National PBM Drug Monograph
Lanthanum Carbonate (Fosrenol®)

VHA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Executive Summary

- **Indications:** Lanthanum carbonate (Fosrenol®) is a non-calcium, non-aluminum gastrointestinal phosphate binder, approved by the FDA to reduce serum phosphate in patients with end-stage renal disease (ESRD).

- **Efficacy:** In a randomized controlled trial of lanthanum carbonate for 6 weeks in patients with ESRD on hemodialysis (HD), treatment was reported to reduce serum phosphorus by 0.95 ± 1.39 mg/dL and 1.13 ± 2.01 mg/dL with daily doses of 1350 mg and 2250 mg, respectively, a difference that was statistically significant compared to placebo (P<0.001). In the lanthanum carbonate treatment group, approximately 45% of patients achieved serum phosphorus levels of ≤ 5.5 mg/dL, compared to less than 10% of patients on placebo. Another randomized controlled trial of 4 weeks duration (after 6 weeks titration) in patients with ESRD on hemodialysis, reported that 65% of patients on lanthanum carbonate achieved control serum phosphorus of ≤ 5.9 mg/dL, compared to 38% of patients receiving placebo (ARR 27%, NNT=4 patients to achieve serum phosphorus ≤ 5.9 mg/dL with 4 weeks treatment lanthanum carbonate). The mean difference in serum phosphorus with lanthanum carbonate of 1.91 mg/dL was statistically significant (P<0.0001) compared to placebo. The mean treatment difference in calcium phosphorus product (Ca X P) at the end of the treatment phase was statistically significant between lanthanum carbonate and placebo (P<0.0001). Results of a 4-week, double-blind, placebo-controlled follow-up after open-label titration with lanthanum carbonate reported that lanthanum carbonate maintained control serum phosphate (4.03-5.58 mg/dL) compared to placebo in patients on HD or continuous ambulatory peritoneal dialysis (CAPD) (64.7% lanthanum carbonate vs. 21.4% placebo; P=0.016). The mean serum phosphate at the end of treatment with lanthanum carbonate was statistically significant compared to placebo (4.84±0.93 mg/dL vs. 6.29±0.96 mg/dL, respectively; P<0.001).

- **Safety:** The most frequently reported adverse events in patients taking lanthanum carbonate are gastrointestinal, that usually resolved with continued dosing. Nausea and vomiting occurred in 11% and 9% of patients on lanthanum carbonate compared to 5% and 4% of patients on placebo, respectively. In two long-term (6 months and 2 years) studies comparing lanthanum carbonate to alternate therapy, drug therapy with lanthanum carbonate was discontinued in 14% of patients due to adverse events. Nausea, diarrhea, and vomiting were the most common adverse events resulting in discontinuation of therapy. Lanthanum carbonate should be used with caution in patients with acute peptic ulcer, ulcerative colitis, Crohn's disease, or bowel obstruction, as these patients were not included in the clinical trials with lanthanum carbonate. It is recommended that medications known to interact with antacids not be taken within 2 hours of lanthanum carbonate. Lanthanum carbonate is not metabolized and is not a substrate or inhibitor of the cytochrome P450 enzymes. The extent and potential adverse consequences of lanthanum accumulation in the organs of humans with kidney disease who receive oral lanthanum supplements is unknown.

- **Laboratory monitoring:** It is recommended that serum phosphate levels be monitored as needed during dose titration and regularly once maintenance dose is achieved.

- **Dose:** The initial recommended total daily dose of lanthanum carbonate is 750 mg to 1500 mg, with dose titration every two to three weeks until desirable phosphate level is achieved. Doses in clinical trials were generally increased in increments of 750 mg per day. A total daily dose of 1500 mg to 3000 mg per day will be required in most patients to reduce serum phosphate levels to less than 6mg/dL. Doses up to 3750mg per day were evaluated in patients with ESRD. The total daily dose of lanthanum should be divided and taken with or immediately after meals. Lanthanum carbonate is available in 250mg and 500mg chewable tablets and should be chewed thoroughly before swallowing. The tablets do not require water to be swallowed, which may benefit those with fluid restrictions. The tablets should not be swallowed intact.

- **Cost:** The monthly drug cost for initial therapy with lanthanum carbonate in patients with ESRD and hyperphosphatemia is approximately $56.00 to $113.00, depending on the dose. The annual cost for chronic therapy with lanthanum carbonate at the usual maintenance doses of 1500 mg to 3000 mg per day are approximately $1,350 to $2,700.

- **Recommendations:** It is recommended that lanthanum carbonate be available for nonformulary use, restricted to Nephrology Service for use in patients with ESRD on dialysis. Lanthanum carbonate should not be considered unless the patient has received an adequate trial of a calcium-based phosphate binder without the desired results (refer to nonformulary criteria for use of non-calcium, non-aluminum phosphate binders at www.pbm.va.gov or http://vaww.pbm.va.gov). Determination of whether the patient should receive treatment with lanthanum carbonate or sevelamer hydrochloride should be at the discretion of the clinician.

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Introduction[1-10]

Lanthanum carbonate (Fosrenol®, Shire Pharmaceuticals) received FDA approval for marketing in the U.S. on October 6, 2004. Lanthanum is a non-calcium, non-aluminum gastrointestinal phosphate binder indicated to reduce serum phosphate in patients with end-stage renal disease (ESRD).[1]

Patients with ESRD lose the ability to maintain phosphorus and calcium balance and can develop hyperphosphatemia, a condition that has been associated with complications including secondary hyperparathyroidism, soft tissue and vascular calcifications, and an increase in morbidity and mortality.[2,3] According to the 1997 US Renal Data System, 45% of patients on dialysis die from cardiovascular disease.[4] Soft tissue and vascular calcifications have been associated with an increased risk of morbidity and mortality in hemodialysis patients, especially from cardiovascular disease.[2,5] Studies have also reported an association between excessive calcium intake and coronary artery calcification in ESRD patients.[6,7] Cardiovascular disease has been found in adult patients with ESRD on hemodialysis more commonly than normal subjects of the same age group.[8] The exact mechanisms of these outcomes are unclear but may be related to elevated serum phosphorus and elevated calcium x phosphorus products (Ca X P).[2,4,9]

