# A Post-Marketing Surveillance Study to Evaluate the Efficacy and Safety of Sevelamer Carbonate in the Management of Chronic Kidney Disease-Related Hyperphosphatemia in the Philippines

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## Abstract

**Introduction:** This is a prospective, post marketing surveillance study that aims to determine the efficacy and safety of sevelamer carbonate in hyperphosphatemic chronic kidney disease (CKD) patients in the Philippines.

**Methods:** Adult CKD patients with serum phosphorous levels >1.78 mmol/L and whose physician had decided to treat with sevelamer carbonate 800 mg were enrolled in the study and followed-up for a minimum of three visits from baseline within a six-month period. The primary endpoint was the change in serum phosphorous levels from baseline to the sixth month. Adverse events were noted and recorded during the treatment period.

**Results:** There were 233 patients included in the study from five centers in Metro Manila from 2010 to 2013. Of the 233 patients, 199 were on chronic dialysis, 33 were not on dialysis, and 1 had no data. There was a statistically significant (*P*-value <0.0001) reduction in serum phosphorous levels from baseline after treatment with sevelamer carbonate. There were 16 patients reported to have adverse drug reactions, 13 of whom had serious adverse events (SAE) and three were non-serious. Of the 13 patients with SAEs, only one was possibly/probably related to sevelamer carbonate and all three non-SAEs were possibly/definitely related to sevelamer carbonate.

**Conclusion:** The results showed sevelamer carbonate to be effective in lowering serum phosphorous levels and the most common adverse events were related to the gastrointestinal tract (1.4%). There were sixteen patients with adverse events, three of which were non-serious, while 13 were reported to be serious adverse events. Only one was probably related to the drug.

**Keywords:** chronic kidney disease, hyperphosphatemia, sevelamer carbonate

## Introduction

Chronic kidney disease (CKD) is associated with multi-systemic disorders brought about by impaired excretion and retention of metabolic wastes, excess water, and electrolytes as well as disorders of mineral metabolism.[1] One of these retained minerals is phosphorous, leading to hyperphosphatemia. Disorders of mineral metabolism are highly associated with cardiovascular and fracture-related mortality and morbidity in hemodialysis patients.[2,3]

Hyperphosphatemia stimulates the release of parathyroid hormone (PTH), which in turn stimulates phosphaturia. However, due to renal insufficiency, PTH-induced renal excretion of phosphorous does not take place. An ever-increasing serum phosphorous level leads to further release of PTH and eventual development of secondary hyperparathyroidism and a high calcium x phosphorous product.[4,5] What ensues thereafter is a series of events leading to debilitating and life-threatening complications like renal osteodystrophy and metastatic calcification.[6]

There are various medications used to reduce serum phosphorous levels in CKD. The most commonly used are phosphate binders. These drugs bind dietary phosphorous in the gastrointestinal tract and prevent their systemic absorption.[7] Calcium-based phosphate binders like calcium carbonate have been most commonly used in the Philippines for many years, but are associated with the development of hypercalcemia.[8,9] In one study the former was observed to be associated with an increase in renal osteodystrophy-related complications.[10, 11,12,13,14] Aluminum hydroxide has also been used for this purpose, but is associated with toxicity and accumulation of aluminum in bone.[1,9,15] Dietary phosphate restriction alone (independent of plasma calcitriol or calcium) has been found to lower plasma PTH in renal failure and prevent hyperplasia of parathyroid glands. Control of dietary phosphate may be the most important strategy to prevent secondary hyperparathyroidism.[16,17] Unfortunately, poor compliance to a low-phosphorous diet and intake of phosphate binders as well as associated adverse effects of phosphate binders have contributed to unsuccessful long-term management of hyperphosphatemia.[9]

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Sevelamer ($C_6H_{12}ClNO$) is a polymeric amine that binds dietary phosphate without the associated adverse effects of aluminum- and calcium-based phosphate binders. In animal studies on its metabolism and pharmacokinetics, sevelamer was observed to be completely unabsorbed, with greater than 99% of the drug recovered from the feces of rats.[16,18] In a pilot study on the efficacy and safety of sevelamer, treatment resulted in a statistically significant decrease in mean serum phosphorous levels from baseline to end of treatment.[19] A total of 75% of patients with stage IV and 70% of patients with stage V chronic kidney disease achieved the target serum phosphorous at the end of treatment and it was well tolerated.[20] To date, no study on the efficacy and safety of sevelamer carbonate has been done in the Philippines. Therefore, the objective of this study is to evaluate the efficacy and safety of sevelamer carbonate in hyperphosphatemic chronic kidney disease (CKD) patients in the Philippines.

