New Drugs and Novel Concepts
13 – 17 June 2016

The Treatment Concepts of Hyperphosphatemia in CKD and New Phosphate Binders

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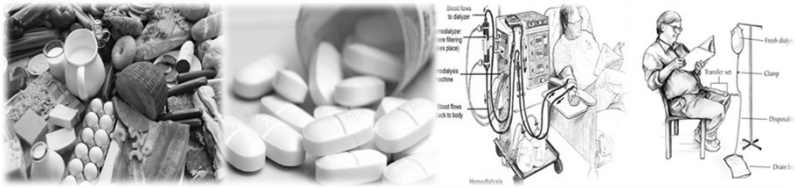
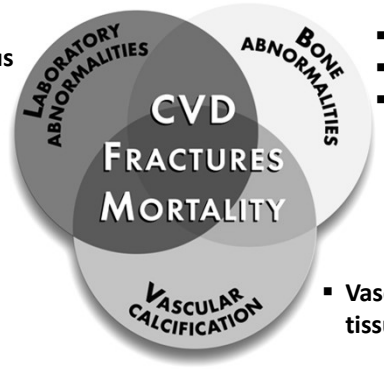
Talk Outlines:

Hyperphosphatemia as a CKD complication:

- ✪ Phosphate homeostasis
- ✪ Hyperphosphatemia and its consequences
- ✪ Treatment options: Current and new drugs



CHRONIC KIDNEY DISEASE– MINERAL AND BONE DISORDER



- **Calcium**
- **Phosphorus**
- **iPTH**
- **Vitamin D**

- **Bone turnover**
- **Bone mineralization**
- **Bone volume, linear growth, or strength**

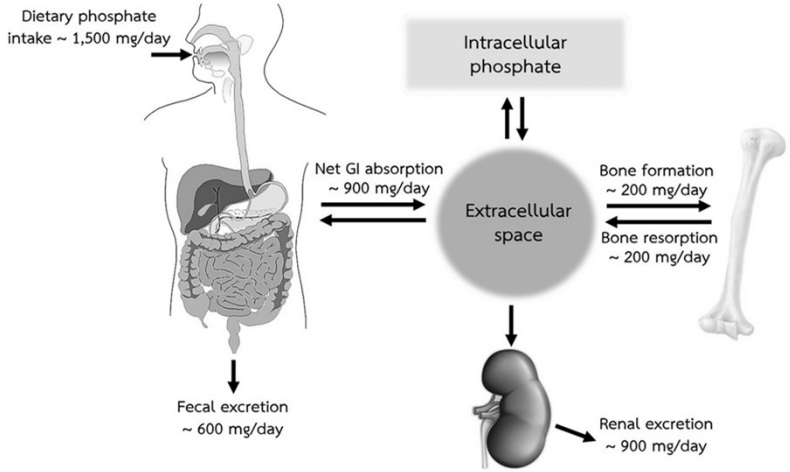
- **Vascular or other soft tissue calcification**

CKD-MBD

From: KDIGO CKD-MBD guideline 2009

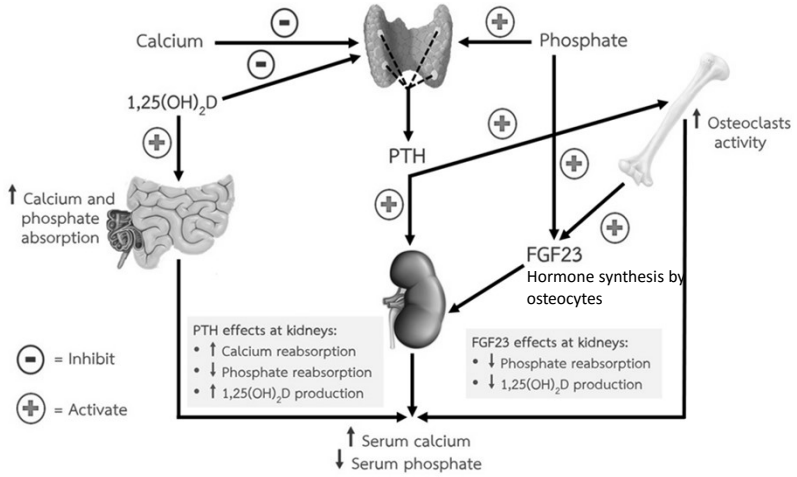
Kidney Int. 2006 Jun;69(11):1945-53.
Adv Chronic Kidney Dis 2007;14(1):3-12.

Phosphate Balance:



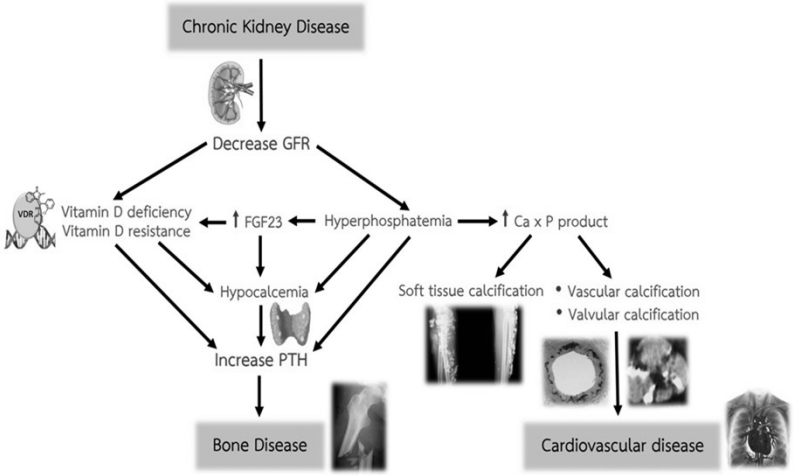
Semin Dial 2007; 20(4): 295-301.