Data from over 6,000 patients on hemodialysis for at least one year were examined to assess the level of serum phosphorus and its effect on mortality. A serum phosphorus level of > 6.5 mg/dl was found in over 39% of patients. The relative mortality risk was reported to be 13% higher in patients with serum phosphorus between 6.6-7.8 mg/dl compared to those with 4.6-5.5 mg/dl (reference range). The relative mortality risk increased to 34% in patients with serum phosphorus between 7.9-16.9 mg/dl. The adjusted relative risk of mortality in patients with a serum phosphorus level greater than 6.5 mg/dl was 27% higher compared to patients with a level < 6.5 mg/dl ($P<0.001$). One explanation for the increased mortality associated with an elevated phosphorus level is thought to be the association with an elevated Ca X P. It was also reported that a Ca X P > 72 mg^2/dl^2 was associated with a 34% higher relative mortality risk compared to patients with a Ca X P within the reference range of 42 and 52 mg^2/dl^2 ($P<0.01$).[4]

Treatment guidelines recommend levels of serum phosphorus 3.5 to 5.5 mg/dL and a Ca X P < 55 mg/dl in patients with chronic kidney disease (CKD) with kidney failure (Stage 5) or those on dialysis.[9] Serum phosphorus levels may be maintained by dietary restriction of phosphate to less than 1 gram/day, inhibition of intestinal phosphate absorption with calcium-based phosphate-binders (e.g., calcium acetate, calcium carbonate) or non-calcium, non-aluminum phosphate binders (e.g., sevelamer hydrochloride, lanthanum carbonate), and dialysis. Oral calcium-based phosphate binders as well as non-calcium, non-aluminum gastrointestinal phosphate binders are recommended in patients with Stage 5 CKD to lower serum phosphorus levels.[9] Aluminum-containing salts are also effective phosphate-lowering agents, but their use is limited by reports of aluminum toxicity such as osteomalacia, anemia, and dementia.[9] The non-calcium, non-aluminum phosphate binders have been developed to offer an alternative to aluminum or calcium-based phosphate binders that may be limited by side effects including aluminum toxicity or constipation, hypercalcemia, and potential increased risk for cardiovascular calcifications, respectively.[9] The non-calcium, non-aluminum phosphate binder sevelamer hydrochloride, is reserved for patients on dialysis according to national VA criteria for nonformulary use (refer to nonformulary criteria for use of non-calcium, non-aluminum phosphate binders at www.pbm.va.gov or http://vaww.pbm.va.gov).

Pharmacology[1]

Lanthanum is a naturally occurring rare earth element. Lanthanum carbonate acts by dissociating in an acidic upper gastrointestinal tract to release lanthanum ions that bind to dietary phosphate during ingestion, forming insoluble lanthanum phosphate complexes. This results in a reduction in serum phosphate and Ca X P.[1]

Pharmacokinetics[1]

C_{max}	Protein binding	t½	Metabolism	Elimination	Excretion	Food effect/Timing
1.0 ng/ml	> 99%	53 hrs	NA	Biliary	94-99% feces (rats/dogs)	Food effect: not studied Timing (during/30min post): negligible effect on systemic levels

In patients with ESRD, mean plasma lanthanum concentrations were 0.6 ng/ml after one year, with minimal elevations with increased doses within the therapeutic dose range.

FDA Approved Indication(s) and Off-Label Uses[1]

Lanthanum carbonate is FDA approved to reduce serum phosphate in patients with ESRD.

Dosage and Administration[1]

General Recommendations: Lanthanum carbonate is available in chewable tablets that should be chewed thoroughly before swallowing. The tablets do not require water to be swallowed. The tablets should not be swallowed intact. The total daily dose should be administered in divided doses that should be taken with or immediately after meals.

Availability	Initial Total Daily Dose	Titration Interval	Usual Maintenance Daily Dose	Lab Monitoring
250 mg 500 mg chewable tablets	750 mg (3 X 250 mg tablets) to 1500 mg (3 X 500 mg tablets)	Increase by 750 mg every 2 to 3 weeks until serum phosphate goal is achieved	1500 mg to 3000 mg (doses up to 3750 mg daily have been evaluated)	Serum phosphate levels should be monitored as needed during titration and regularly once on maintenance dose

Adverse Events[1]

The most frequently reported adverse events in patients taking lanthanum carbonate are gastrointestinal (i.e., nausea and vomiting), that usually resolved with continued dosing. Adverse events in placebo-controlled trials are shown below.

Adverse Event[a]	Placebo, % (n=95)	Lanthanum, % (n=180)
Nausea	5	11
Vomiting	4	9
Dialysis graft occlusion	1	8
Abdominal pain	0	5

[a]Adverse events reported in double-blind, placebo-controlled trials of 4 to 6 weeks duration that occurred more frequently in patients on lanthanum carbonate compared to placebo (≥ 5%)

Adverse events reported in comparative trials with lanthanum carbonate are included in the following table.

Adverse Event[a]	Study A		Study B	
	Lanthanum, % (n=682)	Alternate therapy, % (n=676)	Lanthanum, % (n=533)	Calcium carbonate, % (n=267)
Nausea	36	28	16	13
Vomiting	26	21	18	11
Dialysis graft complication	26	25	3	5
Diarrhea	23	22	13	10
Headache	21	20	5	6
Dialysis graft occlusion	21	20	4	6
Abdominal pain	17	17	5	3
Hypotension	16	17	8	9
Constipation	14	13	6	7
Bronchitis	5	6	5	6
Rhinitis	5	7	7	6
Hypercalcemia	4	8	0	20

[a]Adverse events reported in ≥ 5% of patients in either treatment group during two comparative studies with lanthanum

Long-term safety: Adverse events during Study A (2 year, open-label, active-controlled trial) and Study B (6-month, open-label, comparative trial) are shown in the table above. Drug therapy was discontinued in 14% of

patients enrolled in these studies. Nausea, diarrhea, and vomiting were the most common adverse events resulting in discontinuation of therapy.

