PUBLIC SUMMARY DOCUMENT
Product: Lanthanum carbonate hydrate, chewable tablet, 500 mg, 750 mg and 1000 mg, Fosrenol®, Shire Australia Pty Ltd
Sponsor: Shire Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application

To seek a Section 100 Highly Specialised Drug listing for the management of, and a Section 85 Authority Required PBS listing for the maintenance of hyperphosphataemia in patients with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where

(a) serum phosphate is greater than 1.6 mmol per L; or
(b) the serum calcium times phosphate product is greater than 4.0

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

At the March 2007 meeting the PBAC rejected a submission for an Authority required listing of lanthanum for the treatment of hyperphosphataemia in adults with chronic renal failure on dialysis whose serum calcium levels are at least 2.6 mmol/L 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.

3. Registration Status

Lanthanum carbonate was registered on 8 November 2005 for the indication:

- hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

4. Listing Requested and PBAC's View

Authority Required

Maintenance therapy, following initiation and stabilisation of treatment with lanthanum carbonate, of hyperphosphataemia in a patient with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where:

(a) serum phosphate is greater than 1.6 mmol per L; or
(b) the serum calcium times phosphate product is greater than 4.0

Section 100

Private hospital authority required

Management of hyperphosphataemia in a patient with chronic kidney disease on dialysis whose serum phosphate is not controlled on other products and where:

(a) serum phosphate is greater than 1.6 mmol per L; or
(b) the serum calcium times phosphate product is greater than 4.0

Management includes initiation, stabilisation and review of therapy as required

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Lanthanum carbonate would provide an alternative non calcium-based phosphate binder for patients with chronic kidney disease who require treatment for hyperphosphataemia.

6. Comparator

The submission nominated sevelamer hydrochloride as the main comparator. This was accepted as the appropriate comparator by the PBAC.

7. Clinical Trials

No changes were made to the lanthanum-calcium data from three trials and the sevelamer DCOR trial results presented in the previous submission. One new trial (SPD405-310) of lanthanum versus sevelamer was presented, a small, open-label pilot study of phosphate control. The re-submission also included 14 new trials comparing sevelamer and calcium for use in the indirect analyses of lanthanum versus sevelamer for three biochemical outcomes, phosphate control, calcium control, and calcium-phosphate control. The mortality result comparing the lanthanum Trial LAM-IV-307 and the sevelamer DCOR trial were re-presented based on indirect analysis.

The key trials published at the time of submission are as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Lanthanum versus sevelamer randomised trial (n=1)		
SPD405-310	Clinical Study Report: A Multi-Centre, Open Label, Randomised, Parallel Group Pilot Study to Assess the Efficacy and Safety of Lanthanum Carbonate and Sevelamer Hydrochloride in Patients Receiving Haemodialysis for End Stage Renal Disease.	2007 World Congress of Nephrology, Rio de Janeiro, Brazil.
Lanthanum vs. calcium randomised trials (n=3)		
LAM-IV-301	Clinical Study Report: 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.	Nephron Clin Pract. 2005; 100(1):c8-19.
LAM-IV-303	Clinical Study Report: 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.	Nephrology Dialysis Transplantation 2003; 18(Suppl 4): 682.
LAM-IV-307 (control=std. therapy*)	Clinical Study Report: 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.	Clinical Nephrology 2006; 65(3): 191-202.
Sevelamer vs. calcium randomised trials (n=14)		
DCOR Trial (Suki)	Effects of Sevelamer and Calcium-Based Phosphate Binders on Mortality in Hemodialysis Patients: Results of a Randomized Clinical Trial. Effects of Sevelamer and Calcium-Based	Suki, W.N. (2008Journal of Renal Nutrition 18(1): 91-98. Suki, W.N. (2007