Phosphate Homeostasis:

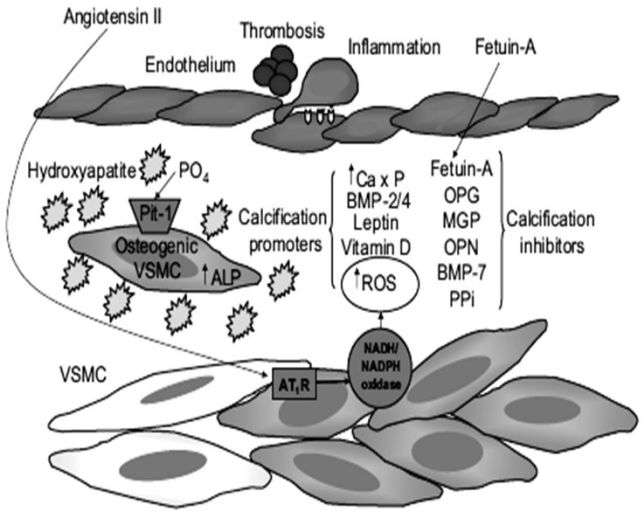


J Am Board Fam Med 2009; 22(5): 57Å-81.

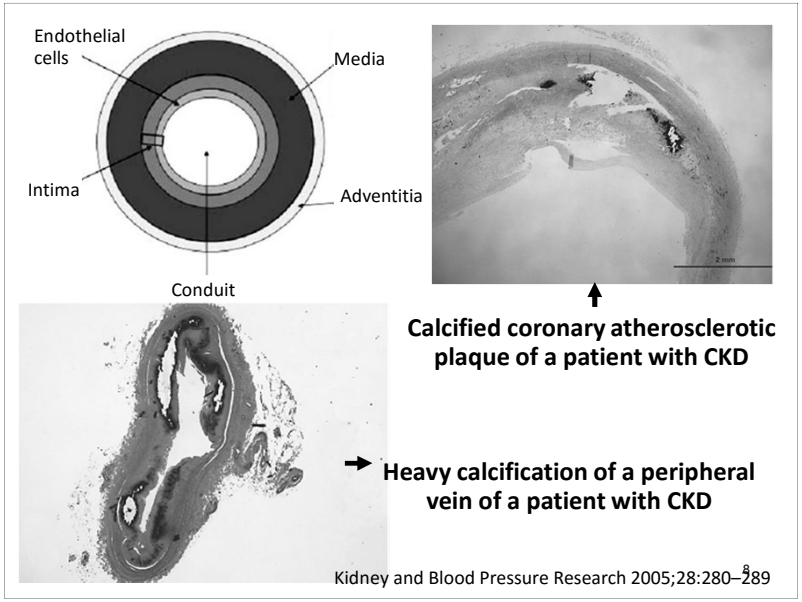
Hyperphosphatemia Consequences:



J Am Board Fam Med 2009; 22(5): 57Å-81.



Circulation 2007;116;85-97



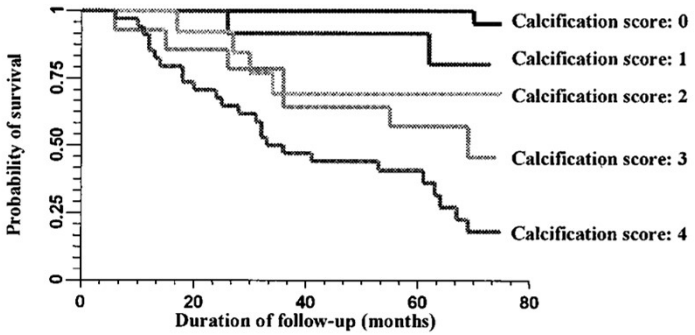
Calcified coronary atherosclerotic plaque of a patient with CKD

Heavy calcification of a peripheral vein of a patient with CKD

Kidney and Blood Pressure Research 2005;28:280–289

Why do we need to concern about bone metabolism disorder in CKD patients?

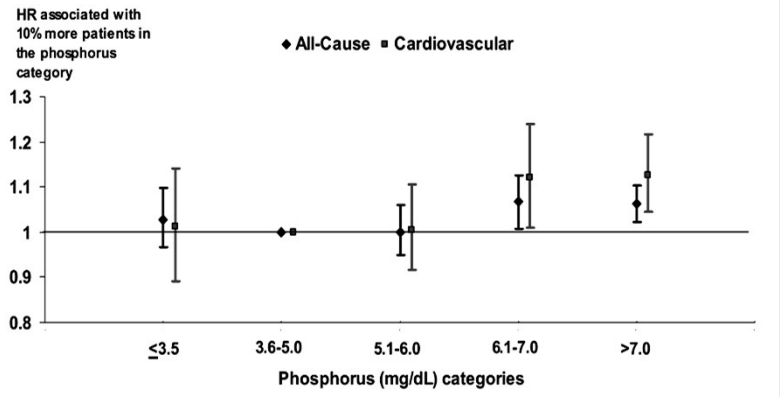
Arterial calcification increases mortality risk



Probability of all-cause survival according to calcification score. Comparison between curves was highly significant (χ^2=42.66, P<0.0001).

Hypertension 2001;38:938–42.

Patient all-cause and cardiovascular mortality risk associated with 10%more facility patients within each serum phosphorus category versus reference category



American Journal of Kidney Diseases 2008;52(3):519-30.