Experimental studies have demonstrated tissue accumulation of lanthanum in rats given oral lanthanum supplements.[10] The potential adverse consequences of such accumulation are unknown. The extent of lanthanum accumulation in the organs of humans with kidney disease who receive oral lanthanum supplements is unknown.

Look-alike/Sound-alike Error Risk Potential

As part of a pilot program, the VA PBM and Center for Medication Safety queried a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonological similarities, as well as similarities in dosage form, strength and route of administration. By incorporating similarity scores as well as clinical judgment, it was determined that the following drug names may pose as potential sources of drug name confusion.

Drug Name	Potential Name Confusion	Potential Severity[a]	Probability
Lanthanum Carbonate (generic)	Aluminum hydroxide	Minor-Moderate	Remote
	Lithium carbonate	Moderate-Major	Remote
Fosrenol (brand)	Fiorinal	Minor	Remote
	Fosfree	Minor-Moderate	Remote
	Fer-In-Sol	Minor-Moderate	Remote

[a] Depending on the dose

Contraindications[1]

There are no known contraindications to lanthanum carbonate.

Warnings/Precautions[1]

General: Lanthanum carbonate should be used with caution in patients with acute peptic ulcer, ulcerative colitis, Crohn's disease, or bowel obstruction, as these patients were not included in the clinical trials with lanthanum carbonate.

Patient Information: Patients should be informed that lanthanum carbonate tablets should be chewed thoroughly before swallowing and should not be swallowed intact. The total daily dose should be administered in divided doses and taken with or immediately after meals.

Long-term Effects: The fracture rate and mortality of lanthanum carbonate has been evaluated for up to three years, without a reported increase in these events compared to alternative therapy. The manufacturer sates that the treatment duration of this evaluation is not long enough to determine if there is an effect on fracture rate or mortality beyond the time period of the clinical program.

Carcinogenesis, Mutagenesis, Fertility Impairment: Oral doses of lanthanum carbonate of up to 2.5 times the maximum recommended dose in humans for up to 104 weeks did not show evidence of carcinogenic potential in rats. Doses of 1.3 times the maximum recommended dose in humans for up to 99 weeks did show an increase in the incidence of glandular stomach adenomas in male mice. Lanthanum carbonate tested negative for mutagenic activity in *in vitro* studies. Studies of oral lanthanum carbonate tested negative in micronucleus assays in the mouse, and negative in micronucleus and unscheduled DNA synthesis assays with intravenous lanthanum carbonate in the rat. In male or female rats, fertility or mating performance was not affected with lanthanum carbonate up to 3.4 times the maximum recommended dose in humans.

Pregnancy Category C: Lanthanum carbonate is not recommended for use in pregnant women. There have not been any adequate well-controlled studies in this patient population. In addition, the effect of lanthanum carbonate on absorption of vitamins and nutrients has not been studied in pregnant females. Studies in rats have shown that at a dose 3.4 times the human dose there was no evidence of harmful effects to the fetus. Reductions in maternal food consumption and body weight gain, increases in post-implantation loss, reductions in fetal weights, and delayed fetal ossification, were seen in pregnant female rabbits exposed to 5 times the human dose. When lanthanum carbonate

was administered to rats at 3.4 times the human dose from implementation through lactation, a delay in eye opening, reduction in body weight gain, and delay in sexual development of the offspring occurred.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Since many drugs are excreted in human milk, it is recommended that lanthanum carbonate be used with caution in nursing women.

Demographics (Age): In clinical trials with lanthanum carbonate, there was no difference in the overall safety or effectiveness between patients 65 years of age or older compared to younger patients. Thirty-two percent of patients included in the clinical trials were 65 years of age or older, and 9.3% of patients were 75 years of age or older. The use of lanthanum carbonate is not recommended in pediatric patients as the effect of deposition of lanthanum into developing bone including growth plate found in long-term animal studies, is unknown in pediatric patients.

Drug Interactions[1]

It is recommended that medications known to interact with antacids not be taken within 2 hours of lanthanum carbonate, although *in vitro* studies with lanthanum carbonate did not show formation of insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol, or enalapril. The pharmacokinetics of warfarin, digoxin, or metoprolol were not affected by lanthanum carbonate in healthy volunteers. Concomitant administration of citrate-containing compounds does not affect the absorption of lanthanum carbonate. Lanthanum carbonate is not metabolized and is not a substrate or inhibitor of the cytochrome P450 enzymes.

Efficacy Measures

The efficacy measures relating to the effect of lanthanum carbonate on laboratory values in two randomized, placebo-controlled trials are included below:

Primary endpoints
- Reduction of serum phosphorus to $\leq$ 5.9 mg/dL
- Reduction of serum phosphorus levels

Secondary endpoints
- Effect on serum calcium levels
- Effect on Ca X P
- Effect on PTH levels

In addition, one comparison trial of the effects on laboratory parameters with calcium carbonate (abstract) was available at the time of the review. The effects of one year of treatment with lanthanum carbonate compared to calcium carbonate on renal bone disease were evaluated in a published, randomized, open-label trial. The long-term effects of lanthanum carbonate on cardiovascular outcomes have not been established.

Clinical Trial Data[11-17]

Reduction in serum phosphorus (RCTs): Two publications of randomized, double-blind, placebo-controlled trials in patients with ESRD on hemodialysis were identified:[11-12] one was a dose-finding study that also evaluated the effect on serum phosphorus after withdrawal of lanthanum carbonate;[11] the other trial randomized patients to 4 weeks of treatment with lanthanum carbonate or placebo, after a 6-week dose titration phase.[12] Results of a randomized, double-blind, placebo-controlled study of 4 weeks duration after open-label titration in patients on hemodialysis or CAPD are also reported.[13]

The study by Finn et al,[11] reported a statistically significant reduction in serum phosphorus of 0.95 $\pm$ 1.39 mg/dL and 1.13 $\pm$ 2.01 mg/dL with daily doses of 1350 mg and 2250 mg, respectively ($P<0.001$) for 6 weeks compared to placebo. In the lanthanum carbonate treatment group, 46.2% of patients on 2250 mg per day and 43.3% of patients receiving 1350 mg per day achieved serum phosphorus levels of $\leq$ 5.5 mg/dL compared to 9.4% of patients on placebo (refer to Appendix 1 for details of clinical trial). Calcium levels were lower in all lanthanum dose groups at the end of the treatment phase compared to pre-study values (except for 225 mg/day), although the values were not provided.