## Methods

This is a three-year multicenter, open-label, non-randomized, non-comparative, prospective observational post-marketing surveillance (PMS) study.

Included in the study were adult male or female patients ≥18 years old, diagnosed with CKD, whether on dialysis or not. For non-dialyzed patients, serum phosphorous levels were >1.78 mmol/L while in dialyzed patients, serum phosphorous levels were >1.48 mmol/L. Patients may or may not be on a phosphate binder and their physician had decided to treat with sevelamer. Patients signed a data release consent form. On the other hand, those excluded from this study were patients who were pregnant or lactating, those with allergy to sevelamer, or those who were previously on sevelamer prior to inclusion in the study.

The study was approved by the Institutional Review Board and respective ethics committees of each center and conducted in accordance with Good Clinical Practice Guidelines[21] and the Declaration of Helsinki.[22] Patients who fulfilled the inclusion/exclusion criteria were enrolled in the study. A written informed consent was obtained from the patients or their guardians before any investigative procedure began. Patients were prescribed sevelamer carbonate according to the investigator's clinical judgment and were followed-up for a minimum of three follow-up visits from baseline within a six-month period according to the physician's clinical practice management. All patients receiving sevelamer carbonate within the three-year post marketing surveillance period was included in the study. Serum phosphorous levels and adverse drug reactions at baseline and during all follow-up visits were recorded to assess the drug's efficacy and safety.

### Efficacy and safety endpoints

The serum phosphorus value, date of the blood draw, and the prescribed dose of sevelamer carbonate at the time of the blood draw were recorded on a monthly or quarterly basis, depending on the physician's clinical practice and judgment. Serum phosphorus measurements three months prior to starting sevelamer carbonate therapy were taken and recorded along with the date of the blood draw. If another phosphate binder was being taken, information regarding the type of phosphate binder and the prescribed dose at the time of the blood draw was obtained. The date of initiation of sevelamer carbonate treatment was recorded. The serum phosphorus levels were measured during three follow-up visits.

### Safety evaluation

Safety was evaluated based on adverse drug reactions (ADRs), which were noted and assessed if related to the use of sevelamer carbonate. ADRs that occurred during the course of treatment with sevelamer carbonate were recorded on the ADR case report form. If the ADR was serious, the ADR was recorded on the serious drug reaction (SDR) case report form and reported within 24 hours of the physician's first knowledge of event.

### Data management and analysis

Serum phosphorus levels were collected and summarized over time using descriptive statistics, which utilized the number of observations, range, mean, and standard deviation. In addition, the percentage of patients with controlled serum phosphorus levels were summarized over time. The data formed from this analysis was added as part of the descriptive portion of the final analysis. The change in serum phosphorous levels was analyzed using one-way analysis of variance (ANOVA). A *p*-value of <0.05 was considered statistically significant.

## Results

Two hundred thirty-three patients were enrolled from five tertiary hospitals in Metro Manila from 2010 to 2013. Of the 233, 199 patients were on chronic dialysis, 33 were not on dialysis, and one had no data on any form of renal replacement therapy. Of the 199 dialyzed patients, 76 were female while 123 were male. Among the 33 non-dialyzed patients 19 were female and 14 were male. (Table I)

Of the 233 patients, 86 (36.91%) used a prior phosphate binder, while 147 (63.09%) did not use any. One hundred ninety-nine (199) of the 233 patients underwent dialysis, 180 (90.10%) underwent hemodialysis, 17 (1.37%) on peritoneal dialysis, and one patient on both hemodialysis and peritoneal dialysis. There was no data on the type of renal replacement therapy for one patient.

**Table I.** Demographic profile of hyperphosphatemic CKD patients treated with sevelamer (n=233)

| | n | % |
|---|---|---|
| Sex | | |
| Female | 96 | 41.2 |
| Dialyzed | 76 | 32.62 |
| Non-dialyzed | 19 | 8.15 |
| No data | 1 | 0.43 |
| Male | 137 | 58.8 |
| Dialyzed | 123 | 52.79 |
| Non-dialyzed | 14 | 6.01 |

**Table II.** Serum phosphorous statistics (mmol/L) over time (pre-sevelamer)

| | Visit 1 | Visit 2 | Visit 3 |
|---|---|---|---|
| **Dialyzed** | | | |
| Number of observations | 67 | 26 | 7 |
| Range | 0.63-4.55 | 0.88-3.62 | 2.00-3.80 |
| Average | 2.29 | 2.3 | 2.83 |
| Standard deviation | 0.8 | 0.67 | 0.51 |
| *p*-value | | 0.248 | 0.8 |
| **Non-dialyzed** | | | |
| Number of observations | 5 | 3 | 0 |
| Range | 0.68-3.49 | 2.01-3.36 | 0 |
| Average | 1.92 | 2.55 | 0 |
| Standard deviation | 0.95 | 0.58 | 0 |
| *p*-value | | 0.039* | 0 |

*Note: *significant at 5% level of significance*

**Table III.** Serum phosphorus statistics (mmol/L) over time (post-sevelamer) for dialyzed and non-dialyzed patients

| | Base-line | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 |
|---|---|---|---|---|---|---|---|---|---|
| **Dialyzed** | | | | | | | | | |
| No. of observations | 153 | 180 | 166 | 153 | 77 | 45 | 31 | 6 | 8 |
| Range | 0.84-6.25 | 0.71-4.74 | 0.69-4.35 | 0.65-4.81 | 0.76-3.86 | 0.71-3.40 | 0.71-3.23 | 0.66-2.31 | 1.10-3.04 |
| Mean | 2.27 | 2.13 | 2.05 | 1.98 | 1.85 | 1.98 | 1.79 | 1.61 | 1.76 |
| SD | 0.68 | 0.76 | 0.73 | 0.71 | 0.69 | 0.66 | 0.68 | 0.54 | 0.91 |
| **Non-dialyzed** | | | | | | | | | |
| No. of observations | 31 | 27 | 23 | 21 | 9 | 2 | 0 | 0 | 0 |
| Range | 1.70-6.10 | 0.92-3.71 | 1.14-4.20 | 0.93-4.10 | 0.66-3.16 | 0.98-2.05 | 0 | 0 | 0 |
| Mean | 2.33 | 1.73 | 2.01 | 1.96 | 1.88 | 1.52 | 0 | 0 | 0 |
| SD | 0.91 | 0.64 | 0.7 | 0.75 | 0.82 | 0.54 | 0 | 0 | 0 |

**Table IV.** ANOVA table on the mean serum phosphorous levels (mmol/L) over time (post-sevelamer) in dialyzed and non-dialyzed patients

| Source | DF | SS | Adj(SS) | MS | Fc | *P*-Value |
|---|---|---|---|---|---|---|
| Dialyzed patients | 196 | 299.7111 | 294.2285 | 1.5012 | 5.7 | <0.0001* |
| Visit | 10 | 10.4608 | 10.4608 | 1.0461 | 3.97 | <0.0001* |
| Error | 609 | 160.3694 | 160.3694 | 0.2633 | | |
| Total | 815 | 470.5412 | | | | |
| Non-dialyzed patients | 32 | 33.819 | 36.3928 | 1.1373 | 2.83 | <0.0001* |
| Visit | 5 | 8.5182 | 8.5182 | 1.7036 | 4.24 | <0.002* |
| Error | 75 | 30.1256 | 30.1256 | 0.4017 | | |
| Total | 112 | 72.4627 | | | | |

*Note: *significant at 5% level of significance*

As for the type of membrane dialyzer used by the patients, 41 patients (22.28%) used F8 and 20 patients used FX80 (10.87%). Majority of dialysis patients used synthetic high-flux membrane dialyzers.

### Effectiveness evaluation

Of the 199 dialyzed patients, 49 (24.62%) had serum phosphorus levels higher than 1.78mmol/L, while 150 patients (75.38%) had serum phosphorus levels ranging from 1.48 mmol/L to 1.78mmol/L. Meanwhile, all of the 33 non-dialyzed patients had serum phosphorus levels higher than 1.78mmol/L.

As for the pre-sevelamer treatment values' statistics for dialyzed and non-dialyzed patients summarized over time, the number of patients seen decreased on each follow-up. It was likewise noted that the serum phosphorus levels decreased throughout the three visits of observation (Table II).

Table III summarizes the post-sevelamer treatment values' statistics summarized over time. One-way ANOVA, demonstrated a significant difference ($p<0.0001$) in the mean serum phosphorous levels from baseline through the eight follow-up visits. (Table IV)

### Safety evaluation

Sixteen patients reported an adverse drug reaction, 13 were serious adverse events and three non-serious. (Tables V & VI) Of the thirteen serious adverse events (SAE) reported, nine of the patients expired.

## Discussion

Three hundred patients were targeted for enrollment for the post-marketing surveillance. However, only 233 patients screened from five hospitals completed the study. Most of the patients came from one private hospital (Makati Medical

**Table V.** Safety evaluation

| | | |
|---|---|---|
| **Serious adverse events** | | |
| 1 | Patient expired – CAD; Aspiration pneumonia | Not related to sevelamer |
| 2 | Patient expired – Multi organ failure; Stage 4 colon cancer | Not related to sevelamer |
| 3 | Patient expired – Prostatic Cancer; Obstructive jaundice; Neoplasm | Not related to sevelamer |
| 4 | Patient expired – Cardiac arrest | Not related to sevelamer |
| 5 | Patient expired – CKD stage 5; Septic shock | Not related to sevelamer |
| 6 | Patient expired – Acute coronary syndrome | Not related to sevelamer |
| 7 | Patient expired – Hemorrhagic stroke | Not related to sevelamer |
| 8 | Patient expired – Septic shock | Not related to sevelamer |
| 9 | Patient expired – Septic shock | Not related to sevelamer |
| 10 | Patient underwent kidney transplant | Not related to sevelamer |
| 11 | Patient underwent kidney transplant | Not related to sevelamer |
| 12 | Patient had palpitations, weakness and abdominal discomfort | Possibly/probably related to sevelamer |
| 13 | Pneumonia and CAD | Not related to sevelamer |
| **Non-serious adverse events (NSAE)** | | |
| 1 | Abdominal pain and vomiting, dizziness, headache, nausea | Possibly/definitely related to sevelamer |
| 2 | Epigastric discomfort | Possibly related to sevelamer |
| 3 | Vomiting | Definitely related to sevelamer |

Center, 39.9%) and one government hospital (National Kidney and Transplant Institute, 36.9%). There were more males (N=137, 58.8%) than females (N=96, 41.2%) in the study, with an average age of 59 (± 15.0) years old. Of the 233 included, only 224 had data up to the first visit.

On the objective of efficacy, there was deviation from the original plan of the PMS that serum phosphorus levels would be collected at least three months prior to including patients in the study. As noted for the pre-sevelamer PMS, the run-in for dialyzed patients during the first visit included 67 patients but decreased to 26 patients on the second visit, and finally seven patients on the third visit prior to entering the PMS; whereas the run in for non-dialyzed patients during the first visit included five patients but decreased to three patients on the second visit, and finally no patient on the third visit prior to entering the PMS. There was no statistically significant difference in the serum phosphorus levels.

There were 153 dialyzed patients with baseline phosphorus values post-sevelamer run in. Phosphorus levels were obtained on the first visit (n=180) and on the second visit (n=166). Likewise, there were 31 non-dialyzed patients with baseline phosphorus values post-sevelamer run in. Phosphorus levels were otherwise obtained on the first visit (n=27) and on the second visit (n=23) for these patients. None of the patients had followed the original protocol of having serum phosphorus levels three months prior to inclusion in the PMS and following-up to completion for three visits within six months of taking sevelamer carbonate. One-way ANOVA demonstrated that there was a statistically significant decline in serum phosphorus levels from baseline after starting patients on sevelamer carbonate, even if the number of patients on various follow-up visits was inconsistent and that there were decreasing numbers of patients on subsequent follow-up visits (intention to treat analysis).

There were sixteen patients who developed adverse drug reactions (ADR); thirteen were serious adverse events (SAE) and three non-serious. Of the 13 patients with SAEs, only one was possibly/probably related to sevelamer carbonate and all three non SAEs were possibly or definitely related to sevelamer carbonate. Three patients experienced non SAEs and made up 1.4% (3/220) of the non-serious adverse events reported. The SAE possibility related to sevelamer carbonate based on causality were palpitations with weakness and abdominal discomfort. Of the non SAEs, abdominal discomfort (pain, vomiting, and epigastric pain) was the most common complaint.

As reflected in the product insert of sevelamer carbonate (Renvela®) the most frequently occurring adverse event in a short-term study (over eight-week observation period) was gastrointestinal in nature–vomiting (three percent) and nausea (three percent). Long—term studies for sevelamer hydrochloride with the same moiety as sevelamer carbonate also demonstrated gastrointestinal complaints as the most common AE noted. The findings of gastrointestinal complaints in the PMS were within the reported common AEs with the sevelamer compound (common–more than or equal to 1100 or <1/10) for gastrointestinal disorders.

Drug to drug interaction was not evaluated as this was not included in the protocol for the approved PMS. No data on concomitantly taken medications were obtained.