CKD-MBD Management

National Kidney Foundation
KDOQI
KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE

2003

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES
KDIGO

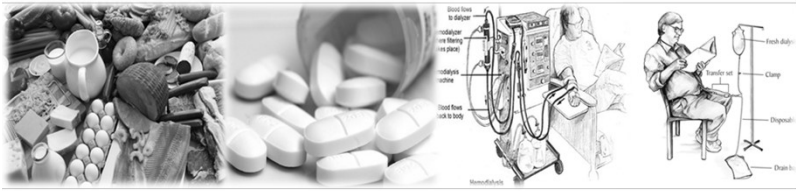
2009

Parameter	Stage 3	Stage 4	Stage 5
GFR (mL/min/1.73m²)	30 – 59	15 – 29	< 15 Or dialysis
Corrected Calcium (mg/dL)	8.4 – 9.5 Not > 10.2	8.4 – 9.5 Not > 10.2	8.4 – 9.5 Not > 10.2
= measure Ca + [0.8x(4 – alb)]	8.5 – 10.0 Not > 10.5	8.5 – 10.0 Not > 10.5	8.5 – 10.0 Not > 10.5
Phosphorus (mg/dL)	2.7 – 4.6	2.7 – 4.6	3.5 – 5.5
	2.5 – 4.5	2.5 – 4.5	Toward normal
Ca x P Product (mg²/dL²)	< 55		
Individualized evaluate Ca and P together (2D)			
iPTH (pg/mL)	35 – 70	70 – 110	150– 300
	Optimal: NOT KNOWN		2-9 x UNL

AJKD 2003;42(4):S12-S28. Kidney Int 2009;76(Suppl 113):S1–S130.

Management of Hyperphosphatemia

- ✪ High phosphate diet restriction
- ✪ Medication: phosphate binders
- ✪ Dialysis intervention: HD or PD



Management of Hyperphosphatemia

- ◆ **Limiting dietary phosphate intake:**
  - ✪ ***KDOQI:*** Dietary phosphorus should be restricted to 800 to 1,000 mg/day when;
    - The serum phosphorus levels are elevated (> 4.6 in CKD $S_{3,4}$ or > 5.5 in CKD S_5)
    - The plasma levels of intact PTH are elevated above target range of the CKD stage

American Journal of Kidney Diseases 2003;42(4):S12-S28.

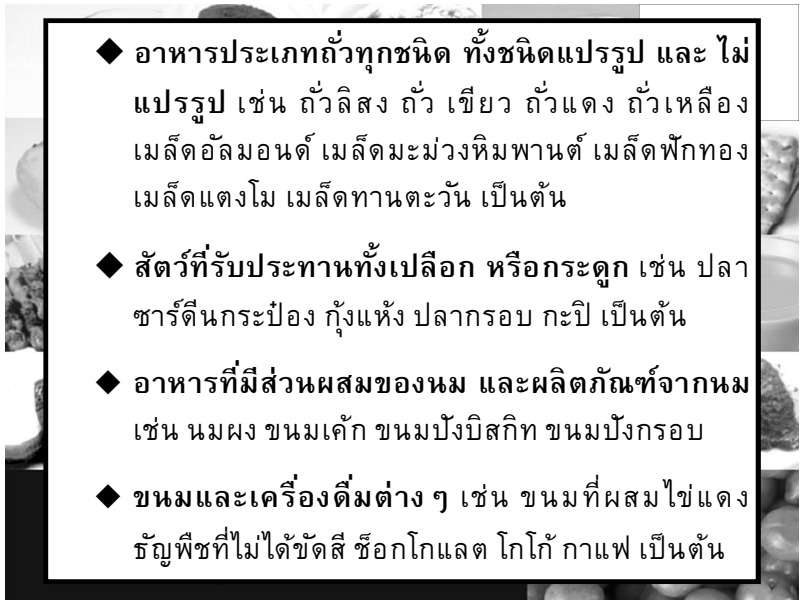
Management of Hyperphosphatemia

KDIGO: In patients with CKD stages 3–5D, we suggest ***limiting dietary phosphate intake*** in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

Primary intervention for the management of CKD–MBD, strongly recommend?

- Insufficient data, esp. in stage 5D
- Helpful in early CKD
- Adjunct to phosphate binders and dialytic removal of phosphate in 5D patients.

Kidney Int 2009;76(Suppl 113):S1–S130.



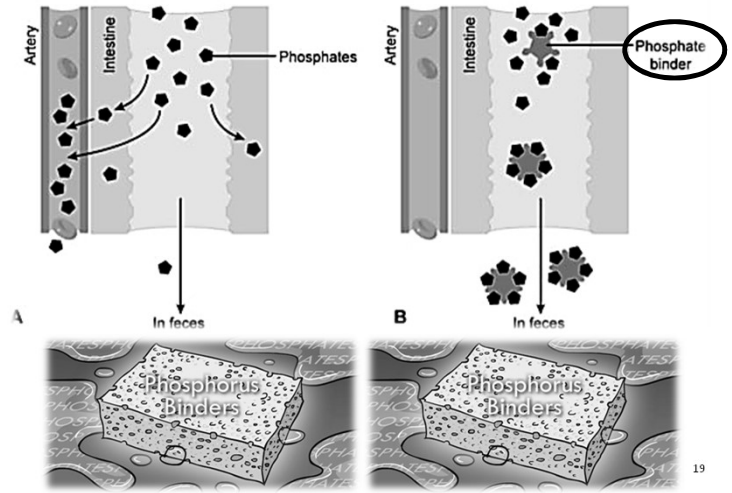
Management of Hyperphosphatemia

If phosphorus or intact PTH levels cannot be controlled within the target range, despite dietary phosphorus restriction,

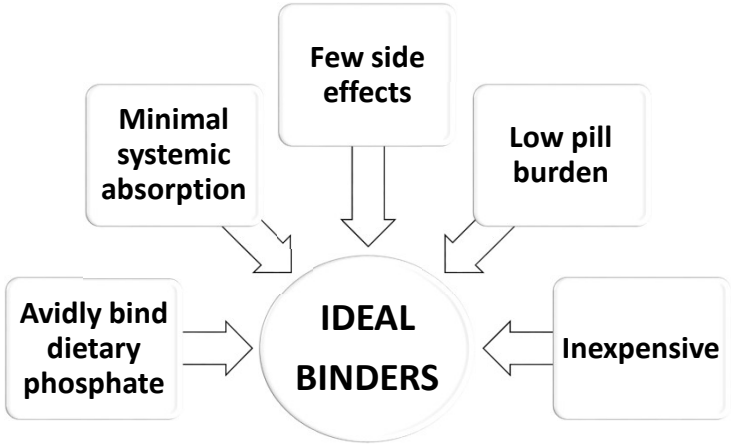
Phosphate binders should be prescribed.