In the study by Joy et al,[12] the primary endpoint evaluation of control serum phosphorus (pre-dialysis serum phosphorus $\leq$ 5.9 mg/dL at the last visit during the treatment phase) was achieved in 65% of patients on lanthanum carbonate compared to 38% of patients receiving placebo (OR 4.7; 95% CI 1.9 to 11.9). The mean difference in serum phosphorus with lanthanum carbonate of 1.91 mg/dL was statistically significant (P<0.0001) compared to placebo (5.94 $\pm$ 1.65 mg/dL with lanthanum carbonate vs. 7.85 $\pm$ 1.96 mg/dL with placebo). Mean differences were statistically significant at daily doses of 1500 mg, 2250 mg, and 3000 mg compared to placebo (refer to Appendix 2 for details of clinical trial). The difference in serum calcium was not statistically significant between lanthanum carbonate and placebo at the end of the treatment phase. The mean treatment difference in Ca X P at the end of the treatment phase was statistically significant between lanthanum carbonate and placebo (P<0.0001).

Dose finding study (open-label with placebo-controlled follow-up): A 4-week, dose-finding, open-label study of 59 patients with CKD on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) reported 70% (35 of 50 patients) achieved a serum phosphorus level of $\leq$ 5.8 mg/dL (mean daily dose after titration was 1278 mg).[14] Results of the 4-week, double-blind, placebo-controlled follow-up with lanthanum carbonate maintained control serum phosphate (4.03-5.58 mg/dL) compared to placebo in patients on HD or CAPD (64.7% lanthanum carbonate vs. 21.4% placebo). The mean serum phosphate at the end of treatment with lanthanum carbonate was statistically significant compared to placebo (4.84$\pm$0.93 mg/dL vs. 6.29$\pm$0.96 mg/dL, respectively; P<0.001). Results are presented in Appendix 3.[13]

Comparison to calcium carbonate (abstract): In an abstract presented at the American Society of Nephrology in November 2002, the reduction of serum phosphorus in 510 patients on lanthanum carbonate was compared to the decrease in 257 patients receiving calcium carbonate. Inclusion criteria were patients on hemodialysis three times per week for at least 3 months. After 5 weeks, it was reported that 57.8% of patients treated with lanthanum carbonate (dose titrated to 375-3000 mg/day) achieved the goal of serum phosphorus $\leq$ 5.58 mg/dL compared to 70.3% of patients receiving calcium carbonate (dose titrated to 1500-9000 mg/day) (P=0.002). The difference of 65.8% and 63.9% of patients on lanthanum carbonate and calcium carbonate, respectively, who achieved goal serum phosphorus at 6 months was not statistically significant. It was also reported in the abstract that there was a statistically significant greater incidence of occurrences of hypercalcemia (defined as > 10.4 mg/dL) in patients treated with calcium carbonate (almost 40%) compared to patients receiving lanthanum carbonate (6%) (P<0.001).[15]

Effect on bone (open-label): One published, randomized, open-label trial evaluated the effects of lanthanum carbonate (median dose 1250 mg/day) compared to calcium carbonate (median dose 2000 mg/day) on renal osteodystrophy in 98 patients on treatment for up to one year and who began hemodialysis or CAPD prior to study enrollment. In the lanthanum carbonate treatment group, 63% received vitamin D compared to 53% in the calcium carbonate group. Of the 63 pairs of evaluable bone biopsies, it was reported that at baseline, 7 of 33 (21%) patients in the lanthanum carbonate group had adynamic bone disease or osteomalacia, compared to 7 of 30 (23%) patients treated with calcium carbonate. At one year, adynamic bone disease or osteomalacia was reported in 3 of 33 (9%) patients in the lanthanum carbonate treatment group compared to 9 of 30 (30%) patients receiving calcium carbonate. The percent of patients with normal bone biopsies were 6% and 0% on lanthanum carbonate and calcium carbonate, respectively, at baseline, compared to 15% and 3%, respectively, at one year. More patients in the calcium carbonate treatment group (49%) experienced hypercalcemia (>10.6 mg/dL) compared to those in the lanthanum carbonate treatment group (6%).[16]

Effect on cognitive function (abstract; open-label): An abstract presented at the 37th Annual Meeting of the American Society of Nephrology in 2004 reported no significant difference in the substudy endpoint of cognitive function (assessed by the Cognitive Drug Research computerized assessment system: simple reaction time, digit vigilance task, choice reaction time, numeric working memory, and picture recognition) in a subgroup of 324 patients treated with lanthanum carbonate compared to controls (aluminum or calcium salts, or sevelamer) after evaluation at 2 years.[17]

Data Compilation Table

Primary Endpoint	Phosphorus ≤ 5.9 mg/dL
Results: Lanthanum carbonate	32/49 (65%)
Results: Placebo	17/44 (38%)
Treatment duration	4 weeks
Odd Ratio (95% CI)	4.7 (1.9 to 11.9)
Absolute Risk Reduction (95% CI)	27% (17 to 37)
NNT (95% CI)	4 (3 to 6)

Acquisition Cost

Drug	Price/ Tablet	Daily Dose [a]	Daily (Monthly) Cost/Patient	Annual Cost/Patient
Lanthanum 250 mg	$0.6258	750 mg (1 tablet TID[a])	$1.88 ($56.32)	$675.65
Lanthanum 500 mg	$1.2516	1500 mg (1 tablet TID[a]) to 3000 mg (2 tablets TID[a])	$3.76 ($112.64) to $7.51 ($225.29)	$1,351.73 to $2,703.46

[a] Divided and taken with meals; TID=divided three times daily

Cost Comparison

Drug	Price/Tablet	Daily Dose	Daily (Monthly) Cost/Patient	Annual Cost/Patient
Sevelamer 400 mg	$0.3808	2-6 tablets TID[a]	$2.29-$6.85 ($68.54-$205.63)	$823-$2,468
Sevelamer 800 mg	$0.7610	1-3 tablets TID[a]	$2.28-$6.85 ($68.49-$205.47)	$822-$2,466
Ca Acetate 667 mg[b]	$0.1047	1-3 tablets TID[a]	$0.31-$0.94 ($9.42-$28.27)	$113-$339
Ca Carbonate 650 mg[c]	$0.0055	1-2 tablets BID-TID[a]	$0.01-$0.03 ($0.30-$0.90)	$3.60-$10.80

