Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

# lanthanum carbonate, 500mg, 750mg, 1,000mg, chewable tablets (Fosrenol®) SMC No. (640/10)

## Shire Pharmaceuticals Ltd

10 September 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and 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 not recommended for use within NHS Scotland.

**Indication under review:** as a phosphate binding agent for use in the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥1.78mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

When compared with placebo, in patients with chronic kidney disease not yet on dialysis, more patients treated with lanthanum carbonate achieved a serum phosphate concentration ≤1.49mmol/L.

The manufacturer did not present a sufficiently robust clinical or economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

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

## Indication

Lanthanum carbonate is indicated as a phosphate binding agent for use in the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥1.78mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

Lanthanum is also 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.

## Dosing Information

750mg to 3,000mg daily, with or immediately after food, with the daily dose divided between meals. Tablets must be chewed and not swallowed whole.

Serum phosphate levels should be monitored and the dose of lanthanum carbonate titrated every 2 to 3 weeks until an acceptable serum phosphate level is reached, with regular monitoring thereafter.

## Product availability date

29 September 2009

## Summary of evidence on comparative efficacy

Hyperphosphataemia is a metabolic disorder associated with chronic kidney disease (CKD) that is linked with increased all-cause and cardiovascular mortality, as well as a spectrum of bone disorders. Phosphate-binders help to reduce blood phosphate levels by attaching to dietary phosphate from within the gut and thus prevent absorption. Lanthanum is a rare element which, when administered as the carbonate salt, acts as a phosphate-binder in the gastro-intestinal tract.

This submission relates to an extension to the marketing authorisation for lanthanum carbonate to allow its use in patients with CKD not on dialysis. The manufacturer wishes to position lanthanum carbonate as second-line therapy in patients whose response to calcium-based phosphate binders has been inadequate, or for whom these agents are contraindicated due to the risk of hypercalcaemic adverse events.

Evidence was presented for this licence extension from one phase II, randomised, double-blind, placebo-controlled 8-week study, conducted in the United States. Patients were 18 years or over, had an estimated glomerular filtration rate of 15 to 59mL/min/1.73m$^2$, had been treated for CKD for more than 2 months and were not expected to begin dialysis for at least 4 months. After screening, eligible patients discontinued any current phosphate-binding therapy and entered a 3 to 4-week run-in period. During this time, serum phosphate levels were assessed and if 2 consecutive levels were >1.49mmol/L and calcium ≥2.0mmol/L, patients were randomised 2:1 to receive lanthanum carbonate 250mg three times daily or placebo. Randomised patients (n=121) took study drug during or immediately after meals, for 2 weeks. Over the next 2 weeks (weeks 3 to 4), the dose could be titrated weekly, to a maximum of

1,000mg three times daily, in order to achieve a target serum phosphate level of <1.29mmol/L. The final dose was then taken for another 4 weeks (weeks 5 to 8) although another titration was permissible at week 6 if phosphate levels had increased to ≥1.29mmol/L or decreased to <0.87mmol/L. Continued treatment with vitamin D analogues and calcium supplements for hypocalcaemia was permitted.

The primary end-point was the percentage of patients in the modified intention-to-treat (mITT) population (defined as all patients who received at least one dose of study drug and had at least one post-dose serum phosphate measurement) who had serum phosphate concentrations ≤1.49mmol/L after 8 weeks of lanthanum carbonate or placebo treatment. The results were compared using Fisher's exact test and used the last observation carried forward method for missing values. Secondary end-points included changes in serum phosphate and calcium, intact parathyroid hormone (iPTH), calcium-phosphorus product and 24-hour urinary excretion of phosphorus.

At end of treatment, 45% (25/56) of lanthanum carbonate patients and 26% (9/34) of the placebo group had a serum phosphate level ≤1.49mmol/L. The difference between groups (18%) was not significant.

From baseline mean serum phosphate levels of 1.71±0.03mmol/L in the lanthanum carbonate group and 1.74±0.04mmol/L in the placebo group, at the end of treatment, mean decreases were 0.18±0.03mmol/L and 0.06±0.04mmol/L respectively, a significant difference of 0.12mmol/L. For iPTH, mean serum baseline levels were 183.5±19.5pg/mL in the lanthanum carbonate group and 179.3±24.4pg/mL in the placebo group. At the end of treatment, mean levels had decreased by 23.8±8.6pg/mL in the lanthanum carbonate group and increased by 8.8±11.0pg/mL in the placebo group, a significant difference. From baseline mean serum calcium levels of 2.22±0.02mmol/L in the lanthanum carbonate group and 2.24±0.02mmol/L in the placebo group, at the end of treatment there was a slight increase in mean level in the lanthanum carbonate group of 0.03±0.01mmol/L and a slight decrease in the placebo group of 0.02±0.02mmol/L, and this difference was significant.