American Journal of Kidney Diseases 2003;42(4):S12-S28.

Phosphate Binder Mechanism



The Ideal Phosphate Binders



Drugs 2014;74: 863–877.

N Engl J Med 2010;362:1312-24.

Management of Hyperphosphatemia

Current phosphate binders:

- Calcium-based phosphate binders: *usually Calcium carbonate*, Calcium acetate
- Non-calcium-based phosphate binders:
  Magnesium hydroxide, Magnesium carbonate,
  Magnesium carbonate/Calcium carbonate,
  Magnesium carbonate/Calcium acetate
  *Aluminium hydroxide (1980s)***
  (Usually not use in US)

N Engl J Med 2010;362:1312-24.
American Journal of Kidney Diseases 2003;42(4):S12-S28.

Management of Hyperphosphatemia

Current phosphate binders:

- Non-calcium, non-aluminum, non-magnesium containing phosphate binders:

  Sevelamer (polymer-based):
  Sevelamer HCl (approved in 1998)
  Sevelamer carbonate (approved in 2009)

  Lanthanum: Lanthanum carbonate
  (approved in 2004)

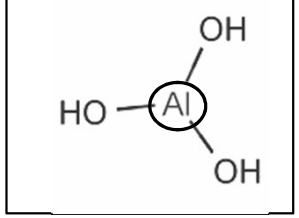
N Engl J Med 2010;362:1312-24.
American Journal of Kidney Diseases 2003;42(4):S12-S28.

Management of Hyperphosphatemia

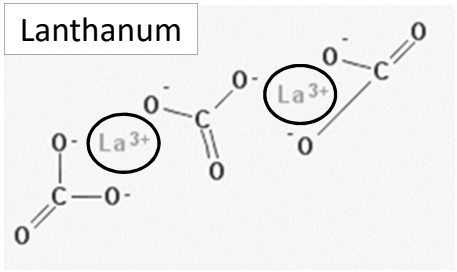
Current phosphate binders:

- Metal – based phosphate binders:

Aluminum



Lanthanum



Drugs 2014;74: 863–877.

Phosphate Binding Capacity

Phosphate binder	RPBC by g of compound listed in available product
Calcium carbonate (index value)	1.0
Calcium acetate	1.0
Magnesium carbonate (anhydrous weight, Magnebind)	1.7
"Heavy" magnesium carbonate (hydrated weight, OsvaRen)	1.3
Aluminum hydroxide	1.5
Aluminum carbonate	1.9
Sevelamer (carbonate or hydrochloride)	0.75
Lanthanum carbonate	2.0[a]

RPBC, relative phosphate-binding coefficient.
[a]Lanthanum carbonate tablet or wafer sizes are marketed as mg of elemental lanthanum. If based on mg of lanthanum carbonate the RPBC (relative to mg of $CaCO_3$ would be 1.2 instead of 2.0.

Semin Dial 2011;24(1):41-9.

Management of Hyperphosphatemia

Use of Phosphate Binders:

- *Calcium-based phosphate binders* are effective in lowering serum phosphorus levels and may be used as the *initial binder therapy*.
- Total dose of elemental calcium should not exceed 1,500 mg/day and total calcium intake should not exceed 2,000 mg/day

American Journal of Kidney Diseases 2003;42(4):S12-S28.

Management of Hyperphosphatemia

- **Ca-based phosphate binders limitation:**
  - ↑ *Serum Ca level:* 25 – 45% of Ca absorbs from GI tract → ↑ episodes of hypercalcemia
  - ↓ *serum PTH level* → adynamic bone disease
  - *Vascular calcification:* progression of arterial calcification

Kidney Int 2009;76(Suppl 113):S1–S130.
American Journal of Kidney Diseases 2003;42(4):S12-S28.

Management of Hyperphosphatemia

Calcium-based phosphate binders should restrict the dose or not be used in patients with CKD stages 3 – 5D who are:

- Hypercalcemic
- Arterial calcification
- Adynamic bone disease
- Serum PTH levels are persistently low

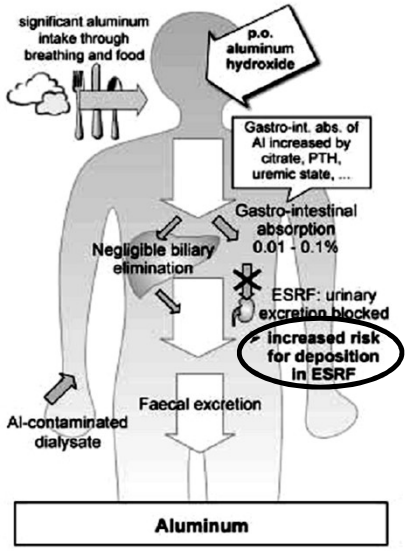
prefers non-calcium based phosphate binders

Kidney Int 2009;76(Suppl 113):S1–S130.
American Journal of Kidney Diseases 2003;42(4):S12-S28.

Management of Hyperphosphatemia

- **Use of Phosphate Binders:**
  - In patients with *serum phosphorus levels > 7.0 mg/dL, aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only*, to be replaced thereafter by other phosphate binders.
  - In such patients, more frequent dialysis (or high flux HD) should also be considered.

American Journal of Kidney Diseases 2003;42(4):S12-S28.



Aluminum deposition:

Leads to systemic Aluminum toxicity manifested as;

- Encephalopathy: neurotoxin
- Alzheimer's and other neurodegenerative processes
- Osteomalacia:
  - ✱ Impairs mineralization of the matrix; interfering with calcium deposition
  - ✱ Inhibits the bone-building osteoblasts
- Anemia and partial resistance to EPO: Influencing intestinal iron absorption, transport in the serum and uptake by cells.

Seminars in Dialysis 2006;19(3):195–99. Nephrol Dial Transplant 2002;17(Suppl 2): 9–12.