## Conclusion

This post marketing surveillance study showed that sevelamer carbonate was effective in lowering serum phosphorus levels. The most common adverse events were related to the gastrointestinal tract (1.4%). While there were 5.9% reported serious adverse events, only 0.5% was probably related to the drug in the PMS. There were three patients reported to have non-serious adverse reaction among the remaining 220 patients who had no serious ADRs.

## References

1. **Lowrie EG, Lew NL**; Death Risk in Hemodialysis Patients: The Predictive Value of Commonly Measured Variables and an Evaluation of Death Rate Differences between Facilities. Am J Kidney

Dis. 15(5):458-482, 1990.
2. **Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM**; Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 15(8):2208-2218, 2004.
3. **Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, Akizawa T, Kurokawa K, Bommer J, Piera L, Port FK**; Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 67(3):1179-1187, 2005
4. **Noordzij M, Korevaar JC, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT**. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: association with mortality in dialysis patients. Am J Kidney Dis. 46(5):925-932, 2005.
5. **Slinin Y, Foley RN, Collins AJ**. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. J Am Soc Nephrol. 16(6):1788-1793, 2005.
6. **Block GA, Hulbert-Shearon TE, Levin NW, Port FK**; Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 31(4):607-617, 1998.
7. **Schaefer K, von Herrath D.** Prophylaxis and therapy of renal osteopathy: Phosphate binding agents. J Nephrol. 6(4): 177-81, 1993.
8. **Bechtel U, Mucke C, Feucht HE, Schiffl H, Sitter T, Held E**; Limitations of pulse oral calcitriol therapy in continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis. 25(2):291-296, 1995.
9. **Delmez JA, Slatopolsky E**; Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. Am J Kidney Dis. 19(4):303-317, 1992.
10. **D' Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, Swanepoel C, Pejanovic C, 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. (85):S73-78, 2003.
11. **Behets GJ, Verberckmoes SC, Oste L, Bervoets AR, Salome M, Cox AG, Denton J, De Broe ME, D'Haese PC** ; Localization of lanthanum in bone of chronic renal failure rats after oral dosing with lanthanum carbonate. Kidney Int. 67(5):1830- 1836, 2005.
12. **Feng L, Xiao H, He X, Li Z, Li F, Liu N, Chai Z, Zhao Y, Zhang Z**; Long-term effects of lanthanum intake on the neurobehavioral development of the rat. Neurotoxicol Teratol. 28(1):119-124, 2006.
13. F**osrenol Package Insert**. Physician's Desk Reference. 60th ed. Montvale NJ: Thomson PDR, 2006.
14. **Slatopolsky E, Liapis H, Finch J**. Progressive accumulation of lanthanum in the liver of normal and uremic rats. Kidney Int. 68(6):2809-2813, 2005.
15. **Jenkins DA, Gouldesbrough D, Smith GD, Cowie JF, Winney RJ**; Can Low-Dosage Aluminum Hydroxide Control the Plasma Phosphate Without Bone Toxicity? Nephrol Dial Transplant. 1989;4(1):51-56.
16. **Hercz G, Coburn JW**; Prevention of phosphate retention and hyperphosphatemia in uremia. Kidney Int Suppl. 22:S215-220, 1987.
17. **Hsu CH**; Are We Mismanaging Calcium and Phosphate Metabolism in Renal Failure? Am J Kidney Dis. 29(4):641-649, 1997.
18. **Petersen JS, Rosenbaum DP, Burke SK**. Sevelamer, a phosphate-binding polymer, is a non-absorbed compound. Clin Pharmacokinet. 41(7):517-23. 2002.
19. **Mahdavi H, Kuizon BD, Gales B, Wang HJ, Elashoff RM, Salusky IB**. Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. Pediatr Nephrol. 2003 Dec;18(12):1260-4.
20. **Ketteler M., Rix M, Fan S. Pritchard N, Oestergaard O, Chasan-Taber S, Heaton J, Duggal A, Kaira PA**; Efficacy and Tolerability of Sevelamer Carbonate in Hyperphosphatemic Patients Who Have Chronic Kidney Disease and Are Not on Dialysis. CJASN July 2008 vol. 3 no. 4 1125-1130 National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 42(4 Suppl 3):S1-201, 2003.
21. **International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use** (1996). Guideline for Good Clinical Practice. Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
22. **World Medical Association Declaration of Helsinki.** (1989). Available from: https://history.nih.gov/research/downloads/helsinki.pdf.