	Phosphate Binders on Mortality in Hemodialysis Patients.	Kidney International Advance Online Publication, 29 August 2007.
	A Comparison of Sevelamer and Calcium-Based Phosphate Binders on Mortality, Hospitalization, and Morbidity in Hemodialysis: A Secondary Analysis of the Dialysis Clinical Outcomes Revisited (DCOR) Randomized Trial Using Claims Data.	St. Peter, W.L., Liu, J., Weinhandl, E., et al. (2008).American Journal of Kidney Diseases 51(3): 445-454.
	DCOR Study: assessing economic impact of sevelamer vs. calcium-based phosphate binders on hospitalization and morbidity in hemodialysis patients using CMS data [abstract no: TH-PO847].	St.Peter, W., Liu, J., Fan, Q., et al. (2006). Journal of the American Society of Nephrology 17(Abstracts): 287a.
	DCOR Study: assessing impact of sevelamer vs. calcium-based phosphate binders on hospitalization and morbidity in hemodialysis patients using CMS data [abstract no: TH-PO846].	St.Peter, W., Liu, J., Fan, Q., et al. (2006). Journal of the American Society of Nephrology 17(Abstracts): 287a.
	A prospective, randomized trial assessing the impact on outcomes of sevelamer in dialysis patients - the DCOR trial [abstract no: SP392].	Suki, W., Zabaneh, R., Cangiano, J., et al. (2006). Nephrology Dialysis Transplantation 21(Suppl 4): iv145.
	The DCOR trial - a prospective, randomized trial assessing the impact on outcomes of sevelamer in dialysis patients [abstract no: TH-PO745].	Suki W, Zabaneh R, Cangiano J et al Journal of the American Society of Nephrology 16: 281a.
	The DCOR Trial: a prospective, randomized trial assessing the impact on outcomes of sevelamer in dialysis patients.	Suki W, Zabaneh R, Cangiano J et al American Society of Nephrology. Philadelphia, Pennsylvania: 2005
De Santo	Sevelamer worsens metabolic acidosis in hemodialysis patients.	De Santo N.G., Frangiosa A, Anastasio P et al.J Nephrol 2006; 19 [Suppl 9]: S108–S114.
Ferreira	Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients.	Ferreira, A., Frazao, J.M., Monier-Faugere, M.-C., et al. (2008)Journal of the American Society of Nephrology 19(2): 405-412.
Gallieni	Comparison of sevelamer HC1 and calcium carbonate in the treatment of hyperphosphatemia in dialysis patients: a randomized clinical trial - Calcium Carbonate Sevelamer Evaluation (CaCSE) study [abstract no: SA-PO867].	Gallieni, M., Cicchetti, T., Salvadori, M., et al. (2005). Journal of the American Society of Nephrology 16: 746a.
Kinugasa	The PBSG. Effects of PB-94 (sevelamer hydrochloride), a phosphate binder, on the treatment of hyperphosphatemia in hemodialysis patients - a randomized, open	Kinugasa E, Koshikawa S, J Am Soc Nephrol 2001; 12: 755A

	label, dose titration study of PB-94 versus Caltan tablet 500 (calcium carbonate).	
Sadek	Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs. calcium carbonate in dialysis patients: an open-label, randomized study.	Sadek T, Mazouz H, Bahloul H et al. Nephrol Dial Transplant 2003; 18: 582–589.
Shaheen	Efficacy and safety of sevelamer. Comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients.	Shaheen F.A., Akeel N.M., Badawi L.S., Souqiyyeh M.Z.Saudi Medical Journal 2004; 25: 785–791.
Bleyer	A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. An open label, cross-over study of the new phosphate binder renagel in the management of hyperphosphatemia in ESRD patients [abstract].	Bleyer AJ, Burke SK, Dillon M et al Am J Kidney Dis 1999; 33: 694–701 Bleyer, A.J., Garrett, B., Kant, K.S., et al. (1997). Journal of the American Society of Nephrology 8(Program & Abstracts): 548a.
RIND Trial (Block)	Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Accelerated vascular calcification and relative hypoparathyroidism in incident haemodialysis diabetic patients receiving calcium-based phosphate binders. Accelerated vascular calcification in diabetic patients new to hemodialysis treated with calcium salts as compared to sevelamer [abstract no: SA-PO818]. Calcium containing phosphate binders are associated with increased mortality risk in hemodialysis patients compared to sevelamer.	Block, GA, Spiegel, DM, Ehrlich, J. et al. Kidney Int 2005; 68: 1815–1824. Block, G.A., Raggi, P., Bellasi, A., et al. (2007). Kidney international 71(5): 438-41. Galassi, A., Spiegel, D.M., Bellasi, A., et al. (2006). Nephrology Dialysis Transplantation 21(11): 3215-3222. Galassi, A., Spiegel, D., Newbold, C., et al. (2005). Journal of the American Society of Nephrology 16: 735a Spiegel D.M. et al. 2006 XLIII Congress of the European Renal Association (ERA)/European Dialysis and Transplant Association (EDTA). July 15-18 2006 Glasgow, United Kingdom..
Hervas	Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate.	Hervas J.G., Prados D, Cerezo S Kidney Int 2003; 63 [Suppl 2]: S69–S72.
Liu	A comparison of sevelamer hydrochloride with calcium acetate on biomarkers of bone turnover in hemodialysis patients.	Liu, Y.L., Lin, H.H., Yu, C.C., et al. (2006Renal failure 28(8): 701-7.
CARE Trial (Quniba 2004)	Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate	Qunibi WY, Hootkins RE, McDowell LL et al. Kidney

	Renagel Evaluation (CARE Study). Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis: Results of the CARE study.	Int 2004; 65: 1914–1926 Qunibi, W.Y. and Nolan, C.R. (2004 Kidney International, Supplement 66(90): S33-S38..
CARE-2 Trial (Quniba 2008)	A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. 18. Cardiovascular calcification (CVC) in hemodialysis (HD) patients: study design and preliminary mineral data of the calcium acetate sevelamer evaluation-2 (CARE-2) study [abstract no: PUB386]. Coronary artery calcification (CAC) in hemodialysis patients (HDP): preliminary results from the calcium acetate renagel evaluation-2 (CARE-2) study [abstract no: TH-PO845].	Qunibi W, Moustafa M, Muenz LR et al CARE-2 Investigators Am J Kidney Dis. 2008 Jun; 51(6):952-65. Epub 2008 Apr Qunibi, W., Horwith, G., Kessler, P., et al. (2005) Journal of the American Society of Nephrology 16(Oct Abstracts Issue): 866a. Qunibi, W., Moustafa, M., Kessler, P., et al. (2006). Journal of the American Society of Nephrology 17(Abstracts): 286a.
Treat to Goal Trial (Chertow)	Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. [O106] Sevelamer is more effective than calcium in the management of mineral metabolism and arterial calcification [abstract]. Lipid lowering effect of renagel, a novel phosphate binder [abstract]. Long-term comparison of a calcium-free phosphate binder and calcium carbonate--phosphorus metabolism and cardiovascular calcification. Sevelamer is more effective at controlling disorders of mineral metabolism than calcium-based phosphate binders in	Chertow G.M., Burke S.K., Raggi P. Kidney Int 2002; 62: 245–252. Asmus, H.G., Braun, J., Krause, R., et al. (2005). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association European Renal Association 20(8): 1653-61 Bommer, J., Asmus, G., Braun, J., et al. (2002). European Dialysis and Transplant Association: -14. Bommer, J. and European Renagel Investigators, G. (2001)Nephrology Dialysis Transplantation 16(6): A122. Braun, J., Asmus, H.G., Holzer, H., et al. (2004). Clinical nephrology 62(2): 104-15. Chertow, G.M., Dillon, M.A., Amin, N., et al. (2001) Journal of the American