[a] BID=divided twice daily; TID=divided three times daily
[b] 253 mg elemental calcium per gram
[c] 400mg elemental calcium per gram

Cost-Effectiveness Analysis

Results of a cost-effectiveness evaluation were presented at the 37th Annual Meeting of the American Society of Nephrology in 2004.[18] A clinical pathway model was used to the compare the cost per quality of life-year (QALY) of treatment with lanthanum carbonate in patients with ESRD inadequately controlled on calcium carbonate and a serum phosphorus > 5.6 mg/dL, and in three subgroups of patients with serum phosphorus 5.6-6.5 mg/dL, 6.6-7.9 mg/dL, and > 7.9 mg/dL. Results were compared to continuing on calcium carbonate. Cost per QALY was calculated at 2, 5, and 10 years over the remaining lifetime of a cohort of 1,000 patients with ESRD. The analysis reported that second line therapy with lanthanum carbonate costs an additional 215K British pounds over the 1,544K British pounds for lifetime treatment with calcium carbonate. Reported benefits were 24 life years that translated into 15 QALYs benefit with lanthanum carbonate. It was reported that treatment with lanthanum carbonate resulted in a benefit of 124 QALYs in patients in the subgroup of phosphorus > 7.9 mg/dL. There was a greater benefit in the 6.6-7.9 mg/dL subgroup, although the magnitude was not provided. It was concluded in the abstract that it is cost-effective to treat patients who are not adequately controlled on calcium carbonate with lanthanum carbonate.

Conclusions

Lanthanum carbonate has been reported to statistically significantly reduce serum phosphorus in patients with CKD on dialysis compared to placebo in three published, randomized, placebo-controlled trials; and to achieve goal serum phosphorus. Efficacy of lanthanum carbonate appears comparable to treatment with calcium carbonate (although it was reported that more patients experienced a serum calcium > 10.4 mg/dL with calcium carbonate), however results are only available in abstract form. There are no published clinical trials comparing lanthanum carbonate to sevelamer hydrochloride. The long-term skeletal or cardiovascular effects of treatment with lanthanum carbonate have yet to be established.

Published randomized controlled trials are needed to confirm the comparable efficacy and to determine the long-term consequence of difference in calcium levels or Ca X P between treatment with lanthanum carbonate and calcium-based or other non-aluminum, non-calcium phosphate binders. An economic evaluation published in abstract form, concluded that it would be cost-effective to use lanthanum carbonate in patients with ESRD who are not able to maintain a phosphate level $\leq$ 6.5 mg/dL on treatment with calcium carbonate. Clinical trials comparing lanthanum carbonate to sevelamer are not available to determine if there is a preference when deciding to treat patients who are inadequately controlled on a calcium-based phosphate binder.

Recommendations

It is recommended that lanthanum carbonate be available for nonformulary use, restricted to Nephrology Service for use in patients with ESRD on dialysis. Lanthanum carbonate should not be considered unless the patient has received an adequate trial of a calcium-based phosphate binder without the desired results (refer to nonformulary criteria for use of non-calcium, non-aluminum phosphate binders at www.pbm.va.gov or http://vaww.pbm.va.gov). Determination of whether the patient should receive treatment with lanthanum carbonate or sevelamer hydrochloride should be at the discretion of the clinician.

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17. Altmann P, Finn WF. Lanthanum carbonate has shown no negative effects on cognitive function compared with standard therapy: results from a 2-year study. Poster presented at the annual meeting of the American Society of Nephrology, St. Louis, MO, 2004. Abstract.
18. Brennan A, Akehurst R, Sakai H, et al. Assessing the potential cost-effectiveness of lanthanum carbonate in the control of hyperphosphatemia. Poster presented at the annual meeting of the American Society of Nephrology, St. Louis, MO, 2004.

Appendix 1: Evidence Table (Finn et al)

<table>
<tr><th>Trial</th><th>Inclusion/Exclusion/Endpoints</th><th>Treatment</th><th>Results</th><th>Adverse Events/Withdrawals</th></tr>
<tr>
<td>Finn et al, 2004[11]

R, DB, PC</td>
<td><u>Inclusion criteria</u>
18 yrs of age, ESRD, HD 3 times/wk X 6 months; eligible for treatment phase if P ≥ 5.6 mg/dL after placebo run-in and at least 80% compliant with placebo

<u>Exclusion criteria</u>
Requiring > 4 g elemental Ca to achieve P control; prescribed aluminum salts; serum Ca > 11.0 mg/dL; severe HPT (PTH > 1,000 pg/ml); clinically significant abnormal lab values; significant GI disease (Crohn's disease or ulcerative colitis)

Patients withdrawn from trial if phosphorus > 10 mg/dL or < 2.0 mg/dL, if Ca X P > 80 mg^2/dL^2, or if PTH increased by > 500 pg/ml above baseline

<u>Endpoints</u>
Primary: change in predialysis phosphorus levels after 6 wks treatment
Secondary: minimum clinically effective dose, time to first achieve significant reduction in phosphorus and if effect sustained
Other: Effect of treatment withdrawal on serum phosphorus; effect of treatment of serum Ca and PTH levels</td>
<td><u>Run-in phase</u>
1-3 wk SB placebo

196 patient in placebo run-in phase (51 patients not eligible for treatment phase: 27 low phosphorus levels, 4 serious AEs, 2 exceeding safety criteria, 18 other including protocol violations/consent withdrawn)
145 enrolled in treatment phase (144 included in ITT as 1 patient did not have efficacy data available)

<u>Treatment phase</u>
Randomized to placebo or lanthanum daily dose of 225 mg, 675 mg, 1350 mg, or 2250 mg (divided 3 times daily with meals or twice daily if only 2 meals per day) for 6 weeks