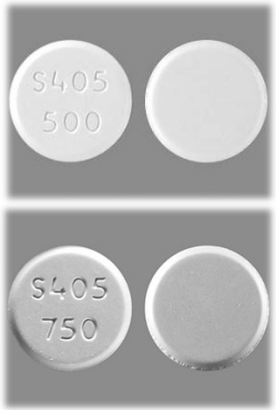
Management of Hyperphosphatemia

- **Lanthanum:** Lanthanum carbonate
  - Non-calcium, non-aluminium phosphate binders → FDA approve indication in adult ESRD patients (on HD, CAPD)
  - Chewable tablet:

    250 mg, 500 mg, 750 mg and 1,000 mg

    AVAILABLE IN THAILAND
  - Administration: taking with meal /or immediately after meals by chewing /or crushing the tablet completely before swallowing.

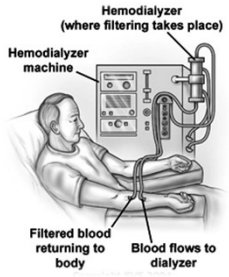
LANTHANUM CARBONATE (FOSRENOL®)



PILL CRUSHER

US FDA approve since 2004

Management of Hyperphosphatemia



Initial : 1,500 mg ORALLY per day in divided doses with meals

Titrate in increments of 750 mg/day at intervals of 2 to 3 weeks

Maintenance : 1,500 to 3,000 mg ORALLY per day in divided doses with meals

Important Safety Information

Lanthanum carbonate is *contraindicated* in patients with bowel obstruction, ileus, and fecal impaction.

- Serious cases of GI obstruction, ileus, and fecal impaction have been associated with lanthanum use, some requiring surgery or hospitalization.

Risk factors: altered GI anatomy, hypomotility disorders, and concomitant medications.

- Instruct patients to chew or crush the tablet completely to reduce the risk of serious adverse gastrointestinal events.

https://www.fosrenol.com/oral-powder/dosing-and-administration [33]

To reduce serum phosphate in patients with ESRD

FOSRENOL Oral Powder:
Added to applesauce. Adding to administration options.

- **With a familiar dosing schedule and flexible dosing strengths[1]**

U.S. available since May 2015
Dosage available: 750 mg, 1,000 mg

The first FDA-approved phosphate binder that is specifically formulated to be mixed with applesauce or other similar food, and not liquid

https://www.fosrenol.com/oral-powder/dosing-and-administration [34]

Lanthanum Carbonate Oral Powder

Sprinkle and eat[1]

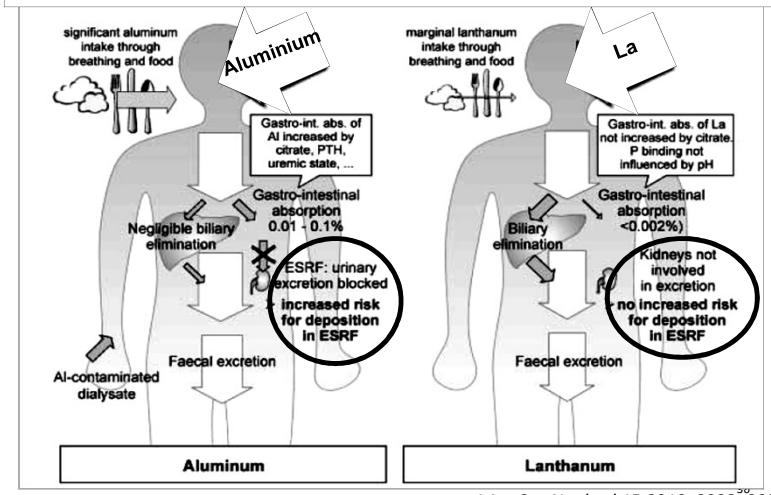
- Instruct patients to sprinkle the powder on a small quantity of applesauce or other similar food. The food should be consumed immediately

Instruct patients that they MUST NOT[1]...

- open a FOSRENOL Oral Powder packet before they are ready to use it
- attempt to dissolve FOSRENOL Oral Powder in liquid because it is insoluble
- store food mixed with FOSRENOL Oral Powder for future use

https://www.fosrenol.com/oral-powder/dosing-and-administration [35]

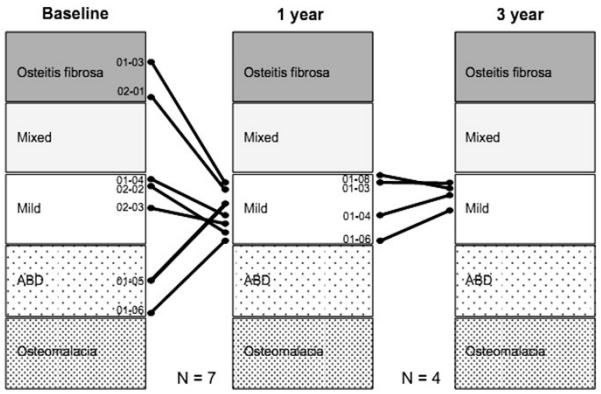
Calcium : 25-45% absorbs from GI tract
(Curr Med Res Opin. 2008 Mar;24(3):708)



J Am Soc Nephrol 15:2219–2228, 2004

Long Term ADRs/La Toxicity:

BONE Lanthanum carbonate did not show toxicity on osteoblast in animal models (renal failure rats)



Int J Nephrol Renovasc Dis 2012;5:81-9.

Ther Apher Dial. 2011;15(2):176–184.[37]

Long Term ADRs/La Toxicity:

BRAIN/CNS

Cognitive function in Stage 5 chronic kidney disease patients on hemodialysis: No adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy

P Altmann[1], ME Barnett[2,3] and WF Finn[4], on Behalf of the SPD405-307 Lanthanum Carbonate Study Group

[1]Oxford Kidney Unit, Oxford Radcliffe Hospitals NHS Trust and University of Oxford, Oxford, UK; [2]Charles R Drew University, Los Angeles, California, USA; [3]Barnett Research & Communications, Torrance, California, USA and [4]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

No evidence of CNS toxicity was demonstrated after 2 years.

