PUBLIC SUMMARY DOCUMENT

Product: Lanthanum Carbonate Hydrate, chewable tablet, 500 mg (base), 750 mg (base), 1 g (base), Fosrenol®

Sponsor: Orphan Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application:

To seek an Authority required listing for the treatment of hyperphosphataemia in adult patients with chronic renal failure on dialysis whose serum calcium levels are at least 2.60 mmol/L.

2. Background:

This drug has not previously been considered by the PBAC.

3. Registration Status:

Lanthanum carbonate is TGA-registered for the treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

4. Listing Requested and PBAC's View:

Authority required
Initial treatment of hyperphosphataemia, for up to 8 weeks, in adult patients with chronic renal failure on dialysis whose serum calcium levels are at least 2.60 mmol/L.

Continuing treatment of hyperphosphataemia, in adult patients with chronic renal failure on dialysis who have demonstrated a response, defined as serum calcium levels less than 2.60 mmol/L, following the completion of an 8-week trial with lanthanum carbonate.

The PBAC did not comment on the requested restriction.

5. Clinical place for the proposed therapy:

Lanthanum carbonate would provide an alternative therapeutic to calcium-based phosphate binders for the treatment of hyperphosphataemia in adult patients with chronic renal failure who need haemodialysis or continuous ambulatory peritoneal dialysis.

6. Comparator:

The submission nominated calcium carbonate as the main comparator, which was considered appropriate by the PBAC.

7. Clinical Trials

The scientific basis of the comparison was a pivotal randomised trial (LAM-IV-301) comparing lanthanum with calcium carbonate on phosphate level control in adult patients with chronic renal failure on dialysis over 6-month period; 2 supportive trials: LAM-IV-303 which is a 1-year trial comparing lanthanum to calcium on bone histomorphometry and LAM-IV-307, which is a 2-year comparative safety study. The following table lists the trials as published at the time of submission.

Trial ID	Title
Pivotal trial	
LAM-IV-301	A Phase III Open Label, Comparator Controlled Parallel Group Study to Assess the Efficacy and Safety of Lanthanum Carbonate for reduction of Gastrointestinal Phosphate Absorption and Maintenance of Control of Serum Phosphate in Chronic Renal Failure Patients Receiving Hemodialysis <u>Publications</u> Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, Backs W, Jamar R, Vosskuhler A. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract. 2005;100(1):c8-19. Hutchison AJ, on Behalf of the Lanthanum Study G. The novel, non-aluminium, non-calcium phosphate binder, Fosrenol, is an effective treatment for hyperphosphataemia and has a good safety profile [abstract]. Journal of the American Society of Nephrology: JASN. 2002;13(September, Program and Abstracts):385a-6a.
Supportive trials	
LAM-IV-303	A Phase III, Multi-Centre, Open Label, Study to Investigate the Effect of Lanthanum Carbonate compared with Calcium Carbonate on Renal Bone disease in Chronic Renal Failure Patients Receiving Dialysis <u>Publications</u> Freemont AJ, Hoyland JA, Denton J; Lanthanum Carbonate SPD405-303 Study Group. The effects of lanthanum carbonate and calcium carbonate on bone abnormalities in patients with end-stage renal disease. Clin Nephrol. 2005 Dec; 64(6):428-37. D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, Swanepoel C, Pejanovic S, Djukanovic L, Balducci A, Coen G, Sulowicz W, Ferreira A, Torres A, Curic S, Popovic M, Dimkovic N, De Broe ME. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl. 2003 Jun; (85):S73-8. Spasovski GB.Sikole A.Gelev S.Masin-Spasovska J.Freemont T.Webster I.Gill M.Jones C.De Broe ME.D'Haese PC. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. Nephrology Dialysis *Transplantation*. 21(8):2217-24, 2006 Aug. Freemont T. Malluche HH. Utilization of bone histomorphometry in renal osteodystrophy: demonstration of a new approach using data from a prospective study of lanthanum carbonate. Clinical Nephrology.63(2):138-45, 2005 Feb. De Broe ME, D'Haese PC, Freemont TJ, Webster i> Gill M, Spasovski GB. Comparative effects of lanthanum carbonate (fosrenol) and calcium carbonate on renal bone disease in dialysis patients: results from a large, long-term clinical trial [abstract]. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association European Renal Association. 2003; 18(Suppl 4):682. Freemont A, Jones C. The effects of the phosphate binders lanthanum carbonate and calcium carbonate on bone: a comparative study in patients with chronic kidney disease [abstract]. 41st Congress European Renal Association European Dialysis and Transplantation Association Lisbon, Portugal, May 15 18, 2004. 2004:106.
LAM-IV-307	An Open Label, Randomized, Multicenter, Phase III, Comparator Controlled Parallel Group Study to Assess the Long-Term Safety and Efficacy of Lanthanum Carbonate