	hemodialysis patients [abstract].	Society of Nephrology 12(Program & Abstracts): 195a-196a
	Determinants of progressive vascular calcification in haemodialysis patients.	Chertow, G.M., Raggi, P., Chasan Taber, S., et al. (2004).Nephrology Dialysis Transplantation 19(6): 1489-96.
	The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients.	Chertow, G.M., Raggi, P., McCarthy, J.T., et al. (2003). American Journal of Nephrology 23(5): 307-314.
	In hemodialysis patients, sevelamer (renagel) attenuates coronary artery and aortic calcification and reduces LDL-C, APO-B, and HS-CRP compared with calcium acetate (PHOSLO) [abstract].	Chertow, G.M., Goodman, W.G., Toto, R.D., et al. (2002).Journal of the American Society of Nephrology 13(September, Program & Abstracts): 386a.
	Cardiovascular calcification progression - A comparison of sevelamer and calcium-based phosphate binders.	Raggi, P. (2005). Blood Purification 23(SUPPL. 1): 20-23.
	Sevelamer preserves and calcium reduces trabecular bone mineral density [abstract no: SA-PO924].	Raggi, P., Burke, S.K., Chasen Taber, S., et al. (2003) Journal of the American Society of Nephrology 14(Nov): 502a.
	Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer.	Raggi, P., Bommer, J. and Chertow, G.M. (2004).The Journal of heart valve disease 13(1): 134-141.
	Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients.	Ferramosca, E., Burke, S., Chasan Taber, S., et al. (2005) American Heart Journal 149(5): 820-5.
	Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis: a randomized clinical trial.	Garg, J.P., Chasan Taber, S., Blair, A., et al. (2005). Arthritis and rheumatism 52(1): 290-5.
	Thoracic vertebral bone density increases with renagel and decreases with calcium-based phosphate binder therapy - a two year study [abstract].	James, G., Raggi, P., Boulay, A., et al. (2003). Nephrology Dialysis Transplantation 18(Suppl 4): 681

8. Results of Trials

The PBAC noted that phosphate reduction trends were better with calcium compared to lanthanum, whereas calcium reduction is superior with lanthanum compared to calcium. The

re-submission concludes that these analyses demonstrate that lanthanum carbonate and sevelamer are not different in terms of phosphate reduction, reduction in serum calcium and effect on calcium-phosphate product. Calcium was significantly better ($P \leq 0.05$) in phosphate reduction in the sevelamer analysis. Calcium trended better ($P > 0.05$) in phosphate reduction in the lanthanum analysis, and in calcium-phosphate product control in the sevelamer analysis. The data suggest that both lanthanum and sevelamer are inferior to calcium in phosphate reduction although the phosphate reduction differences are small and may not be clinically important, the levels of significance are borderline and the meta-analysis have major heterogeneity. The PBAC noted that because of these data limitations, it would be difficult to conclude that sevelamer is worse than lanthanum in phosphate reduction. The most reliable comparison of lanthanum and calcium on phosphate reduction is the week 5 result from Trial LAM-IV-301 showing 57.8 % of lanthanum patients achieving phosphate control compared with 70.3 % of calcium patients ($p=0.002$). The submission did not specifically address the clinical implication of the finding of inferior phosphate control for lanthanum compared to calcium.

The re-submission concluded that these analyses "demonstrate no evidence that treatment with lanthanum negatively impacts survival compared to standard therapy or treatment with sevelamer" (p115, re-submission), and "that the data suggest greater trends in favour of mortality for lanthanum carbonate than for the DCOR data for overall survival (15 % versus 9 %, respectively) and for patients >65 years (31 % versus 22 %, respectively)" (p115, re-submission). These are the same mortality data presented in the previous submission. The PBAC noted that the trials compared are clinically different, neither mortality analysis result reached statistical significance, and there is no background randomised data relating biochemical control to mortality.

The re-submission presented new data consisting of one supplemental pilot trial (Trial SPD405-310) which provides head-to-head safety data of lanthanum versus sevelamer. By adverse event type, severity, and body system category the reported adverse event profiles for lanthanum and sevelamer were considered similar.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed equi-effectiveness in phosphate control, calcium control, and calcium-phosphate control, plus equi-effectiveness in mortality reduction to sevelamer.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective average daily doses are estimated as 1936 mg for lanthanum and 5231 mg for sevelamer based on a dose relativity of 2.7 using a 2-step indirect analysis. First, using Trial LAM-IV-301 the lanthanum:calcium carbonate dose relativity was found to be 0.52, and using a meta-analysis of the six sevelamer-calcium carbonate trials the sevelamer:calcium dose relativity was found to be 1.4. Secondly, the dose relativity of sevelamer-calcium is then the ratio of the two values or 2.7 (= 1.4/0.52). The meta-analysis on which the dose relativity is based uses trials that are widely variable clinically, which made the calculation of equi-effective doses somewhat uncertain.

11. Estimated PBS Usage and Financial Implications

The PBAC noted that in the calculation of the price based on the cost-minimisation analysis the submission assumed that the three different strengths of lanthanum would be used equally. Given the pricing of the different strengths of lanthanum the PBAC expressed concern that should the utilisation of the three different strengths vary from those estimated in the submission then the price arising from the cost-minimisation analysis would no longer be valid. The PBAC requested that the Pharmaceutical Benefits Pricing Authority (PBPA) monitor the distribution of the usage among the different strengths of lanthanum and use this information to maintain this equi-effective price.

The likely number of patients/year accounting for market share as necessary were estimated in the submission to be less than 10,000 in Year 5. This large increase on the previous submission was due to updated figures from ANZDATA (2007) on the prevalence of dialysis and its rate of growth, and an increase in the proportion of eligible dialysis patients from 11 % to 52 % with the listing proposed in this submission (phosphate > 1.6 mmol/L or calcium-phosphate product > 4 $mmol^2/L^2$) compared to the listing previously requested with calcium > 2.6 mmol/L.

The financial savings/year to the PBS excluding co-payments minus any savings in use of other drugs were estimated in the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended listing on a cost minimisation basis compared to sevelamer. The equi-effective average daily doses were estimated as 1936 mg for lanthanum and 5231 mg for sevelamer based on the dose relativity of 2.7 using a 2-step indirect analysis.

In making the recommendation the PBAC recognised a need for another non-calcium option for the treatment of hyperphosphataemia in patients with chronic kidney disease, and considered that the evidence presented generally support the claim that lanthanum is no worse than sevelamer. The PBAC noted however that there was heterogeneity between the studies used in the meta-analysis, with large variability across the trial designs, which made the calculation of equi-effective doses somewhat uncertain.

The PBAC noted the mortality data comparing lanthanum and sevelamer. There appeared to be no mortality difference.

Although the hearing highlighted that there have been 50,000 patient years of post marketing experience, ongoing monitoring should be in place and regular safety updates should be provided to the PBAC.

The PBAC noted that in the calculation of the price based on the cost-minimisation analysis the submission assumes that the three different strengths of lanthanum would be used equally. Given the pricing of the different strengths of lanthanum the PBAC expressed concern that should the utilisation of the three different strengths vary from those estimated in the submission then the price arising from the cost-minimisation analysis would no longer be valid. The PBAC requested that the PBPA monitor the distribution of the usage among the different strengths of lanthanum and use this information to maintain this equi-effective price.

The PBAC also recommended that the restriction for sevelamer be updated to reflect the listing of lanthanum. The intent of the restriction is for lanthanum or sevelamer to be used second line after calcium, and that lanthanum should not be used in combination with sevelamer.

Recommendation

LANTHANUM CARBONATE, tablet, 500 mg, 750 mg and 1000 mg, Fosrenol®, Shire Australia Pty Ltd. (7.4)

Restriction:

Authority Required

Maintenance therapy, following initiation and stabilisation of treatment with lanthanum carbonate, of hyperphosphataemia in a patient with chronic kidney disease on dialysis whose serum phosphate is not controlled on calcium and where:

(a) serum phosphate is greater than 1.6 mmol per L; or

(b) the serum calcium times phosphate product is greater than 4.0.

at the commencement of therapy.

NOTE: Not to be used in combination with sevelamer

Maximum quantity: 90

Number of repeats: 5

Section 100 (Highly Specialised Drugs Program)

Private hospital authority required

Management of hyperphosphataemia in a patient with chronic kidney disease on dialysis whose serum phosphate is not controlled on calcium and where:

(a) serum phosphate is greater than 1.6 mmol per L; or

(b) the serum calcium times phosphate product is greater than 4.0.

at the commencement of therapy.

Management includes initiation, stabilisation and review of therapy as required.

NOTE: Not to be used in combination with sevelamer

Pack size: 90

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

Shire welcomes the PBAC's decision to recommend Fosrenol, a non-calcium, non-resin phosphate binder for the treatment of hyperphosphataemia in dialysis patients with chronic kidney disease.