of the randomised population completed the study (54.2% on lanthanum carbonate and 57.7% on calcium carbonate).

Throughout the maintenance phase there was no significant difference between the two groups in the primary outcome defined as the proportion of patients within target for serum phosphate. At 25 weeks, 65.8% of lanthanum treated patients and 63.9% of calcium carbonate patients had target serum phosphate levels of ≤1.8 mmol/l, with serum phosphate levels of 1.73±0.46mmol and 1.72±0.477mmol, respectively. Both treatments reduced levels of calcium x phosphate product with no significant difference between treatments.

In the six month extension to the comparator study, patients treated with calcium carbonate could switch to lanthanum treatment, resulting in 518 patients entering this phase, 333 patients from the lanthanum group and 185 patients who switched from calcium carbonate. At the end of the six-month extension phase, 63% of patients who had received lanthanum throughout the study, and 58.4% of patients who had switched had serum phosphate levels within the target range (1.76±0.56mmol/l [5.5±1.7mg/dl] and 1.83 ± 0.52mmol/l [5.7±1.6mg/dl], respectively). At the end of a further 2 year extension of this study, 69% of the 46 patients who had received lanthanum throughout the whole three years had serum phosphate levels ≤ 1.8mmol/l (≤ 5.6mg/dl).

## Summary of evidence on comparative safety

In the active-comparator study, most adverse effects of lanthanum carbonate were in the gastro-intestinal tract and occurred with a similar frequency overall in both treatment groups. About 7% more patients reported vomiting, and 3% more experienced diarrhoea and nausea, on lanthanum than calcium carbonate.

Both the six month and 2 year open extensions of the above comparator study were primarily concerned with safety and tolerability. The incidence of hypercalcaemia in lanthanum carbonate patients remained low at <1% throughout the trial period, while in patients previously randomised to calcium carbonate it fell significantly during the open extension from 20% to 2.7%. Serum lanthanum levels increased minimally with dose but not duration of lanthanum exposure.

In a 24 month open, safety and tolerability study in 1359 patients randomised to either lanthanum carbonate or standard phosphate binder therapy the number of patients who had to discontinue or change their therapy was similar in both groups. Mean plasma levels of lanthanum increased initially then levelled out with no further accumulation over time. A small bone biopsy study suggested that lanthanum carbonate does not adversely affect bone but showed a trend towards normalising of histomorphometric parameters in lanthanum patients.

## Summary of clinical effectiveness issues

The practical advantages of this new treatment are that the tablets are taste neutral, can be taken without fluid and potentially fewer tablets may be required.

There are no head to head studies with the only other non-aluminium, non-calcium phosphate binder, sevelamer. In the 24 month, comparative study of tolerability with standard treatment there was a higher number of withdrawals in the lanthanum arm compared to standard treatment. Patients on standard therapy were allowed to switch to a different phosphate binder and still remain in the study while no switching could be allowed for patients on lanthanum and therefore they could only discontinue from the study. This was the explanation given for the higher discontinuation rates. The discontinuation rates in other studies were also quite significant, however tolerability of phosphate binder therapy is problematic and patients who had discontinued during the early parts of the studies did have the option to re-titrate their lanthanum carbonate dose and re-enter the long-term extension phases.

Long-term effects on bone have still to be fully established. There is experience of lanthanum carbonate use out to six years but only in a small number of patients. Lanthanum carbonate takes more than ten years to reach steady state in bone therefore it has not yet reached steady state in patients who have been treated so far and there is still some concern over the effects of long-term treatment on bone and other tissue toxicity. Once lanthanum treatment has been discontinued, accumulated lanthanum is cleared slowly from bone which potentially could prolong the time to resolution of adverse effects.

## Summary of comparative health economic evidence

A cost-utility analysis was performed of an 8 week trial of second line lanthanum carbonate after failure to reach phosphate level targets on calcium carbonate versus continuing with carbonate calcium for the treatment of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis. After the 8 week trial patients who had not achieved the target phosphate level of ≤1.8mmol/l on lanthanum carbonate were assumed to switch back to calcium carbonate.

A Markov model was developed whereby patients could move between nine phosphate level states distributed above and below the target level. The transition probabilities between the states were derived from the phase III trial active comparator trial of lanthanum carbonate compared to calcium carbonate. The 37% of patients who failed to reach the target phosphate level on calcium carbonate at the end of the 25 week randomised control trial phase of this trial were assumed to switch to lanthanum carbonate. Relative risk of mortality data for the nine phosphate level states, from a large US observational study of haemodialysis patients, was combined with survival analysis in order to derive estimates of the life years gained with the second line trial of lanthanum carbonate, A utility value of 0.59 for established renal failure was applied to determine QALYs. Only direct drug costs were included in the evaluation. The base case results were an incremental cost per life year gained of £3,965 and £6,741 per QALY gained. Inclusion of dialysis costs increases the cost per QALY to £41,000.

The survival modelling was necessary and seems to have been robustly performed, and sensitivity analysis confirmed the cost-effectiveness ratio is likely to be within acceptable limits after allowing for uncertainty in the data. The manufacturer has provided evidence that, though there are no data directly comparing lanthanum carbonate and sevelamer (the only other non-calcium, non-aluminium phosphate binder), they appear to have broadly equivalent efficacy,

## Patient and public involvement

## Budget impact

The manufacturer estimated an incremental budget impact of £526,336 over a 5 year period from 2006. This includes savings from switching patients from calcium carbonate.

## Guidelines and protocols

Treatment of Adults and Children with Renal Failure: Standards and Audit Measures. 3rd Edition. London. Royal College of Physicians of London and the Renal Association, 2002.

Chronic Kidney Disease in Adults: UK Guidelines for identification, management and referral published by the Renal Association in June 2005.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 14 February 2007.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The reference, shaded grey is additional to those supplied with the submission.*


Joy MS, Finn WF, on behalf of the LAM-302 Study Group. Randomized, double-blind, placebo-controlled, dose-titration Phase III study assessing the efficacy and tolerability of lanthanum carbonate: A new phosphate binder for the treatment of hyperphosphataemia. Am J Kidney Diseases 2003; 42: 96–107.

D'Haese PC, Spasovski GB, Sikole A et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl 2003; 85: S73–S78.

Finn WF, on behalf of the SPD 405-307 Lanthanum Study Group.Lanthanum carbonate versus standard therapy for the treatment of hyperphosphataemia: safety and efficacy in chronic maintenance haemodialysis patients Clin Nephrol 2006;65:191-202

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): c61–71. Epub 2005 Oct 14.

Finn WF, Joy MS,on behalf of the lanthanum study group. A long-term, open-label extension study on the safety of treatment with lanthanum carbonate, a new phosphate binder, in patients receiving hemodialysis. Curr Med Res Opin 2005; 21(5): 657–664.

Hutchison AJ, Maes B, Vanwallaghem J. Efficacy, tolerability, and safety of lanthanum carbonate ion hyperphosphatemia: A 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract 2005; 100: C8–C19.

Freemont T, Malluch HH. Utilization of bone histomorphometry in renal osteodystrophy: demonstration of a new approach using data from a prospective study of lanthanum carbonate. Clin Nephrol 2005; 63(2): 138–145.

Lanthanum carbonate. NDA#021468 Drugs@FDA *www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm*