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# Lanthanum Carbonate

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## Contents



## Abstract

▲ Lanthanum carbonate is a novel, non-aluminium, non-calcium phosphate binding agent that forms a water-insoluble compound, lanthanum phosphate, in the gut.

▲ Lanthanum carbonate (elemental lanthanum 375–3000 mg/day) reduced serum phosphorus levels compared with placebo in two randomised, double-blind, multicentre 4-week trials in patients with chronic renal failure receiving regular haemodialysis.

▲ In two large, randomised trials in patients with chronic renal failure requiring haemodialysis, lanthanum carbonate (elemental lanthanum 375–3000 mg/day) was as effective as calcium carbonate and/or other conventional phosphate binders in reducing and maintaining serum phosphorus levels (≤5.6 mg/dL over 6 months and ≤5.9 mg/dL over 2 years).

▲ Lanthanum carbonate was generally well tolerated. Most adverse events were mild-to-moderate in severity, with gastrointestinal events being the most common.

▲ The tolerability profile of lanthanum carbonate was similar to those of conventional phosphate binders; however, hypercalcaemic episodes occurred significantly less frequently over 6 months with lanthanum carbonate than with calcium carbonate.

▲ In a randomised 1-year trial, numerically fewer lanthanum carbonate (elemental lanthanum ≤3750 mg/day) recipients had renal bone disease at study end than at baseline; however, in the calcium carbonate ≤9000 mg/day group, numerically more patients had renal bone disease at study end compared with baseline.

| Features and properties of lanthanum carbonate (Fosrenol®) [dosages given as the amount of elemental lanthanum] | |
|---|---|
| **Indication** | |
| Hyperphosphataemia in patients with chronic renal failure requiring dialysis | |
| **Mechanism of action** | |
| Binds dietary phosphate in the gut to form lanthanum phosphate, an insoluble compound that is poorly absorbed across the gut wall | |
| **Dosage and administration** | |
| Usual dosage | 225–3000 mg/day |
| Minimum clinically effective dosage | >675 mg/day |
| Frequency of administration | Total daily dosage is divided into two or three doses. Taken with or immediately after meals |
| Route of administration | Oral |
| **Pharmacokinetic profile** | |
| Minimal systemic absorption after 6 months (375–4718 mg/day) | <0.001% of administered dose |
| Mean plasma or serum concentration after ≤2 years of treatment (225–3750 mg/day) | ≤1.1 ng/mL |
| **Adverse events** | |
| Most frequent | Gastrointestinal, e.g. nausea, vomiting and diarrhoea |

Hyperphosphataemia develops in patients with chronic renal failure as a result of reduced renal phosphate excretion.[1] Only a brief overview of hyperphosphataemia is provided here; an extensive review is available in a recent issue of *Drugs*.[1] The incidence of hyperphosphataemia has not been directly reported; however, the incidence of chronic renal failure requiring renal replacement therapy (dialysis or transplantation) is estimated to be at least 120–130 per million population in the UK.[2] In the US, the incidence of end-stage renal disease (i.e. patients with chronic renal failure requiring renal replacement therapy)[3] is approximately 334 per million population, which is expected to increase dramatically over the next 30 years.[4] **1**

An important goal in the treatment of patients with chronic renal failure is normalisation of serum phosphorus levels; hyperphosphataemia is associated with reduced serum calcium levels[1,5] that leads to secondary hyperparathyroidism,[1,6] and renal bone disease.[6] Poor serum phosphorus level control and elevated serum calcium × phosphorus product levels[1,5] may be associated with soft tissue[1,5,7] or cardiac and/or vascular[1,5] calcification. Patients with chronic renal failure taking calcium-containing oral phosphate binders may develop a positive calcium balance[5,6] that further elevates the calcium × phosphorus product levels,[5,6] which may be associated with hypercalcaemia,[6] metastatic and/or cardiac calcification[6] and also adynamic bone disease.[6] Moreover, hyperphosphataemia is associated with increased cardiovascular mortality and morbidity.[1]

Current treatment options for hyperphosphataemia include the use of oral phosphate binders (to reduce gastrointestinal absorption of dietary phosphate), lowering dietary phosphate intake, and the removal of phosphate by dialysis.[1] Patients usually require treatment with an oral phosphate binder[1] since it is difficult to decrease dietary phosphate without a significant reduction in protein intake, which increases the risk of malnutrition.[1] In addition, dialysis techniques are generally unable to remove sufficient phosphate.[7] Lanthanum carbonate (Fosrenol®)**2**, an aluminium- and calcium-free phosphate binder,[8] was investigated because of its low solubility[8] and reduced potential for adverse events associated with the use of calcium- or aluminium-containing phosphate binders.[9]

The focus of this profile is the use of lanthanum carbonate for the treatment of hyperphosphataemia in patients with chronic renal failure receiving regular haemodialysis. Lanthanum carbonate may also be an effective oral phosphate binder in patients receiving continuous ambulatory peritoneal dialysis, according to a preliminary report from a small trial (n = 10);[10] however, this patient group is not discussed further. In clinical trials, the dosage of lanthanum carbonate was generally reported as the quantity of elemental lanthanum (1907.58mg of lanthanum carbonate = 1000mg of elemental lanthanum).[11]

## 1. Pharmacodynamic Profile

All pharmacodynamic data are available as abstracts and/or posters.[11-17] Reported dosages are for lanthanum carbonate unless stated otherwise.

### Preclinical Studies

- Lanthanum carbonate [$La_2(CO_3)_3$] contains the trivalent cation lanthanum[8] that has a high affinity for phosphate.[14] *In vitro* phosphate binding studies indicated that lanthanum carbonate is 97.5%, 97.1% and 66.6% bound to phosphate at pH 3, 5 and 7, respectively, and thus has a similar phosphate-binding capacity to aluminium hydroxide.[14] Compared with calcium carbonate and calcium acetate, lanthanum carbonate binds phosphate with greater effectiveness at pH 3 (both 0% vs 97.5%) and with similar effectiveness at pH 5 (both ≈92% vs 97.1%).[14]

**1** The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US Government.

**2** The use of trade names is for product identification purposes only and does not imply endorsement.

• Lanthanum phosphate, the compound formed when phosphate binds to lanthanum,[8] has a low aqueous solubility and, according to an *in vitro* study, is poorly absorbed across the gut wall.[15] Compared with a vehicle control, lanthanum carbonate 16–31 mg/kg reduced absorption of radiolabelled phosphate across the gut wall of a rat isolated gut preparation by 23–37% after 3 hours.[15] The mean percentage absorption of phosphate after 1 hour was 50.2% with lanthanum carbonate at all doses versus 59.6% with aluminium hydroxide (dosage not reported) and 77% with control preparations.[15]

• According to an *in vivo* study in five-sixths nephrectomised rats (a model of chronic renal failure), lanthanum carbonate is as effective as aluminium hydroxide and more effective than calcium carbonate or sevelamer (all dosages 1000 mg/kg/day) in reducing urine phosphate levels.[14] Reductions in urine phosphate levels are indicative of phosphate binding potency.[14] Urine phosphate excretion after 6 weeks' treatment was broadly similar after administration of lanthanum carbonate or aluminium hydroxide (0.021 vs 0.011 mg/day) and was 8- and 18-fold lower with lanthanum carbonate than with calcium carbonate and sevelamer (0.021 vs 0.176 and 0.369 mg/day).[14]

• *In vivo* animal studies showed that lanthanum carbonate (up to 2000 mg/kg/day) had no adverse CNS or cardiovascular effects and no direct effects on calcium, vitamin D or parathyroid hormone (PTH) metabolism.[14] Moreover, the potential for acute or long-term toxicity was low in animals receiving supratherapeutic dosages of lanthanum carbonate in single- or multiple-dose studies.[13]

• In *in vivo* animal studies, lanthanum carbonate was associated with bone mineralisation defects; however, this was attributed to phosphate depletion caused by excessive dietary phosphate binding, rather than a direct effect of lanthanum on bone.[12,16,17] The effects of lanthanum carbonate on bone in patients with chronic renal failure are discussed in section 4.

### In Humans

• A study in 14 healthy volunteers demonstrated that lanthanum carbonate 9000 mg/day (elemental lanthanum 4718 mg/day) over 3 days is superior to placebo in reducing urine phosphorus levels, which indicated binding of lanthanum carbonate to phosphates in the gut and, therefore, decreased systemic absorption of phosphate.[11] The mean cumulative quantity of phosphorus excreted in the urine with lanthanum carbonate was about one-third that with placebo (858.2 vs 2447.5mg, $p < 0.05$).[11]

• Moreover, lanthanum carbonate 9000 mg/day (elemental lanthanum 4718 mg/day) did not significantly affect serum sodium, calcium, creatinine, phosphate or PTH levels, urine creatinine levels, or any ECG parameters.[11] The effect of lanthanum carbonate on phosphorus, calcium and PTH levels in patients with chronic renal failure is discussed in section 3.

## 2. Pharmacokinetic Profile

The pharmacokinetic profile of lanthanum carbonate has been evaluated in healthy volunteers[11,18-23] and patients with chronic renal failure requiring haemodialysis[18,24-29] (see sections 3 and 4). The distribution of lanthanum in tissues following lanthanum carbonate treatment[30,31] and excretion of lanthanum[30] has been investigated in animal studies. Where stated, pharmacokinetic parameters were determined using noncompartmental methods,[20,21] plasma lanthanum concentrations were measured using an inductively coupled plasma mass spectrometry assay[27,29] and oral lanthanum carbonate was administered either with[11,18,19,29] or immediately after[21,22,27] food. Most pharmacokinetic data are currently available as abstracts and/or posters.[11,18-26,28,30,31]

• Lanthanum carbonate appears to have a favourable absorption profile as an oral phosphate binder, with less than 0.001% of the administered dose absorbed systemically during up to 6 months' treatment with lanthanum carbonate (elemental lanthanum 375–4718 mg/day).[11,25] Mean plasma or serum lanthanum concentrations were very low (≤1.1

ng/mL) after up to 2 year's treatment with therapeutic dosages of lanthanum carbonate (elemental lanthanum 225–3750 mg/day).[24,26,27,29]

- Furthermore, there was no accumulation in plasma of elemental lanthanum over 2 years in recipients of standard dosages of lanthanum carbonate.[26,28] In a nonblind, comparative study, the mean plasma lanthanum concentration at 6 weeks was 0.5 ng/mL versus 0.5–0.6 ng/mL at all subsequent timepoints up to 2 years in 632 lanthanum carbonate recipients (intent-to-treat [ITT] analysis).[26] In a 2-year extension study of a 6-month trial,[25] mean serum lanthanum concentrations were 0.15–1.16 ng/mL at the start of extension treatment versus 0.15–0.8 ng/mL at the end of treatment.[28]

- There were no clinically relevant or statistically significant differences between pre- and postdialysis mean maximum plasma concentration ($C_{max}$) or area under the plasma concentration-time curve values of lanthanum following a single dose of lanthanum carbonate (elemental lanthanum 1000mg) in patients with chronic renal failure.[18] $C_{max}$ values were ≤1.1 ng/mL at both timepoints, with differences pre- and postdialysis thought to be an artefact of the dialysis process.[18]

- In healthy volunteers, tolerability of lanthanum carbonate was poor if taken before eating, thus this regimen was not evaluated further (data not reported).[23] Lanthanum carbonate can be taken during or after meals (section 5).[23]

- The elimination half-life of elemental lanthanum was about 36 hours in a multiple-dose study in healthy volunteers receiving lanthanum carbonate (elemental lanthanum 1000mg) three times daily for 5 days (n = 6).[22] Approximately 0.000031% of the dose of elemental lanthanum was recovered in the urine.[22]

- In healthy volunteers, coadministration of lanthanum carbonate with metoprolol,[21] digoxin[20] or warfarin[19] had no clinically relevant effects on the pharmacokinetic parameters of the coadministered agent.

### Lanthanum Excretion and Tissue Distribution in Animals

- An oral dose of lanthanum is eliminated via the faeces.[30] The limited amount of systemically absorbed lanthanum (simulated in rats by an intravenous administration) was also excreted in the faeces, with the majority eliminated by the biliary system.[30]

- *In vivo* studies found that a proportion of absorbed lanthanum is deposited in tissues (particularly bone and liver[30] or liver and brain[31]). Nonetheless, toxicity studies in animals indicated a low potential for toxic effects with supratherapeutic dosages of lanthanum carbonate (section 1).

- In addition, lanthanum appears to have a low potential to cross the blood-brain barrier.[30] Median lanthanum concentrations in brain tissue were 0.007–0.059 μg/g wet tissue in animals receiving lanthanum carbonate up to 2000 mg/kg/day.[30]

## 3. Therapeutic Efficacy

The efficacy of lanthanum carbonate in the treatment of hyperphosphataemia has been evaluated in short-[24,27,32] and longer-term[25,26] trials of up to 2 years' duration in patients with chronic renal failure requiring regular haemodialysis. The dosage of lanthanum carbonate was generally reported as the amount of elemental lanthanum.

Patients included in the trials had chronic renal failure requiring haemodialysis[25,32] (three times a week[24,26,27]) for at least 2–3[25-27] or ≥6[24] months prior to enrolment. Further inclusion criteria were age (≥12[26] or ≥18[25,27] years) and in one trial,[26] a serum phosphorus level of >5.9 mg/dL. Baseline patient characteristics for all randomised[26] or evaluable patients[24,25,27] (where stated) included a mean age of 53–60 years[24-27,32] and a mean time on haemodialysis of 2.5–4.3 years.[24,25,27]

Patients entered a screening and washout period of 1–3 weeks[25-27,32] or a 1- to 3-week single-blind placebo run-in period[24] followed, in all but the dose-ranging trial,[24] by a nonblind dose-titration period of 4–6 weeks.[25-27,32]

Primary efficacy endpoints included serum phosphorus levels[27,32] or the reduction in serum phosphorus levels[24] at endpoint. The primary endpoint was not clearly specified in one of the longer-term studies,[25] although the main aim of the study was to assess serum phosphorus level control (defined as a level of ≤5.6 mg/dL) during the dose-titration and maintenance periods. Tolerability was the primary endpoint of the other longer-term study.[26] Other measures of efficacy included serum phosphorus level control[24,26,27,32] (defined as a level of ≤5.9[26,27] or ≤5.6[32] mg/dL), the time at which a significant reduction in serum phosphorus levels was first achieved[24] and changes in serum calcium levels,[26,27,32] calcium × phosphorus product levels,[24,26,27,32] PTH levels[26,27,32] and calcium × phosphate product levels.[25] Where reported, ITT analyses were conducted,[25-27,32] unless stated otherwise.

## Short-Term Therapy

The efficacy of lanthanum carbonate has been evaluated in three randomised, double-blind, placebo-controlled trials of 4–6-weeks' duration: a dose-ranging trial (n = 144);[24] a multicentre phase III trial (n = 93);[27] and a trial in Chinese patients (n = 61).[32] Data from two of the trials are available as abstracts plus posters.[24,32]

In the dose-ranging trial,[24] patients with a serum phosphorus level of ≥5.6 mg/dL were randomised to receive placebo or lanthanum carbonate (elemental lanthanum 225, 675, 1350 or 2250 mg/day) for 6 weeks following the placebo run-in period.

In the other two trials,[27,32] only patients with a serum phosphorus level of >5.9[27] or >5.6[32] mg/dL entered the 4-[32] or 6-week[27] dose-titration period where the dosage of lanthanum carbonate (elemental lanthanum 375–3000[27] or 750–3000 mg/day[32]) required to achieve serum phosphorus level control (≤5.9[27] or ≤5.6[32] mg/dL) was established on an individual basis. Thereafter, patients were randomised to receive either placebo (n = 31[32] and 44[27]) or their maintenance doses of lanthanum carbonate (n = 30[32] and 49[27]) for the 4-week[27,32] dose-maintenance double-blind phase. The maintenance dosages of elemental lanthanum in the 6-week phase III trial[27] were ≥750 (9% of patients), 1500 (20%), 2250 (29%) and 3000 mg/day (42%).

Between 52% and 69% of patients completed randomised treatment.[24,27,32] A proportion of lanthanum carbonate and placebo recipients received vitamin D supplementation during the 4-week dose-maintenance period of the phase III trial (26% vs 18% of patients).[27]

### *Serum Phosphorus Levels and Control*

- In short-term studies, lanthanum carbonate was significantly more effective than placebo at improving hyperphosphataemia in patients with chronic renal failure.[24,27,32]
- In the dose-ranging trial,[24] reductions in serum phosphorus levels were significantly greater with the two highest dosages of lanthanum carbonate (elemental lanthanum 1350 mg/day [−0.95 mg/dL; n = 30] or 2250 mg/day [−1.13 mg/dL; n = 26]) than with placebo (n = 32) [both $p < 0.001$ vs placebo].[24] Serum phosphorus levels were similar in all treatment groups at baseline (6.55–7.42 mg/dL) and reported reductions were from baseline to the end of the double-blind treatment period.[24] Lanthanum carbonate was clinically effective at dosages exceeding elemental lanthanum 675 mg/day.[24] Reductions in serum phosphorus levels were dose-related (linear up to 1350 mg/day).[24]
- Mean serum phosphorus levels were significantly lower at endpoint with lanthanum carbonate (elemental lanthanum 375–3000[27] or 750–3000 mg/day[32]) than with placebo (5.1 vs 7.2 mg/dL; $p < 0.001$[32] and 5.94 vs 7.85 mg/dL; $p < 0.0001$[27]) in the other two trials.[27,32] In addition, there was a significant difference in serum phosphorus levels favouring lanthanum carbonate versus placebo recipients at all timepoints during the randomised period of the phase III trial ($p < 0.01$).[27]
- Lanthanum carbonate effectively maintains serum phosphorus level control.[27,32] More patients receiving lanthanum carbonate achieved serum phosphorus level control at study end than patients receiving placebo, in the phase III trial[27] (59% vs 23%; values estimated from graph, $p < 0.01$) and the trial in Chinese patients[27] (60% vs 10%, $p < 0.001$).

• Lanthanum carbonate was effective in reducing serum phosphorus levels early in treatment.[24,27] Significant reductions in mean serum phosphorus levels occurred with lanthanum carbonate treatment in the first week (with elemental lanthanum 2250 mg/day) or second week (with elemental lanthanum 1350 mg/day) in the dose-ranging trial ($p < 0.05$),[24] and in the first week of the dose-titration period in the phase III trial (7.15 vs 7.55 mg/dL at the end of the washout period, $p < 0.0001$).[27]

### *Other Endpoints*

• Lanthanum carbonate also proved beneficial in terms of other endpoints in the phase III trial (figure 1).[27] Patients receiving lanthanum carbonate achieved significantly lower mean serum calcium × phosphorus product and PTH levels than placebo recipients at study end compared with the dose-titration period (baseline) [$p < 0.01$].[27] From baseline to endpoint, mean serum calcium, calcium × phosphorus product and PTH levels remained stable in the lanthanum carbonate group, but either decreased (serum calcium level) or increased (calcium × phosphorus product and PTH levels) significantly in placebo recipients (all $p < 0.05$).[27]

• Improvements in serum calcium × phosphorus product levels were also shown in the other two trials.[24,32] Mean serum calcium × phosphorus product levels were significantly lower with lanthanum carbonate than with placebo at study end (49 vs 67 $mg^2/dL^2$; values estimated from graph, $p < 0.001$) in one trial.[32] These levels decreased from baseline to endpoint in lanthanum carbonate recipients (elemental lanthanum 1350 mg/day) [−7.2 mg/dL, $p < 0.005$] and increased in patients receiving placebo (8.4 mg/dL, $p < 0.001$) or the lowest dosage of lanthanum carbonate (elemental lanthanum 225 mg/day) [8.0 mg/dL, $p < 0.005$], in the dose-ranging trial.[24]

• Moreover, the mean serum PTH and calcium levels were similar between the lanthanum carbonate and placebo groups during the dose-maintenance phase of the trial in Chinese patients.[32]

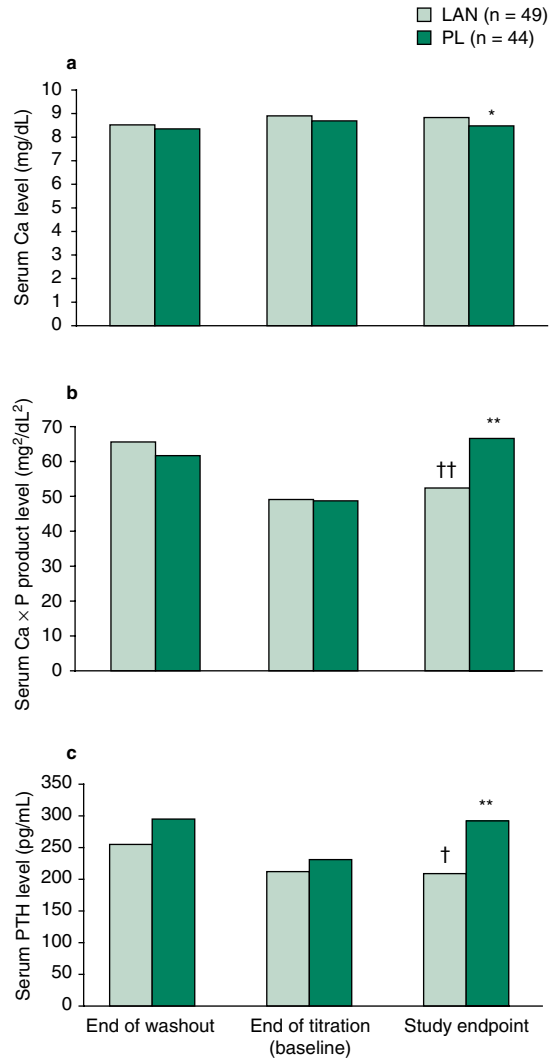


**Fig. 1.** Efficacy of lanthanum carbonate (LAN) on secondary endpoints in patients with hyperphosphataemia. Mean serum (**a**) calcium (Ca), (**b**) calcium × phosphorus (Ca × P) product and (**c**) parathyroid hormone (PTH) levels at various timepoints. This randomised, double-blind, placebo (PL)-controlled, multicentre phase III trial enrolled patients aged ≥18 years with chronic renal failure requiring regular haemodialysis for a minimum of the previous 2 months.[27] Patients entered a washout period of 1–3 weeks and those patients with a serum phosphorus level of >5.9 mg/dL then entered a nonblind dose-titration period of 6 weeks, where the dose required to achieve serum phosphorus level control (≤5.9 mg/dL) was established on an individual basis. Thereafter, patients were randomised to receive PL or LAN (elemental lanthanum 375–3000 mg/day) with meals, for the double-blind dose-maintenance 4-week phase. Intent-to-treat analysis was conducted. * $p < 0.05$, ** $p < 0.0001$ vs end of titration (baseline); † $p < 0.01$, †† $p < 0.0001$ vs PL at study end.

## Longer-Term Therapy

The longer-term efficacy of lanthanum carbonate has been evaluated in two randomised, nonblind, multicentre trials.[25,26] The 6-month trial compared the efficacy of lanthanum carbonate (n = 510) with that of calcium carbonate 1500–9000 mg/day (n = 257).[25] In the 2-year trial,[26] patients received lanthanum carbonate (n = 632) or their pre-study conventional phosphate binder (n = 633), which was either calcium carbonate (33.5% of 642 randomised patients), calcium acetate (44.9%), sevelamer (16.4%) or other (5.0%) [study drug not reported for 0.3% of patients].

In the 6-month nonblind trial,[25] only patients with a serum phosphorus level of >5.6 mg/dL entered the dose-titration period, where the dose required to achieve serum phosphorus level control (≤5.6 mg/dL) was established on an individual basis; median dosages were elemental lanthanum 2250 mg/day and calcium carbonate 3000 mg/day.[25] Following dose-titration, patients continued therapy for a further 20 weeks[25] or up to a total of 104 weeks[26] during the dose-maintenance phase of each trial.

Preliminary long-term data are also available from nonblind extension studies of the dose-ranging trial[24] (up to 48-week extension),[33] the 6-month phase III trial[25] (a 6-month extension[34] and a further 2-year extension [giving a total of 3 years' treatment][28]) and both the dose-ranging[24] and the placebo-controlled phase III trial[27] (≈12-month extension[35] including patients from both trials[24,27]). An additional analysis[36] of efficacy data from a 6-month trial[25] and its 6-month extension[34] is included.

Efficacy data from a 1-year study (see section 4)[29] of renal osteodystrophy in patients receiving lanthanum carbonate or calcium carbonate are also discussed.

In the longer-term trials[25,26,29] and extension studies,[28,33-35] patients received elemental lanthanum 300–3000[25,26,28,33-35] or ≤3750[29] mg/day, administered as lanthanum carbonate. All data are currently available as abstracts and/or posters.[25,26,28,33-37]

### *Serum Phosphorus Levels and Control*

- Longer-term treatment with lanthanum carbonate is as effective as conventional phosphate binder therapy,[26] including calcium carbonate,[25,37] in improving hyperphosphataemia in patients with chronic renal failure.
- Mean serum phosphorus levels were similar in the lanthanum carbonate and calcium carbonate groups at endpoint in the 6-month trial (each ≈5.3 mg/dL, values estimated from graph)[25] and in the lanthanum carbonate and conventional phosphate binder groups at week 52 in the 2-year trial (6.3 vs 6.2 mg/dL).[26]
- Lanthanum carbonate was as effective as conventional phosphate binders[26] and calcium carbonate[25] in maintaining serum phosphorus level control. Similar proportions of lanthanum carbonate and calcium carbonate recipients had serum phosphorus control from weeks 9 to 25 of the 6-month study[25] according to an on-treatment (OT) analysis (figure 2). In the 2-year trial,[26] mean serum phosphorus levels were maintained at ≤5.9 mg/dL from weeks 16 to 104 in a similar proportion of lanthanum carbonate recipients as conventional phosphate binder recipients (41.3% vs 46.3% at 2 years).
- The longer-term efficacy of lanthanum carbonate was confirmed in several nonblind extension studies.[28,33-35] In general, lanthanum carbonate (elemental lanthanum 300–3000 mg/day) effectively maintained serum phosphorus level control (≤5.6–6.0 mg/dL) for up to 52 weeks (n = 518,[34] n = 77[35] and n = 40[33]) and for up to 2 years (n = 83 [OT analysis]).[28] Out of a subgroup of 45 patients who had received lanthanum carbonate treatment for ≥152 weeks, 31 patients had serum phosphorus level control at study end in the 2-year extension study (OT analysis).[28]

### *Other Endpoints*

- Generally, mean serum calcium and calcium × phosphorus product levels remained stable and were similar in patients receiving lanthanum carbonate or conventional phosphate binders (including calcium carbonate[37]) during treatment of up to 1 years' duration.[26,37] For example, at week 52 in the 2-year trial, mean serum calcium levels were 9.2 versus 9.5

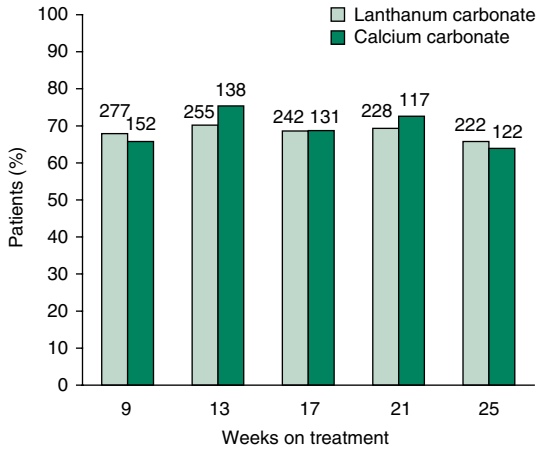


**Fig. 2.** Comparative efficacy of lanthanum carbonate in patients with hyperphosphataemia. Percentage of patients with a mean serum phosphorus level ≤5.6 mg/dL. This randomised, nonblind, multicentre, phase III trial enrolled patients with chronic renal failure aged ≥18 years who had received regular haemodialysis for the previous 3 months.[25] After a 1- to 3-week washout period, patients with serum phosphorus levels >5.6 mg/dL were randomised to receive lanthanum carbonate (elemental lanthanum 375–3000 mg/day) or calcium carbonate 1500–9000 mg/day during a 5-week dose-titration period, followed by a maintenance period of 20 weeks. The number above the bar is the number of evaluable patients at each timepoint.

mg/dL and mean serum calcium × phosphorus product levels were 57.8 versus 59 $mg^2/dL^2$ in lanthanum carbonate and conventional phosphate binder recipients (all values estimated from a graph).[26]

- Moreover, in the 6-month trial,[25] significantly greater reductions in mean serum calcium × phosphate product levels with lanthanum carbonate than with calcium carbonate occurred only at week 9 (−22.3 vs −16.7 $mg^2/dL^2$, p = 0.009).[25]

- Mean[26] or median[36] serum PTH levels remained stable[26] or showed a numerical increase[36] with lanthanum carbonate treatment of up to 1 year, whereas levels showed a numerical decrease with calcium carbonate[36] and/other conventional phosphate binders.[26] For example, mean serum PTH levels remained stable over 1 year (data from second year not reported) in the 2-year trial; lanthanum carbonate recipients and conventional phosphate binder recipients had mean serum PTH levels of 281.5 and 220 pg/mL at 52 weeks (all values estimated from a graph).[26]

## 4. Tolerability

The tolerability of oral lanthanum carbonate in the treatment of patients with hyperphosphataemia was evaluated in clinical trials[24-27,32] and extension studies[28,33-35] discussed in section 3. In addition, a 1-year, randomised, nonblind, multicentre, phase III trial[29] compared the effect of lanthanum carbonate (elemental lanthanum ≤3750 mg/day) with that of calcium carbonate ≤9000 mg/day on renal osteodystrophy in patients with chronic renal failure. Apart from two trials,[27,29] all data are available as abstracts and/or posters.[24,26,28,32-35]

Where stated, analysis of tolerability data was conducted either for the ITT,[25,27,32] OT[29] or randomised[26] patient populations. Statistical analyses of tolerability data were generally not described.[24,26-29,32-35]

### Short-Term Trials

- Lanthanum carbonate has a broadly similar tolerability profile to that of placebo,[24,27,32] with treatment-emergent adverse events generally of a gastrointestinal nature[24,27] and of mild or moderate severity.[32]

- Treatment-related nausea, vomiting, constipation and diarrhoea were each reported by 5–11 patients during the dose-titration period in the phase III trial when all patients received lanthanum carbonate (n = 126).[27] During the 4-week dose-maintenance phase, treatment-related adverse events were uncommon.[27] The most common of these (nausea, vomiting, diarrhoea and dialysis graft occlusion) each occurred with an incidence of <2% in the placebo (n = 44) and lanthanum carbonate (n = 50) groups.[27]

- Moreover, treatment was discontinued because of adverse events in seven patients during dose titration (all drug-related events) and in three patients during the dose-maintenance period (whether these were drug related was not reported).[27]

- In the trial in Chinese patients,[32] the most frequent treatment-emergent adverse events during the randomised double-blind phase were myalgia, coughing, hypotension, dizziness, vomiting and rhi-

nitis, each occurring in 2–5 of the 30 patients receiving lanthanum carbonate and in 0–4 of the 31 patients receiving placebo. Those adverse events leading to withdrawal from the study were of a gastrointestinal nature (number of adverse events leading to withdrawal not reported).[32]

- The overall incidence of treatment-emergent adverse events that may or may not have been drug-related was numerically greater with lanthanum carbonate than with placebo (58% vs 38.6% in the phase III trial[27] and 97% vs 90% in the trial in Chinese patients[32]).
- Serious adverse events were uncommon (n = 4 in each of the placebo and treatment groups) and thought not to be drug-related in the dose-maintenance phase of the phase III trial,[27] although 12.7% of patients reported serious adverse events during the dose-titration period.[27] Whether these latter events were related to lanthanum carbonate treatment was not reported.[27] Three deaths were reported and none were considered drug-related.[27] The only serious adverse event reported in the trial in Chinese patients[32] was not considered to be drug-related.