Mean levels of 24-hour urinary excretion of phosphorus were similar for the two groups at baseline (26.98±1.94mmol/dL and 25.28±2.21mmol/dL for the lanthanum carbonate and placebo groups respectively). By the end of the treatment period, levels for patients in the lanthanum carbonate group had decreased by 7.99±1.56mmol/dL, which was significantly more than the decrease in the placebo group.

## Summary of evidence on comparative safety

The safety profile of lanthanum carbonate in adults with CKD not on dialysis appears consistent with the known safety profile in renal patients receiving dialysis. In the pivotal study described above adverse events (AEs) were experienced by 47% of patients treated with lanthanum carbonate, compared with 61% in the placebo group and, of these, 19% and 17% in each group respectively were considered related to treatment.

AEs were mainly gastrointestinal in nature, with nausea (9.0% in the lanthanum carbonate group and 9.8% in the placebo group) and vomiting (6.4% and 2.4% respectively) being the most common. AEs leading to treatment discontinuation occurred in two patients in the lanthanum carbonate group and four in the placebo group.

*Other data were also assessed but remain commercially confidential.**

## Summary of clinical effectiveness issues

The evidence came from one phase II study involving small patient numbers. For the primary end-point, the difference between the lanthanum carbonate group and the placebo group did not achieve statistical significance. The proportion of patients completing the study was low in each group (54% (43/80) and 68% (28/41) in the lanthanum carbonate and placebo groups respectively).

From a week-by-week plot of the percentage of patients with a phosphate level ≤1.49mmol/L, the effect seemed to peak at week 6 in the lanthanum carbonate group. From a similar plot of changes in serum phosphate, again the effect of lanthanum carbonate appeared to peak at week 6. Therefore, longer-term efficacy data would be useful to determine the overall trend.

The manufacturer wishes to position this product as second-line therapy in patients whose response to calcium-based phosphate binders has been inadequate, or for whom these agents are contraindicated due to the risk of hypercalcaemic adverse events. However, 79% of patients in each study group were naïve to phosphate binder therapy therefore data to support second-line use are lacking.

While the target phosphate level in the US study was <1.29mmol/L, the primary end-point related to those patients who achieved a level ≤1.49mmol/L. These levels are appropriate for a Scottish population, with UK Renal Association guidelines recommending that levels are maintained between 0.9 and 1.5mmol/L. According to the marketing authorisation, lanthanum carbonate is indicated in CKD patients not on dialysis with a phosphate level ≥1.78mmol/L. Baseline levels in patients in the study were around 1.72mmol/L therefore not all study patients would have been eligible for treatment with the licensed product in practice.

The mITT population was small compared with the ITT population, and it is unclear if bias was introduced.

Long-term safety data for lanthanum carbonate in the pre-dialysis population is limited. Safety data are available for dialysis patients treated for up to 6 years but numbers are still relatively low. Long-term effects on bone remain to be fully established.

Lanthanum carbonate is typically administered as one tablet three times daily with meals so the pill burden is lower than with some other phosphate binders.

## Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing calcium-based therapy followed by second-line lanthanum carbonate with a strategy of continued calcium-based phosphate binder therapy alone. The economic analysis focused on pre-dialysis patients with elevated serum phosphate levels who do not respond sufficiently to first-line calcium-based phosphate binders. A decision-analytical model was used which involved a decision-tree followed by a Markov model to extrapolate the data over a lifetime horizon. Patients were modelled as their

CKD progressed from pre-dialysis to dialysis. In the pre-dialysis state, patients in the lanthanum carbonate arm received treatment with calcium-based therapy first-line with non-responders going on to receive a trial with lanthanum carbonate second-line.

In the comparator arm all patients were assumed to continue on calcium-based therapy until they progressed to the dialysis health state where non-responders were then able to receive lanthanum carbonate.

Clinical data were taken from the phase II study in pre-dialysis patients and supplemented with data from a phase III comparative study of lanthanum carbonate and calcium carbonate in dialysis patients and another study from the literature. Patients in the comparator arm progressed to dialysis earlier than patients in the lanthanum carbonate arm based on studies from the literature which identified a link between elevated serum phosphate levels and progression to dialysis. Mortality data by serum phosphate levels for the pre-dialysis and dialysis health states were also taken from the literature. The only resource use included in the model related to dialysis costs due to patients in the calcium-based therapy arm progressing to the dialysis health state earlier than patients in the lanthanum carbonate arm. Utility values for the pre-dialysis and dialysis health states were taken from the literature.

The results indicated that second-line use of lanthanum carbonate dominated calcium-based therapy alone with estimated savings of £118 and a QALY gain of 0.044. The results were driven by a reduced mortality risk from the additional responders to lanthanum carbonate and a reduction in costs associated with delaying progression to dialysis.