<u>Run-out phase</u>
2 wk SB placebo

Daily Ca and phosphorus intake assessed by interview with a dietitian at one of the last 2 sessions of HD during 1st wk of run-in phase, during wks 2, 3, 4 and 6 during the treatment phase, and at the end of the run-out phase</td>
<td>Baseline (mean): age 54-59yrs; 41-66% male; 63-75% black; duration HD 2.5-4.3 yrs
<table>
<tr><th>Treatment</th><th>Primary Endpoint</th><th>P value</th></tr>
<tr><td>Placebo</td><td>0.75±1.47 mg/dL</td><td>NA</td></tr>
<tr><td>Lanthanum</td><td></td><td></td></tr>
<tr><td>2250 mg/d</td><td>-1.13±2.01 mg/dL</td><td><0.001*</td></tr>
<tr><td>1350 mg/d</td><td>-0.95±1.39 mg/dL</td><td><0.001*</td></tr>
<tr><td>675 mg/d</td><td>NA</td><td>NA</td></tr>
<tr><td>225 mg/d</td><td>NA</td><td>NA</td></tr>
</table>
* vs. placebo
<table>
<tr><th>Other Results</th><th>Phosphorus ≤ 5.5 mg/dL*</th><th>Ca X P (mg^2/dL^2)</th><th>P value**</th></tr>
<tr><td>Placebo (n=32)</td><td>3 (9.4%)</td><td>8.4±12.2</td><td><0.001</td></tr>
<tr><td>Lanthanum</td><td></td><td></td><td></td></tr>
<tr><td>2250 mg/d (n=26)</td><td>12 (46.2%)</td><td>-7.4±19.9</td><td><0.075</td></tr>
<tr><td>1350 mg/d (n=30)</td><td>13 (43.3%)</td><td>-7.2±12.4</td><td><0.005</td></tr>
<tr><td>675 mg/d (n=29)</td><td>2 (6.9%)</td><td>NA</td><td>NA</td></tr>
<tr><td>225 mg/d (n=27)</td><td>6 (22.2%)</td><td>8.0±15.6</td><td><0.005</td></tr>
</table>
* n (%); significance not provided; ** end of treatment vs. randomization

<u>Secondary</u>: Significant reduction in phosphorus with lanthanum 2250 mg/d from 1st wk treatment and 1350 mg/d from 2nd wk treatment vs. placebo
<u>Other</u>: Phosphorus: Significant increase phosphorus after run-out phase vs. end of treatment with 2250 mg/d (P=0.001), 1350 mg/d (P=0.0001), and 675 mg/d (P=0.0032); Calcium: Ca levels lower in all lanthanum dose groups at end treatment phase vs. pre-study values except for 225 mg/d (values not provided); statistically significant increase with some lanthanum dose groups during treatment period vs. end of run-out (P value or specific values not provided except for largest mean increase Ca 0.26 mg/dL) ; PTH: no significant difference in PTH levels between lanthanum at different doses or vs. placebo</td>
<td><u>Completed trial</u>
Lanthanum: 2250 mg, 22/26 (85%); 1350 mg, 21/30 (70%); 675 mg, 20/29 (69%); 225 mg, 13/27 (48%)
Placebo: 15/32 (47%)
<table>
<tr><th>AE</th><th>Lanthanum*</th><th>Placebo*</th></tr>
<tr><td>≥ 1 AE</td><td>67%</td><td>63%</td></tr>
<tr><td>W/D AE</td><td>9%</td><td>9%</td></tr>
<tr><td>Nausea</td><td>14%/11%</td><td>6%/3%</td></tr>
<tr><td>Vomiting</td><td>12%/8%</td><td>6%/3%</td></tr>
<tr><td>Abd pain</td><td>6%/6%</td><td>0%/0%</td></tr>
<tr><td>Dialysis graft clotted</td><td>10%/0%</td><td>0%/0%</td></tr>
</table>
* All reports/treatment-related

Study reported no serious AEs or death associated with lanthanum carbonate</td>
</tr>
</table>

Study Conclusions

- Short-term treatment (6 weeks) with lanthanum carbonate decreases serum phosphorus levels by 0.95±1.39 mg/dL to 1.13±2.01 mg/dL with daily doses of 1350 mg and 2250 mg, respectively, in patients with ESRD on HD. These results were statistically significant compared to placebo.

Quality Assessment (Fair)

- No significant differences in baseline characteristics
- Intention to treat analysis
- Dose-finding study to determine minimum effective dose
- Method of patient randomization not reported
- Excluded patients requiring > 4 g elemental Ca to achieve control of serum phosphorus levels
- Not enough information to calculate ARR of the primary endpoint
- Involvement of sponsor not reported

Abd=abdominal; AE=adverse event; ARR=absolute risk reduction; Ca=calcium; Ca X P=calcium-phosphorus product; d=day; DB=double-blind; ESRD=end-stage renal disease; GI=gastrointestinal; HD=hemodialysis; n=number of patients; N=nausea; PC=placebo-controlled; PTH=parathyroid hormone; R=randomized; SB=single-blind; V=vomiting; W/D=withdrawal due to; wk=week; yrs=years

Appendix 2: Evidence Table (Joy et al)

<table>
<tr><th>Trial</th><th>Inclusion/Exclusion/Endpoints</th><th>Treatment</th><th>Results</th><th>Adverse Events/Withdrawals</th></tr>
<tr>
<td>Joy et al, 2003[12]

R, DB, PC</td>
<td><u>Inclusion criteria</u>
18 yrs of age or older, ESRD, HD 3 times/wk X ≥ 2 months; medically stable; eligible for titration phase if phosphorus > 5.9 mg/dL after washout phase

<u>Exclusion criteria</u>
Significant hypercalcemia (serum Ca > 11.0 mg/dL) or hypocalcemia (serum Ca < 7.9 mg/dL); clinically significant abnormal lab values (excluding those of ESRD); severe HPT (PTH > 1,000 ng/L); significant uncontrolled illness or GI disease; life-threatening malignancies or multiple myeloma; exposure to other investigational drugs within 30 days; pregnant or lactating females, or women not using appropriate birth control