### Longer-Term Trials

- Lanthanum carbonate has a generally similar tolerability profile to calcium carbonate[25] and/or other conventional phosphate binders.[26] As occurred in short-term trials, the most common treatment-emergent adverse events associated with up to 2 years' treatment with lanthanum carbonate were of a gastrointestinal nature.[25,26,28,33-35]
- In the 6-month trial,[25] the overall incidence of treatment-emergent adverse events was approximately 78% in both lanthanum carbonate (n = 533) and calcium carbonate (n = 257) treatment groups, with vomiting (18.4% vs 11.2%), nausea (15.9% vs 12.7%) and diarrhoea (12.6% vs 9.7%) the most frequently reported adverse events. Treatment-emergent adverse events occurring in 5–10% of patients in either treatment group were hypotension, headache, dialysis graft occlusion, constipation, cramps, bronchitis and rhinitis, with most of these being of a mild-to-moderate nature.[25]
- The most common treatment-emergent adverse events in the 2-year trial[26] in patients receiving lanthanum carbonate were nausea, vomiting, dialysis graft complication, diarrhoea, dizziness and dyspnoea (figure 3).[26] Adjusted tolerability data are presented since patients receiving conventional phosphate binders had a longer duration of treatment than lanthanum carbonate recipients (422 vs 304 days) [method of data adjustment was not reported].[26]
- Moreover, drug-related adverse events occurred in 21.2% of lanthanum carbonate recipients versus 9.1% of conventional phosphate binder therapy recipients (exposure-adjusted data). The severity and nature of these events was not reported.[26]
- Serious adverse events occurred in 21.4% of patients receiving lanthanum carbonate compared with 30.0% of patients receiving calcium carbonate in the 6-month trial.[25] The nature of these adverse events and their relationship to the drug were not reported.[25]
- The incidence of serious treatment-emergent adverse events in the 2-year trial[26] was 51% in the lanthanum carbonate group versus 47.1% in the conventional phosphate binder group (exposure-adjusted data). These events were renal transplant (6.5% vs 6.6% with conventional phosphate binders), dialysis graft occlusion (6.5% vs 5.6%), myocardial infarction (3.6% vs 4.0%), pneumonia (3.2% vs 4.0%) and cardiac failure (3.2% vs 4.2%).[26] Whether these events were drug related was not reported.[26]
- In a 2-year extension study[28] of the 6-month extension study[34] of the 6-month trial,[25] the majority of treatment-emergent adverse events were of mild or moderate severity. Drug-related adverse events occurred in 23% of patients with between 2 and 6 of the 161 patients experiencing each of the the following drug-related adverse events: diarrhoea, abdominal pain, nausea, constipation, eosinophilia, dyspepsia, hyperparathyroidism (aggravated), myalgia and tooth disorder.[28]

#### *Other Adverse Effects*

- In the 1-year phase III trial[29] on the effect of treatment on the evolution of renal bone disease in

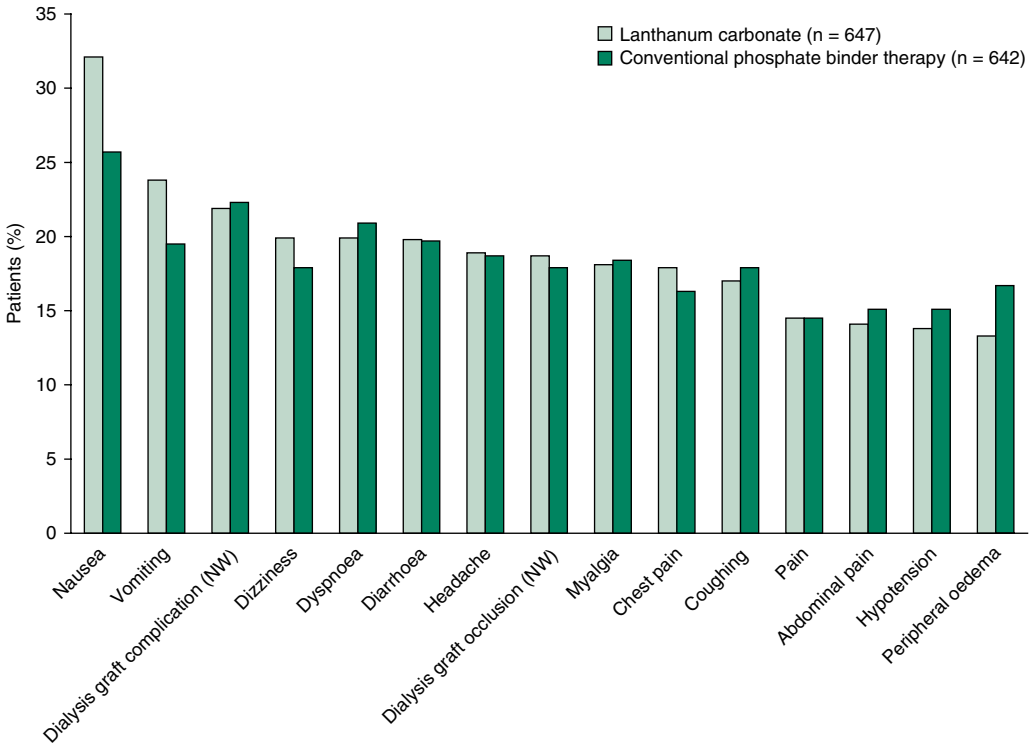


**Fig. 3.** Comparative tolerability of long-term treatment with lanthanum carbonate in patients with hyperphosphataemia. The most frequent treatment-emergent adverse events (occurring in >20% in either treatment group, prior to data adjustment for exposure) in a 2-year, randomised, nonblind, multicentre trial are shown.[26] Data from the conventional phosphate binder group were adjusted for the duration of treatment since these patients received treatment for 422 days compared with 304 days for patients receiving lanthanum carbonate. Patients aged ≥12 years with chronic renal failure requiring haemodialysis three times a week (for at least the previous 2 months) with a serum phosphorus level of >5.9 mg/dL were enrolled in the trial. Patients entered a 1- to 3-week screening and washout period followed by a 6-week dose-titration period where patients were randomised to receive lanthanum carbonate (elemental lanthanum 375–3000 mg/day) or their pre-study conventional phosphate binder treatment (calcium carbonate, calcium acetate or sevelamer). A long-term maintenance period followed, giving a total trial duration of up to 2 years. Criteria for defining adverse events were not reported. All randomised patients were included in the analysis of tolerability data. Data available as abstract and poster. **NW** = Non-WHO-Adverse Reaction Terminology.