	in Chronic Renal Failure Patients Receiving Hemodialysis. Publications Finn WF; SPD 405-307 Lanthanum Study Group. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. Clin Nephrol. 2006 Mar;65(3):191-202. Finn WF, Joy MS, Webster I, Gill M, for the Lanthanum Study G. A long-term (2-year) assessment of the safety and efficacy of lanthanum carbonate (forenol), a non-calcium, non-aluminium phosphate binder for the treatment of hyperphosphataemia [abstract]. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association European Renal Association. 2003;18 (Suppl 4):686.

8. Results of trials

The primary outcome in the key trial LAM-IV-301 showed that lanthanum is inferior to calcium carbonate in controlling serum phosphate at the end of the 5-week titration phase (p=0.002). The slower response in lanthanum patients was attributed to a more cautious approach to dosing lanthanum. At the end of the maintenance phase, proportions of phosphate controlled patients were similar in both arms (p=0.73). However, it should be noted that the analysis from week 5 to week 25 involved only responders, so the similarity in results in the two treatment groups was expected (see comments below). The submission claimed that lanthanum offers similar effectiveness to calcium carbonate as a phosphate binding agent. The Last Observation Carried Forward (LOCF analysis) at the end of the maintenance phase indicated that lanthanum is less effective than calcium carbonate in reducing phosphate levels (p=0.043). This LOCF analysis is likely to be biased in favour of the calcium arm due to patients treated with calcium being withdrawn due to hypercalcaemia rather than hyperphosphataemia.

Primary and Secondary outcomes of the comparative randomised trials (ITT)

Trial	Primary outcome		Lanthanum	Calcium/ Standard	p value
LAM-IV-301 (key trial)	PO_4 controlled patients (PO_4 ≤ 1.80mmol/L) at titration (Wk 5) n/N(%)		262/453 (57.8%)	147/209 (70.3%)	0.002
LAM-IV-307 (supportive trial)	PO_4 controlled patients (PO_4 ≤1.90mmol/L) at maintenance (%)	Wk 52	47.0%	49.2%	NS
		Wk 78	48.1%	51.5%	
		Yr 2	45.9%	48.9%	
LAM-IV-303 (supportive trial)	Bone histomorphometry				
	Secondary outcomes				
LAM-IV-301 (key trial)	PO_4 controlled patients (PO_4 ≤ 1.80mmol/L) at maintenance (Wk 25) n/N(%)*		146/222 (65.8%)	78/122 (63.9%)	0.73
	PO_4 controlled patients (PO_4 ≤ 1.80mmol/L) at maintenance (Wk 25) (LOCF analysis)*		182/510 (35.7%)	111/257 (43.2%)	0.043
	Hypercalcaemic episode (any occurrence above the ULN range) (%)*		5.7%	37.9%	<0.001
LAM-IV-303 (supportive trial)	Hypercalcaemic episode (serum calcium above ULN, >2.65mmol/L) (%)		6%	48%	NR

PO_4 = phosphate, ULN = upper limit of the normal, LOCF = last observation carried forward, NS = not significant, NR = not reported

* These comparisons are confounded by the differential withdrawal of non-responding patients prior to the maintenance phase from week 5 to week 25. These data cannot be viewed as a true comparison between the treatments.