Patients withdrawn from trial if phosphorus > 10 mg/dL or < 2.0 mg/dL

Patients instructed to separate study treatment and medications that potentially interact with antacids by 2 hours. Other phosphate-binders or OTCs with aluminum, calcium, phosphorus, or magnesium were not allowed; patients could be on Vitamin D supplementation; Ca concentration of dialysis fluid constant

<u>Endpoints</u>
Primary: serum phosphorus levels of ≤ 5.9 mg/dL with lanthanum vs. placebo
Secondary: phosphorus control during dose-titration; effect of treatment on serum Ca, Ca X P, and PTH levels</td>
<td><u>Screening/washout phase (n=163)</u>
1-3 wk wash-out of phosphate binders

126 of 163 (77%) patients had a phosphorus level > 5.9 mg/dL and entered dose-titration phase

<u>Dose-titration phase (n=126)</u>
6 wk open-label dose-titration starting with 750 mg elemental lanthanum (as lanthanum carbonate) and weekly titration up to 3000 mg to achieve and maintain phosphorus ≤ 5.9 mg/dL.

Doses 375 mg, 750 mg, 1500 mg, 2250 mg, or 3000 mg elemental lanthanum were divided 3 times daily with meals or twice daily if only 2 meals per day

94 of 126 (75%) patients completed dose-titration phase (10 patients withdrew due to AEs; 7 had phosphorus levels outside limits; 6 withdrew consent; 3 due to protocol violation; 1 kidney transplant; 1 death; 4 for other reasons)

94 enrolled in treatment phase (93 included in ITT as 1 patient did not have efficacy data available)

<u>Treatment phase (n=94)</u>
4 wk DB, randomized to placebo (n=44) or maintenance lanthanum (n=49) daily dose that achieved control of serum phosphorus (no dose adjustments allowed)</td>
<td>Baseline (mean): age 60yrs; 65% male; 40% black; duration HD 3 yrs
Treatment phase: 13 (26%) patients in the lanthanum group and 8 (18%) patients in the placebo group, received vitamin D/analog

<u>Primary:</u> 65% lanthanum vs. 38% placebo had their phosphorus level controlled (OR 4.7; 95% CI, 1.9 to 11.9), after adjustment for pre-randomization phosphorus control

<u>Secondary</u>: Significant reduction in mean phosphorus between lanthanum 1500 mg/d, 2250 mg/d, and 3000 mg/d vs. placebo at study endpoint (P<0.0001). See table below for effect on serum Ca, Ca X P, and PTH
<table>
<tr><th>Results</th><th>Treatment</th><th>End of washout</th><th>End of Titration</th><th>End of Treatment</th></tr>
<tr><td>Phosphorus (mg/dL)</td><td>Lanthanum
Placebo</td><td>7.69±1.61
7.39±1.59</td><td>5.49±1.48
5.62±1.61</td><td>5.94±1.65
7.85±1.96[a]</td></tr>
<tr><td>Calcium (mg/dL)</td><td>Lanthanum
Placebo</td><td>8.52±0.69
8.35±0.89</td><td>8.90±0.66
8.69±0.73</td><td>8.83±0.68
8.48±0.81[b]</td></tr>
<tr><td>Ca X P (mg^2/dL^2)</td><td>Lanthanum
Placebo</td><td>65.6±14.9
61.7±15.4</td><td>49.1±14.3
48.7±14.5</td><td>52.4±14.9
66.6±18.3[c]</td></tr>
<tr><td>PTH (pg/mL)</td><td>Lanthanum
Placebo</td><td>255±181
295±198</td><td>212±182
231±149</td><td>209±152
292±195[d]</td></tr>
</table>
[a] P<0.0001 vs. lanthanum at end of treatment
[b] P<0.05 vs. end of titration; not statistically significant vs. lanthanum
[c] P<0.0001 mean treatment difference vs. lanthanum at endpoint; P<0.0001 vs. end of titration
[d] P<0.01 mean treatment difference vs. lanthanum at endpoint; P<0.0001 vs. end of titration</td>
<td>Completed trial: 82 of 94 (87%)
Lanthanum: Of 49 patients, 4 withdrew (2 due to AEs; 1 exceeded safety criteria; 1 other); 92% completed trial
Placebo: Of 44 patients, 8 withdrew (3 exceeded safety criteria; 2 kidney transplant; 1 withdrew consent; 1 due to AE; 1 other); 82% completed trial

Titration phase: 346 AEs reported by 102 patients; 54 (15.6%) considered to be treatment-related. Of the 10 patients who withdrew due to AEs (other than death), 7 were considered treatment-related (6 nausea; 1 hypertension)
<table>
<tr><th>AE</th><th>Lanthanum[a]</th><th>Placebo[a]</th></tr>
<tr><td>AE overall</td><td>58%</td><td>38.6%</td></tr>
<tr><td>W/D AE[b]</td><td>2</td><td>1</td></tr>
<tr><td>Nausea</td><td>6.0%/<2%</td><td>4.5%/<2%</td></tr>
<tr><td>Vomiting</td><td>6.0%/<2%</td><td>2.3%/<2%</td></tr>
<tr><td>Diarrhea</td><td>4.0%/<2%</td><td>6.8%/<2%</td></tr>
<tr><td>Dialysis graft occlusion</td><td>6.0%/<2%</td><td>2.3%/<2%</td></tr>
<tr><td>Serious AE</td><td>4[c]</td><td>4</td></tr>
</table>
[a] All reports/treatment-related
[b] During treatment phase
[c] 1 each: abdominal pain, gastroenteritis, ventricular arrhythmia, angina (considered not treatment-related)

Three deaths (2 during washout; 1 during titration) considered not treatment-related

Treatment compliance was similar between groups (86-90%)</td>
</tr>
</table>

Study Conclusions

- Short-term treatment (4 weeks) with lanthanum carbonate achieves control serum phosphorus (≤ 5.9 mg/dL) compared to placebo in patients with ESRD on HD [65% lanthanum vs. 38% placebo (OR 4.7; 95% CI, 1.9 to 11.9)]. The mean difference in serum phosphorus with lanthanum carbonate of 1.91 mg/dL was statistically significant (P<0.0001) compared to placebo (5.94 ± 1.65 mg/dL with lanthanum vs. 7.85 ± 1.96 mg/dL with placebo).