The following issues were noted:

- The clinical data used in the economic model to support the use of lanthanum carbonate were not robust. In particular, only one phase II study of pre-dialysis patients on lanthanum carbonate was available in which the primary endpoint was not significant and no comparative data were available in pre-dialysis patients or in the positioning requested by the manufacturer. In addition, a formal indirect comparison was not conducted.
- The comparator may not be appropriate as experts have indicated that patients who do not respond to first-line calcium-based treatments may be unlikely to continue on this treatment in practice. Instead, the dose of the calcium binder may be increased or patients may be switched to a non-calcium phosphate binder such as off-label sevelamer hydrochloride. However a naive indirect comparison of second-line lanthanum carbonate versus second-line sevelamer hydrochloride was provided by the manufacturer and suggested that lanthanum carbonate could be considered cost-effective.
- The response rate of second-line lanthanum carbonate used in the model was based on a very small number of patients and thus is a source of uncertainty.
- The inclusion of future dialysis costs was a key driver of the analysis. Costs relating to patients in the calcium-based therapy arm progressing to the dialysis health state earlier were included in the base case but increased dialysis costs in the lanthanum carbonate arm due to increased survival were not included. Including all dialysis costs increased the ICER to £39k per QALY. When all dialysis costs were excluded the ICER was £9k per QALY.

Due to the comparator not reflecting Scottish practice and the weaknesses with the data used in the economic model, the economic case has not been demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a guideline "Diagnosis and Management of Chronic Kidney Disease" in June 2008. Drug treatment for hyperphosphataemia is not discussed. The guideline notes that no evidence was identified to show that phosphate restriction affects the progression of CKD and recommends that serum phosphate levels should be measured in patients with stages 3 or 4 chronic kidney disease, when rechecking serum creatinine or estimated glomerular filtration rate.

The National Institute for Health and Clinical Excellence (NICE) published a guideline "Chronic Kidney Disease: National clinical guideline for early identification and management in adults in primary and secondary care" in September 2008. It does not discuss drug treatment for hyperphosphataemia, but recommends the routine measurement of phosphate levels in patients with stage 4 or 5 chronic kidney disease only, with frequency being determined by the measured values and clinical circumstances.

The United Kingdom Renal Association published Clinical Practice Guidelines in 2007, including a section on complications of chronic kidney disease. These state that serum phosphate in patients with CKD stages 3 and 4 should be maintained between 0.9 and 1.5mmol/L. Draft guidelines from 2010 do not change this recommendation.

## Additional information: comparators

Relevant comparators in pre-dialysis patients include aluminium hydroxide, calcium salts and sevelamer although it should be noted that most of these products are used off-label in pre-dialysis patients.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost Per Year (£) |
|---|---|---|
| **lanthanum carbonate** | **1.5g to 3g daily, orally** | **1,385 to 1,957** |
| sevelamer hydrochloride | 2.4g to 12g daily, orally | 716 to 3,578 |
| calcium acetate and magnesium carbonate (Osvaren®) | 3 to 12 tablets daily, orally | 146 to 582 |
| calcium acetate (Phosex®) | 3 to 12 tablets daily, orally | 120 to 480 |

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| calcium acetate (PhosLo®) | 6 to 12 capsules daily, orally | 157 to 314 |
| calcium carbonate (Calcichew Forte®) | 3 tablets daily, orally | 240 |
| aluminium hydroxide (Alu-Cap®) | 4 to 20 capsules daily, orally | 46 to 228 |
| calcium carbonate (Calcichew®) | 3 to 6 tablets daily, orally | 102 to 204 |
| calcium carbonate (Adcal®) | 3 to 6 tablets daily, orally | 79 to 158 |

Doses are for general comparison and do not imply therapeutic equivalence, and this is particularly true for these preparations which are titrated according to the individual patient's needs. Costs from eVadis between 2 and 8 July 2010.

## Additional information: budget impact

The net drug budget impact was estimated by the manufacturer to be £10k in year 1 rising to £24k in year 5. These figures assumed that treatment with lanthanum carbonate would replace existing calcium-based phosphate binders.

In year 1 it was estimated that 21 patients would be treated with lanthanum carbonate second-line based on 20% market share and 52 patients would be treated in year 5 based on 50% market share. The gross drug budget impact was estimated to be £10k in year 1 rising to £25k in year 5.

References

The undernoted reference was supplied with the submission.

Sprague SM, Abboud H, Qiu P et al. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. Clin J Am Soc Nephrol 2009; 4**:** 178–185.

This assessment is based on data submitted by the applicant company up to and including 13 August 2010

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

## *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.