The PBAC noted that in the pivotal trial LAM-IV-301, the primary efficacy analysis of the PO_4 control at the end of the 5-week titration period, indicated an inferiority of lanthanum in

phosphate control compared with calcium carbonate. The PBAC was advised that considering the multiple disorders of mineral metabolism (hyperphosphataemia, hypercalcemia and secondary hyperparathyroidism) in end stage renal disease (ESRD) and the complexity of their interrelationship, the sole biochemical measurement of PO_4 level as a surrogate endpoint was questionable.

A post hoc survival analysis on the 2-year safety trial of LAM-IV-307 showed no significant difference in overall survival benefits in lanthanum compared to sevelamer or standard therapies but claimed a benefit in subjects over 65 years. The PBAC was advised this mortality analysis is possibly subject to a range of biases due to the high and differential drop-out rates and the unbalanced co-interventions in the study.

The calcium targets and subgroups considered by the model have been defined to be in line with the boundaries of the calcium bands established by Block et al (2004) (Mineral metabolism, mortality, and morbidity in maintenance hemodialysis." *J Am Soc Nephrol 15(8): 2208-18*) to describe the relative risks of mortality associated with elevated calcium levels. However, as stated in the paper by Block et al (2004), no definitive mortality benefit could be concluded due to the absence of an interventional trial. The study sample was restricted to hemodialysis patients which meant that the extrapolation to peritoneal dialysis patients was inappropriate.

The main thrust of the application was that lanthanum is equi-effective to calcium carbonate in controlling serum phosphate levels and superior to calcium carbonate in avoiding an adverse effect – hypercalcemia. However, the PBAC was advised the pivotal efficacy trial, LAM-IV-301, had some unusual and sub-optimal features that made it difficult to assess the validity of these claims. Study 301 involved a washout, where participants stopped their prior phosphate binder, were assessed for eligibility, randomised and then entered a titration phase of 5 weeks duration. This was followed by a 20 week maintenance phase. The trial was open, unblinded and used envelopes to determine the randomisation sequence. There were several potential sources of bias. In addition, the titration phase (5 weeks) appeared to have been too short to enable true steady state effects to be achieved with lanthanum. Participants only entered the maintenance phase if they achieved the target reduction in phosphate levels, that is, the maintenance phase involved responders only.

The incidences of treatment emergent adverse events were similar for patients treated with lanthanum and calcium carbonate or other standard phosphate binders. There was an increased incidence of nausea and vomiting, and fewer hypercalcaemic episodes in lanthanum treated patients. However, only short term safety data were provided, and lanthanum will be taken longer term. The CARI (Caring for Australasians with Renal Impairment) guidelines have called for bone biopsy studies of long-term lanthanum treatment to satisfy safety concerns. The episodes of hypercalcemia were based on biochemical measurements only and their true clinical significance is not established in the trial results.

9. Clinical Claim

The submission claimed that lanthanum offers similar effectiveness to calcium salts as a phosphate binding agent and has an improved safety profile.

The PBAC rejected the claim as it was not convinced the trial presented adequately supported a conclusion of equivalent efficacy of lanthanum and calcium in reducing PO_4 levels.

Further, there was a lack of data to conclusively link detected treatment effects with subsequent patient relevant outcomes such as a reduction in mortality.

Full details in the Recommendation and Reasons

10. Economic Evaluation

A preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was based on an assumption of similar efficacy in terms of lowered phosphate levels and a lower rate of hypercalcemia and PBAC considered the first was not demonstrated in the pivotal clinical trial based on the results after the 5-week titration period. The resources included were drug costs. The overall comparative costs and outcomes for each alternative and the incremental costs and outcomes are summarised below.

The trial-based incremental cost/extra hypercalcaemic episode avoided over 25 weeks was <$10,000.

A modelled economic evaluation was presented adopting a cost-utility approach (based on a lower rate of hypercalcemia with associated improvement in survival).

The model was based on the assumption that phosphate control is equivalent in patients regardless of whether they receive calcium or lanthanum and regardless of their initial phosphate level. (However, as stated above, the PBAC considered the equi-efficacy of lanthanum and calcium carbonate has not been established.)