Quality Assessment (Fair)

- Intention to treat analysis
- Dose-titration phase to determine effective dose; patient then maintained on effective dose through treatment phase
- Method of patient randomization not reported
- 25% patients did not complete titration phase and were therefore excluded from treatment phase
- Involvement of sponsor not reported

Abd=abdominal; AE=adverse event; ARR=absolute risk reduction; Ca=calcium; Ca X P=calcium-phosphorus product; d=day; DB=double-blind; ESRD=end-stage renal disease; GI=gastrointestinal; HD=hemodialysis; n=number of patients; N=nausea; OTC=over-the-counter; PC=placebo-controlled; PTH=parathyroid hormone; R=randomized; V=vomiting; W/D=withdrawal due to; wk=week; yrs=years

Appendix 3: Evidence Table (Al-Baaj et al)

Trial	Inclusion/Exclusion/Endpoints	Treatment	Results	Adverse Events/Withdrawals
Al-Baaj et al, 2005[13] MC, R, DB, PC, PG	**Inclusion criteria** 18 yrs of age or older, HD or CAPD ≥ 6 months (including renal transplant patients) **Exclusion criteria** Hypercalcemia; severe HPT (PTH > 500 ng/L); serum phosphate > 9.3 mg/dL; other clinically significant abnormal lab values; positive pregnancy test; significant GI disorder including active PUD, Crohn's disease, ulcerative colitis, irritable bowel syndrome, or past or present malignancy; unstable diet; life-threatening malignancy; HIV positive; history of alcohol or substance abuse; inability to comply with treatment Patients withdrawn from trial if phosphorus > 9.3 mg/dL or if felt it would detrimental for patient to continue study Diets monitored; vitamin D supplementation could be continued (but not initiated) and dose could not be changed **Endpoints** **Primary:** reduction serum phosphorus levels to between 1.3 and 1.8 mmol/L (4.03-5.58 mg/dL) at the end of DB phase (visit 9) lanthanum vs. placebo **Secondary:** pre-dialysis serum calcium and PTH changes over time; adverse events	**Washout phase (n=105)** 2 wk wash-out of phosphate binders 46 of 105 (44%) patients had a phosphorus level < 4.03 mg/dL and entered dose-titration phase **Dose-titration phase (n=59)** 4 wk open-label dose-titration starting with 375 mg lanthanum and weekly titration up to 2250 mg to achieve and maintain phosphorus 4.03-5.58 mg/dL Doses were divided 3 times daily with meals 36 of 59 (61%) patients entered treatment phase (9 patients withdrew from dose-titration: 3 due to AEs, 3 at patient's request, 1 protocol violation, 1 phosphorus > 9.3 mg/dL, 1 PTH > 500 ng/L); 14 patients completed titration but did not enter PC phase: 5 recruited to pilot group, 3 protocol violation, 1 noncompliance, 5 uncontrolled phosphate) **Treatment phase (n=36)** 4 wk DB, randomized to placebo (n=19) or maintenance lanthanum (n=17) daily dose that achieved control of serum phosphorus	**Baseline** (mean): age 55yrs; 68% male; 66% CAPD, 34% HD Treatment phase: 250mg/d (lanthanum 0%, placebo 5.3%), 375 mg/d (lanthanum 17.6%, placebo 10.5%), 750 mg/d (lanthanum 29.4%, placebo 26.3%), 1500 mg/d (lanthanum 35.3%, placebo 36.8%), 2250 mg/d (lanthanum 17.6%, placebo 21.1%) **Primary:** 64.7% (11/17) lanthanum carbonate vs. 21.4% (3/14) placebo maintained their reduction in serum phosphate levels (P=0.016) **Secondary:** Significant reduction in mean phosphate between lanthanum carbonate vs. placebo at study endpoint (P<0.001). No difference in serum calcium. See table below for effect on Ca X P and PTH **Results** / **Treatment** / **End of Treatment** / **P value**[a] Phosphate (mg/dL) — Lanthanum: 4.84±0.93; Placebo: 6.29±0.96; <0.001 Ca X P (mg^2/dL^2) — Lanthanum: 44.9±9.3; Placebo: 58.4±10.8; <0.001 PTH (ng/L) — Lanthanum: 216±179; Placebo: 250±226; 0.41 [a] vs. lanthanum at end of treatment Subanalysis of CAPD patients: visit 9: 60% (6/10) lanthanum carbonate controlled serum phosphate vs. 12.5% (1/8) placebo (P=0.066)	**Completed trial:** 34 of 36 (94%) 2 withdrew from placebo group; 1 protocol violation, 1 AE **AE** / **Lanthanum** / **Placebo** AE overall: 47% / 58% Tx AE: 17.6% / 21.1% GI: 4 (3 patients) / 7 (4 patients) Seven patients experienced severe AEs, none thought related to treatment; no deaths occurred during the study Treatment compliance was similar between groups (93-94%) Mean lanthanum levels 0.67±0.98 ng/g vs. 0.14±0.26 ng/g in the lanthanum carbonate and placebo groups, respectively

Study Conclusions

- Short-term treatment (4 weeks) with lanthanum carbonate maintained control serum phosphate (4.03-5.58 mg/dL) compared to placebo in patients on HD or CAPD (64.7% lanthanum carbonate vs. 21.4% placebo). The mean serum phosphate at the end of treatment with lanthanum carbonate was statistically significant compared to placebo (4.84±0.93 mg/dL vs. 6.29±0.96 mg/dL, respectively; P<0.001).

Quality Assessment (Fair)

- Not an intention to treat analysis for primary endpoint
- Dose-titration phase to determine effective dose; patient then maintained on effective dose through treatment phase
- 39% patients were excluded from treatment phase
- Involvement of sponsor not reported

AE=adverse event; Ca X P=calcium-phosphorus product; CAPD=continuous ambulatory peritoneal dialysis; d=day; DB=double-blind; GI=gastrointestinal; HD=hemodialysis; MC=multi-center; n=number of patients; PC=placebo-controlled; PG=parallel-group; PTH=parathyroid hormone; PUD=peptic ulcer disease; R=randomized; Tx: treatment-related; wk=week