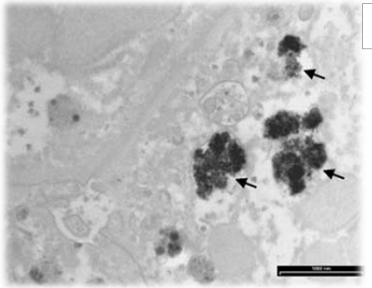
Kidney Int 2007;71:252–9.

Int J Nephrol Renovasc Dis 2012;5:81-9.[38]

Long Term ADRs/La Toxicity:

LIVER

Lanthanum carbonate is excreted via bile, accumulation in the *liver and hepatotoxicity*, which are not observed with aluminum products, were investigated.



J Am Soc Nephrol 15:2219–2228, 2004

No hepatotoxicity was observed.

No liver toxicity in HD patients treated with lanthanum carbonate for 6 years' long-term follow-up.

Int J Nephrol Renovasc Dis 2012;5:81-9.[39]

Common ADRs:

Mostly, ***GI side effects***:

- Nausea [11 – 26 %]
- Vomiting [9 – 18%]
- Abdominal pain [5%]

Others (not serious):

- Peripheral edema [23%]
- Myalgia [21%]

Fosrenol® Product Information

Curr Med Res Opin 2005;21:657-64.[40]

Management of Hyperphosphatemia

- **Sevelamer:** Sevelamer HCl, Sevelamer CO_3
  - Non-calcium, non-aluminium (polymer based) phosphate binders: quaternary amine anion exchange resin → exchanges chloride ions for phosphate ions
  - Pros: Lower LDL and total cholesterol
  - Cons: expensive, low binding capacity
  - Sevelamer HCl can cause acidosis → need to monitor HCO^-_3

Reduced cardiovascular morbidity and mortality

Drugs 2014;74: 863–877. 41

Management of Hyperphosphatemia

- **Sevelamer carbonate (Renvela®)**
  - Buffered form of Sevelamer, same polymeric s… …velamer HCl
  - Dosage for…
    AVAILABLE IN THAILAND
    800 mg tablet and 2.4 g powder
  - Less acidosis, rise HCO^-_3 level

Drugs 2014;74: 863–877. 42

SEVELAMER CARBONATE (RENVELA®)

DO NOT CRUSH OR CHEW

Management of Hyperphosphatemia

- **Sevelamer:** Sevelamer HCl, Sevelamer CO_3
  - Administration: Swallow whole tablet w/ meal, *do not crush or chew the tablet*.
  - Drug interaction: bind with other drugs

    Should administrate another medication 1 hour before or 3 hours after Sevelamer

Adverse reaction: mostly GI side effects (N/V, abdominal pain, bloating, constipation) Metabolic acidosis, peritonitis

Drugs 2014;74: 863–877. 44

Sevelamer carbonate (Renvela®)

Serum phosphorus level in patients	Total daily dose of sevelamer carbonate to be taken over 3 meals per day
5.5 – 7.5 mg/dL	800 mg (1 tab)
> 7.5 mg/dL	1,600 mg (2 tab)

Renvera® Product Information

Other Polymer-Based Phosphate Binders

- Colestilan (colestimide, MCI-196) is an anion-exchange resin that binds bile salts and phosphate. Colestilan is marketed in Japan and Europe.
- Bixalomer (AMG 223, ASP1585, formerly ILY101) is a metal-free, non-absorbed polymeric phosphate-binding agent launched in Japan in 2012.
- Chitosan: a cationic biopolymer → Chitosan chewing gum

Drugs 2014;74: 863–877.

Management of Hyperphosphatemia

Use of Phosphate Binders

Previous studies (systematic review published in KDOQI guideline) showed that:

- All medications currently used as phosphate binders → calcium salts, aluminum salts, magnesium salts, sevelamer, and lanthanum carbonate are effective in lowering serum phosphorus levels.

Kidney Int 2009;76(Suppl 113):S1–S130.
American Journal of Kidney Diseases 2003;42(4):S12-S28.

Management of Hyperphosphatemia

Use of Phosphate Binders

It is reasonable that the choice of phosphate binder takes into:

- Account CKD stage
- The presence of other components of CKD–MBD concomitant therapies
- Side-effect profiles

(not graded)

Kidney Int 2009;76(Suppl 113):S1–S130.

Management of Hyperphosphatemia

Currently available binders have been associated with impaired outcomes

- Calcium-based phosphate binders:
  - Hypercalcemia
  - Vascular calcification
  - Adynamic bone disease
- Aluminum-based phosphate binders:
  - Aluminum toxicity: Blood/Brain/Bone
- Lanthanum, Sevelamer:
- Expensive, large pill size, pill burden (Sevelamer)

Drugs 2014;74: 863–877.

New Lanthanum-Based Phosphate Binder

◆ SPI-014 (RenaZorb®): Lanthanum dioxycarbonate
Second-generation lanthanum-based phosphate binders: Nanopartical technology

2012: A Double Blind, Dose-Ranging, Phase 1 Study In Healthy Volunteers to Assess Safety and the Phosphate Binding Capacity of Lanthanum Dioxycarbonate (SPI-014, RenaZorb®)

Condition	Intervention	Phase
Safety Binding capacity	Drug: Renazorb 1500 mg/day Drug: Renazorb 3000 mg/day Drug: Renazorb 4500 mg/day Drug: Renazorb 6000 mg/day	*Phase 1* Healthy volunteers

https://clinicaltrials.gov/ct2/show/study/NCT01560884

New Lanthanum-Based Phosphate Binder

◆ SPI-014: Lanthanum dioxycarbonate

- The Phase 1 clinical findings showed that

(1) SPI-014 is well-tolerated up to the maximum administered dose of 6,000 mg/day, showing no serious adverse events, low systemic exposure, and no discontinuations of therapy.

(2) SPI-014 resulted in statistically significant reductions in daily urinary phosphorous excretions at 1,500 mg/day; 3,000 mg/day; 4,500 mg/day and 6,000 mg/day) compared to placebo.

SPECTRUM PHARMACEUTICALS:
http://investor.sppirx.com/releasedetail.cfm?releaseid=731677#top

New Lanthanum-Based Phosphate Binder

◆ SPI-014: Lanthanum dioxycarbonate

- Effective phosphate lowering
- Convenient, easy-to-swallow pill formulation
  - ❖ Higher phosphate-binding capacity of RenaZorb® compared to current products, as shown in *in vitro* studies, *allows the manufacturer to offer lower dosing and a smaller, patient-friendly tablet size.*
- Can address substantially the poor compliance associated with current therapies.

SPECTRUM PHARMACEUTICALS:
http://investor.sppirx.com/releasedetail.cfm?releaseid=731677#top

New Lanthanum-Based Phosphate Binder

- RenaZorb® (SPI-014): Lanthanum dioxycarbonate
  - Planning for Phase II Study: Testing of drug on CKD patients to assess efficacy and safety
  - Seeking a licensing partner outside of the U.S., in particular, in Japan and other countries in Asia.

SPECTRUM PHARMACEUTICALS:
http://investor.sppirx.com/releasedetail.cfm?releaseid=731677#top

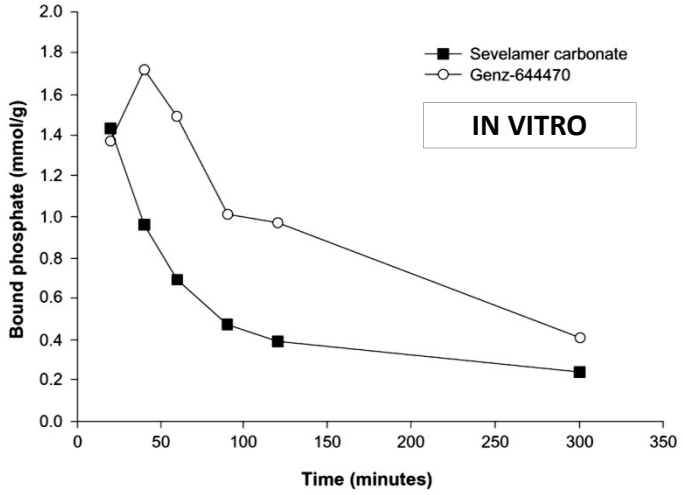
International Journal of Nephrology and Renovascular Disease Dovepress
open access to scientific and medical research
Open Access Full Text Article ORIGINAL RESEARCH

A randomized, double-blind, placebo-controlled, dose-ranging study using Genz-644470 and sevelamer carbonate in hyperphosphatemic chronic kidney disease patients on hemodialysis

Objectives: **PHASE II STUDY**

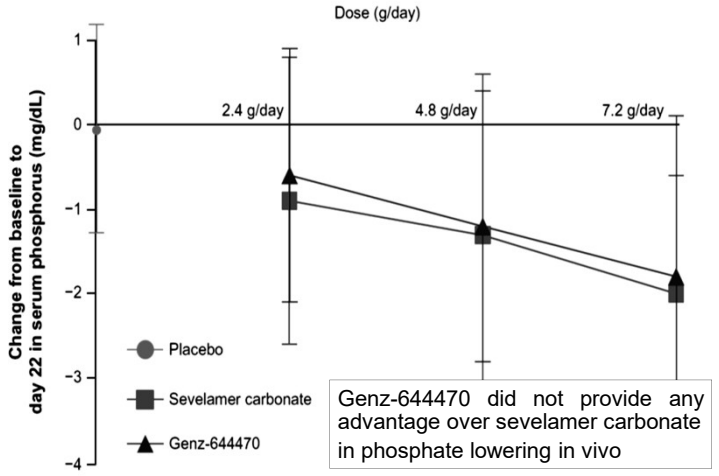
- Evaluating the ability of Genz-644470 to lower serum phosphorus in patients on HD.
- Compared serum phosphorus lowering of Genz-644470 with sevelamer carbonate and placebo.

Int J Nephrol Renovasc Dis 2014;7:141-52.



Competitive phosphate binding of sevelamer carbonate and Genz-644470 in vitro.

Int J Nephrol Renovasc Dis 2014;7:141-52.



Mean (± standard deviation) change in serum phosphorus from baseline to end of treatment (day 22).
ıta for the placebo group are presented for comparison purposes.

Int J Nephrol Renovasc Dis 2014;7:141-52.

NEW PHOSPHATE BINDERS

Iron based phosphate binders

- Iron-magnesium hydroxycarbonate (Fermagate, Alpharen)
- Polymeric complex of iron (III) (SBR-759)
- Sucroferric oxyhydroxide (PA21)
- Ferric citrate (JTT-751, KRX-0502)
- Ferric oxide adipate (PT20)

Drugs 2014;74: 863–877.

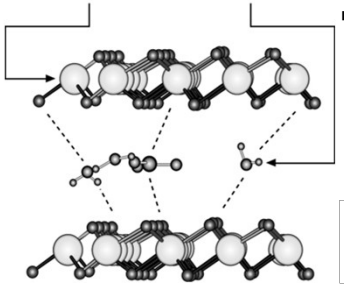
Clin Kidney J 2015;8: 161–167. 57

Iron-magnesium hydroxycarbonate

Fermagate, Alpharen:

$[Mg_4Fe_2(OH)_{12}]^{2+}.CO_3^{2-}.mH_2O$

Cationic Sheets Anion + H_2O layers



- One Phase II study, Two Phase III RCTs → terminated in 2010 (commercial reasons).
- Low binding capacity
- Frequent adverse effects (95% of patients): Mainly GI side effects → diarrhea (48%), dyspepsia (14%), vomiting (14%), feces discoloration (38%)

Restarted Phase III study in 2014
Expected to complete by 2017

Clin J Am Soc Nephrol. 2009 Feb; 4(2): 401–409.