patients with chronic renal failure, fewer lanthanum carbonate recipients (n = 33) had renal bone disease (either adynamic bone disease, osteomalacia or hyperparathyroidism) at study end than at baseline (6 vs 12 patients); in contrast, in the calcium carbonate group, 16 of 30 patients had renal bone disease at study end compared with 13 patients at baseline (primary endpoint was tolerability) [no statistical analysis reported]. Also, of the patients with normal or increased bone turnover at baseline, six patients in the calcium carbonate group (n = 23) compared with one patient in the lanthanum carbonate group (n = 26) had developed adynamic bone disease by study end.[29]

- In addition, there was no accumulation of lanthanum in bone over the study period in lanthanum carbonate recipients in this study (median bone concentration at study end 1.8 μg/g; baseline value not reported).[29]

- Furthermore, hypercalcaemia (serum calcium >10.6 mg/dL) occurred in 49% of calcium carbonate recipients, but in only 6% of lanthanum carbonate recipients in the 1-year trial.[29] In the 6-month trial,[25] hypercalcaemia was reported in 50-fold more patients treated with calcium carbonate than with lanthanum carbonate (20.2% vs 0.4%).[25] The respective incidence of hypercalcaemic episodes (a

serum calcium level of >10.4 mg/dL) was approximately 40% versus 6% ($p < 0.001$).[25]

## 5. Dosage and Administration

Formal dosage recommendations for lanthanum carbonate are not yet available. Nonetheless, in most clinical trials,[25,27,29] dosages of elemental lanthanum 375 or 750 mg/day were used at initiation of treatment and did not exceed 3000 mg/day during treatment. Lanthanum carbonate is clinically effective at elemental lanthanum dosages >675 mg/day.[24] Modal dosages were generally not reported; however, most patients (≈70%) in the placebo-controlled phase III trial[27] and the trial in Chinese patients[32] received elemental lanthanum 2250–3000[27] or 1500–2500[32] mg/day. The maximum tolerated dose is yet to be defined.

Lanthanum carbonate is administered orally as chewable tablets.[27] In clinical trials, lanthanum carbonate tablets contained elemental lanthanum 125, 250[25,27,32] or 500mg.[32]

As with other phosphate binders,[1] lanthanum carbonate is administered at meal times, either with[11,18,19,29] or immediately after food;[21,22,27] thus, the daily dose is divided between two or three meals.[27]

## 6. Lanthanum Carbonate: Current Status

In the treatment of hyperphosphataemia in patients with chronic renal failure requiring haemodialysis, lanthanum carbonate was as effective as calcium carbonate and other conventional phosphate binding agents during longer-term trials and more effective than placebo during short-term trials. This novel phosphate binder was generally well tolerated, with recipients experiencing significantly fewer hypercalcaemic episodes than those receiving calcium carbonate. Sweden is the first EU country to grant approval for lanthanum carbonate[38] and approval is currently being sought in the US and Canada.[39]

## References


1. Albaaj F, Hutchison A. Hyperphosphataemia in renal failure: causes, consequences and current management. Drugs 2003; 63 (6): 577-96
2. The Renal Association. Treatment of adults and children with renal failure [online]. Available from URL: http://www.renal.org/Standards/RenalStandSumm02.pdf [Accessed 2003 Aug 5]
3. National Kidney Foundation. NKF K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification [online]. Available from URL: http://www.kidney.org/professionals/doqi/kdoqi/toc.htm [Accessed 2003 Sep 1]
4. U.S. Renal Data System. USRDS 2003 Annual Data Report: Atlas of end-stage renal disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD [online]. Available from URL: http://www.usrds.org/adr.htm [Accessed 2003 Sep 1]
5. Levin NW, Hoenich NA. Consequences of hyperphosphatemia and elevated levels of the calcium-phosphorus product in dialysis patients. Curr Opin Nephrol Hypertens 2001 Sep; 10 (5): 563-8
6. Malluche HH, Mawad H. Management of hyperphosphataemia of chronic kidney disease: lessons from the past and future directions. Nephrol Dial Transplant 2002 Jul; 17 (7): 1170-5
7. Indridason OS, Quarles LD. Hyperphosphatemia in end-stage renal disease. Adv Ren Replace Ther 2002 Jul; 9 (3): 184-92
8. Locatelli F, D'Amico M. Lanthanum carbonate AnorMED. Curr Opin Cardiovasc Pulmon Renal Invest Drugs 2000; 2 (4): 372-7
9. Loghman-Adham M. Safety of new phosphate binders for chronic renal failure [published erratum appears in Drug Saf 2004; 27(3): 213]. Drug Saf 2003; 26 (15): 1093-115
10. Hutchison AJ, Speake M, Dewberry K, et al. Lanthanum carbonate: a novel non-calcium-containing phosphate binder in CAPD patients [abstract no. O]. Perit Dial Int 1998; 18 Suppl. 2: S38
11. Stewart J. Administration of a novel phosphate binder, Fosrenol™, with food is associated with good tolerability and low systemic absorption [abstract no. SAP0601]. J Am Soc Nephrol 2002; 13 Suppl.: 386A. Plus poster presented at the 35th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2002 Nov 1-4; Philadelphia
12. Behets GJ, Bervoets A, Oste L, et al. Time course and reversibility of the mineralisation defect induced by lanthanum carbonate in chronic renal failure rats [abstract no. F-PO657]. J Am Soc Nephrol 2003 Nov; 14 Suppl.: 205A
13. Damment SJP, Greaves P, Downes N. The toxicology of lanthanum carbonate (Fosrenol®), a new non-aluminum, non-calcium phosphate binder [abstract no. F-PO651]. J Am Soc Nephrol 2003 Nov; 14 Suppl.: 204A. Plus poster presented at the 36th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2003 Nov 14-17; San Diego
14. Damment SJP, Totten W. The pharmacology of a new phosphate binder, lanthanum carbonate [abstract no. W429]. Nephrol Dial Transplant 2003; 18 Suppl. 4: 683. Plus poster presented at the 40th ERA-EDTA World Congress of Nephrology; 2003 Jun 8-12; Berlin
15. Dewberry K, Fox JS, Curtis CG, et al. Lanthanum carbonate an effective inhibitor of phosphate absorption from the intestinal tract [abstract]. Nephrol Dial Transplant 1997; 12 (9): A98