The base case modelled incremental discounted cost/extra discounted QALY gained life-time was $45,000-75,000. The incremental cost per QALY was highly sensitive to time horizon, The model was most sensitive to the model duration, the utility value for End Stage Renal Failure, the annual cost of lanthanum, the targeted calcium level, and the discounting rates.

11. Estimated PBS Usage and Financial Implications:

The submission estimated the net cost to the PBS would be <$10 million. PBAC considered this was a likely underestimate.

12. Recommendation and Reasons

The PBAC acknowledges there is a high clinical need for phosphate binders other than calcium for use in the treatment of hyperphosphataemia in patients with chronic renal failure on dialysis. However, the Committee had concerns about the clinical evidence presented in terms of whether it demonstrates that lanthanum has similar effectiveness to calcium salts in controlling serum phosphate.

The estimate of the extent of mortality benefit with lanthanum in the economic model was based solely on the surrogate measure of serum calcium and used ‘hypercalcemic events’ from the pivotal clinical trial, LAM-IV-301. These events were classified as the occurrence of calcium levels above the upper limit of normal; individuals suffering these events were not necessarily identified as ill or admitted to hospital and it is not clear whether they suffered any short or long term harm. This raised concerns, not whether hypercalcemia has adverse effects, but rather that the trial outcome has not been shown to be clinically significant in

individual patients. In the hearing, it was acknowledged that there is currently no controlled prospective evidence that reducing calcium levels in patients with previously elevated levels leads to changes in mortality rates. The epidemiological data from Block (2004), while it established an association between higher serum calcium and an increased risk of death, did not address this fundamental issue. Thus it was not possible to establish with confidence a quantitative link between the extent of a projected reduction in mortality following any reduction in elevated calcium levels.

Furthermore, the mean serum calcium levels and their respective confidence intervals in the calcium treated group (ie. the high risk group) in trial 301 fell in the range 2.2 – 2.6 mmol/L (approximately 9.0 to < 10.5 mg/dl). Block et al (2004) found these levels (or levels of 2.4 to 2.5 mmol/L) to fall within the non-attributable mortality group. Patients with serum calcium levels greater than 2.65 mmol/L, ie those targeted by the proposed PBS listing, were excluded from the trial, so that the trial population was not representative of the population to be treated under the PBS.

The post hoc survival analysis on the 2-year safety trial of LAM-IV-307 showed no significant difference in overall survival benefits in lanthanum compared to standard therapies but claimed a benefit in subjects over 65 years. However, this mortality analysis was possibly subject to a range of biases due to the high and differential drop-out rates and the unbalanced co-interventions in the study. These concerns also hampered interpretation of the indirect comparison of these data with the results of the DCOR trial of sevelamer.

Another issue that which cast doubt on both the results of the economic modelling and the submission's clinical claim of equi-effectiveness with calcium carbonate in controlling serum phosphate was that the design of trial 301 was flawed. The Committee considered that the only valid efficacy analysis from this trial was PO_4 control at the end of the 5-week titration period. The standard pre-defined Last Observation Carried Forward (LOCF) analysis, indicated lanthanum is significantly inferior to calcium carbonate. The "missing=failure" analysis presented in the pre-PBAC response was a post-hoc analysis and therefore subject to significant limitations. Overall the Committee was not convinced that the trial presented adequately supports a conclusion of equivalent efficacy of lanthanum and calcium carbonate in reducing PO_4.

The PBAC also questioned the appropriateness of the time horizon for the model in end stage renal failure. The incremental cost per Quality Adjusted Life Year (QALY) is highly sensitive to the model's time horizon. The PBAC considered this ICER to be unacceptably high and subject to significant uncertainties.

The Committee therefore rejected the submission because of a high and uncertain cost-effectiveness ratio that primarily resulted from a lack of data to conclusively link detected treatment effects with subsequent patient relevant outcomes such as a reduction in mortality.

The PBAC requested the Secretariat arrange a stakeholder meeting between the Committee and representatives of the sponsors of all the new phosphate binder products for use in end stage renal disease and the relevant peak clinician and consumer associations.

Recommendation
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor is disappointed by the PBAC rejection and will continue to work with the PBAC and clinicians to make PBS-subsidised Fosrenol available to patients with chronic renal failure on dialysis.