16. Behets G, Bervoets A, Dams G, et al. Effects of lanthanum and strontium on osteoblasts in chronic renal failure rats [abstract no. W430]. Nephrol Dial Transplant 2003; 18 Suppl. 4: 683

17. Damment S, Shen V, Webster I. Phosphate supplementation normalizes changes in bone mineralization in uraemic rats given high doses of lanthanum carbonate [abstract no. W431]. Nephrol Dial Transplant 2003; 18 Suppl. 4: 684

18. Sack M. Fosrenol™ (lanthanum carbonate) is well tolerated in patients requiring hemodialysis: results of a phase I clinical trial [abstract no. SA-P0602]. J Am Soc Nephrol 2002; 13 Suppl.: 386A. Plus poster presented at the 35th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2002 Nov 1-4; Philadelphia

19. Fiddler G, Webster I. Lanthanum carbonate does not affect the pharmacokinetics of warfarin [abstract no. 25]. Am J Kidney Dis 2003 Apr; 41 (4): A18

20. Fiddler G, Taubel J. Lanthanum carbonate (Fosrenol™) does not affect the pharmacokinetics of concomitant treatment with digoxin [abstract no. 26]. Am J Kidney Dis 2003 Apr; 41 (4): A18

21. Fiddler G, Täubel J. No pharmacokinetic interaction between lanthanum carbonate and metoprolol [abstract no. 27]. Am J Kidney Dis 2003 Apr; 41 (4): A18

22. Fiddler G, Tanaka T, Webster I. Low systemic absorption and excellent tolerability during administration of lanthanum carbonate (Fosrenol™) for 5 days [poster]. 9th Asian Pacific Congress of Nephrology; 2003 Feb 16-20; Pattaya, Thailand

23. Stewart AJ. Fosrenol™ – a novel non-calcium, non-aluminium phosphate binder – is well tolerated when given during or after food intake [abstract no. PUB397]. J Am Soc Nephrol 2002; 13 Suppl.: 751A

24. Finn W, Joy M, Webster I, et al. Lanthanum carbonate (Fosrenol™) causes significant reductions in serum phosphorus and Ca × P product in a dose-ranging, placebo-controlled study [abstract no. W437]. Nephrol Dial Transplant 2003; 18 Suppl. 4: 686. Plus poster presented at the 40th ERA-EDTA World Congress of Nephrology; 2003 Jun 8-12; Berlin

25. Hutchison AJ. The novel, non-aluminium, non-calcium phosphate binder, lanthanum carbonate (Fosrenol™), is an effective treatment for hyperphosphataemia and has a good safety profile [abstract no. SA-P0599]. J Am Soc Nephrol 2002 Nov 1; 13 Suppl.: 385A-6A. Plus poster presented at the 35th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2002 Nov 1-4; Philadelphia

26. Finn WF, Joy MS, Webster I. Lanthanum carbonate vs. standard therapy in hyperphosphatemia: interim findings from a 2-year safety and outcomes study [abstract no. SU-PO1040]. J Am Soc Nephrol 2003 Nov; 14 Suppl.: 764A. Plus poster presented at the 36th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2003 Nov 14-17; San Diego

27. Joy MS, Finn WF, 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 hyperphosphatemia. Am J Kidney Dis 2003 Jul; 42 (1): 96-107

28. Hutchison A, Webster I. Maintained safety, tolerability and efficacy of lanthanum carbonate (Fosrenol®) during long-term therapy in hemodialysis patients [abstract no. SU-PO1039]. J Am Soc Nephrol 2003 Nov; 14 Suppl.: 764A. Plus poster presented at the 36th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2003 Nov 14-17; San Diego

29. 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 2003 Jun; 63 Suppl. 85: S73-8

30. Damment S, Pennick M, Gill M. The pharmacokinetics of a new non-aluminium, non-calcium phosphate binder, lanthanum carbonate (Fosrenol®) [abstract no. 141]. Am J Nephrol 2004; 24 (1): 106

31. Sacchiero R, Berlove D, Brezzani A, et al. Lanthanum deposition in tissues of renal compromised rats fed lanthanum carbonate for 28 days [abstract no. F-PO658]. J Am Soc Nephrol 2003 Nov; 14 Suppl.: 205A

32. Yang W-C, Chiang S-S, Chen J-B. Efficacy and safety of lanthanum carbonate in the treatment of hyperphosphatemia in Chinese chronic renal failure patients [abstract no. F-PO652]. J Am Soc Nephrol 2003 Nov; 14 Suppl.: 204A. Plus poster presented at the 36th Annual Meeting and Scientific Exposition of the American Society of Nephrology; 2003 Nov 14-17; San Diego

33. Joy MS, Fiddler G, Finn WF, et al. Long-term safety, tolerability and efficacy of lanthanum carbonate in haemodialysis patients: an extension study to a phase II trial [abstract no. W435]. Nephrol Dial Transplant 2003; 18 Suppl.: 685. Plus poster presented at the 40th ERA-EDTA World Congress of Nephrology; 2003 Jun 8-12; Berlin

34. Hutchison A, Webster I, Gill M, et al. Safety and tolerability of lanthanum carbonate in haemodialysis patients: a 12-month study [abstract no. W432]. Nephrol Dial Transplant 2003; 18 Suppl.: 684. Plus poster presented at the 40th ERA-EDTA World Congress of Nephrology; 2003 Jun 8-12; Berlin

35. Finn WF, Joy MS, Webster I, et al. Long-term treatment with lanthanum carbonate (Fosrenol™) is safe and effective in haemodialysis patients [abstract no. W434]. Nephrol Dial Transplant 2003; 18 Suppl.: 685. Plus poster presented at the 40th ERA-EDTA World Congress of Nephrology; 2003 Jun 8-12; Berlin

36. Hutchison A, Al-Baaj F, Webster I, et al. Lanthanum carbonate versus calcium carbonate: effect on parathyroid hormone levels [abstract no. 177]. Am J Nephrol 2004; 24 (1): 119-20

37. Torres A, De Broe ME, D'Haese PC, et al. A 1-year study comparing the safety and efficacy of lanthanum carbonate (Fosrenol®) and calcium carbonate in dialysis patients [abstract no. 138]. Am J Nephrol 2004; 24 (1): 105

38. Shire Pharmaceuticals Group plc. First global approval for Fosrenol® (lanthanum carbonate) [media release]. 2004 March 24

39. Shire Pharmaceuticals Group plc. Shire receives approvable letter from FDA for Fosrenol®; positive step for treatment related to kidney disease in the United States [online]. Available from URL: http://www.shire.com [Accessed 2003 Jul 18]

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