Drugs 2014;74: 863–877. 58

Polymeric complex of iron (III)

- SBR-759 is a polymeric complex of ferric-oxyhydroxide and starch [$Fe^{3+}O(OH)$-starch-saccharose-carbonate complex]
- Formulated as a non-flavored powder in an attempt to reduce the pill burden and improve compliance.
- SBR-759 product development (Phase II trial) was terminated for Western populations in 2010 → Less efficacy than sevelamer (serum phosphate responders 52 vs. 66 %) more GI adverse effects (diarrhea 34 vs. 16%)

Drugs 2014;74: 863–877. 59

SBR-759

At a glance

Highest Development Phases

Discontinued	Hyperphosphataemia

Most Recent Events

01 Dec 2013	Discontinued - Phase-II for Hyperphosphataemia in Japan and Taiwan (PO)
31 Aug 2012	No development reported - Phase-III for Hyperphosphataemia in Japan (PO)
31 Dec 2007	Phase-II clinical trials in Hyperphosphataemia in Germany (PO)

Data available from: http://adisinsight.springer.com/drugs/800023014 60

NEW PHOSPHATE BINDERS

Iron based phosphate binders

- Iron-magnesium hydr… …onate (Fermagate, Al…
- Polymeric co… …of iron (III) (SBR-759)
- Sucroferric oxyhydroxide (PA21)
- Ferric citrate (JTT-751, KRX-0502)
- Ferric oxide adipate (PT20)

DEVELOPMENT TERMINATED

Drugs 2014;74: 863–877.

Clin Kidney J 2015;8: 161–167. [61]

Kidney International 2010;77: 845 – 847. [62]

New Phosphate Binders

Iron-based phosphate binders:

- Sucroferric oxyhydroxide (PA21):
  - US FDA approved in November 2013
  - European Medicines Agency (EMA) in August 2014
  - Japanese approval in September 2015

CKD patients with dialysis

Clin Kidney J 2015; 8(2): 161-7.

Int J Nephrol Renovasc Dis. 2016; 9: 11–19. [63]

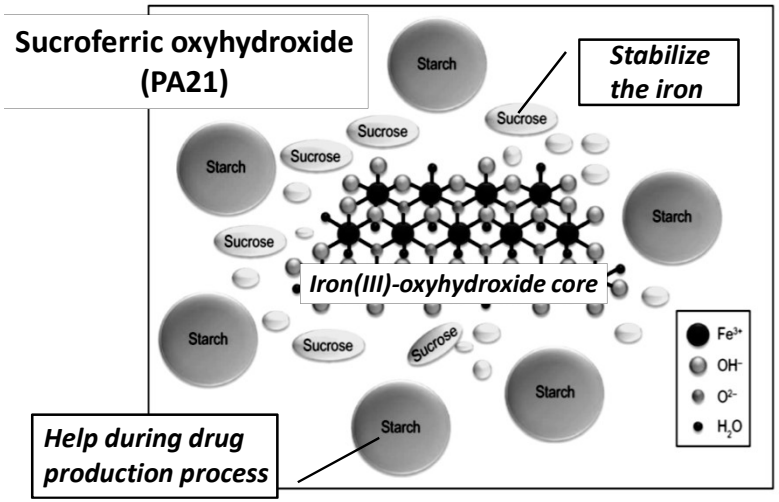


Figure 1 Molecular structure of sucroferric oxyhydroxide consisting of a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches.
Note: Iron(III)-oxyhydroxide is the pharmacologically active part.

Drugs 2015;75: 533–542.

Int J Nephrol Renovasc Dis. 2016; 9: 11–19. [64]

Sucroferric oxyhydroxide (PA21)

Mechanism of Action:

- The *adsorption* of phosphate to the iron complex [the iron(III)-oxyhydroxide core] → *happens in intestinal lumen.*
- The formation of *iron phosphate* through a chemical reaction that is favored by low pH values, such as those *present within the stomach.*

Excretion of bound phosphate in the feces

Int J Nephrol Renovasc Dis. 2016; 9: 11–19. 65

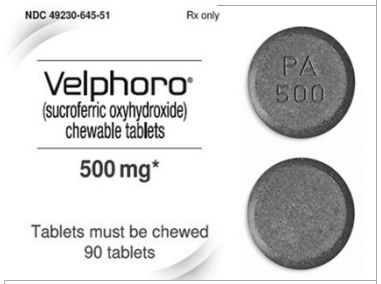
Efficacy, Safety and Tolerability of PA21

Authors Journal, year [Study phase]	Subjects enrolled	Comparator	Duration of study	Main results
Geisser P, Philipp E. Clin Nephrol, 2010 [Phase I] Clin Nephrol 2010;74(1):4-11.	- 8 CKD pts. (S3 – 4)[1] - 8 HD pts.[2] - 8 healthy subjects[3]	*Intervention:* PA21 10 g/day No comparator	7 days	▪ A significant decrease in serum phosphate ▪ ***S/E:*** Diarrhea ▪ Iron uptake was low: 0.06%[1], 0.02%[2], 0.43%[3]
Wüthrich RP, et al. CJASN, 2013 [Phase II – dose finding] Clin J Am Soc Nephrol. 2013;8(2):280-9.	154 HD pts.	▪ PA21 at 1.25, 5.0, 7.5,10.0, or 12.5 g/day ▪ Sevelamer HCl	6 weeks	Similar decrease Pi ▪ SEV 4.8 g/day → -1.06 ±1.35 mg/dL ▪ PA21 5.0 g/day → -1.08±2.12 mg/dL ***S/E:*** Discolored feces (11.4%), hypophos ~ (18%)

Authors Journal, year [Study phase]	Subjects enrolled	Comparator	Duration of study	Main results
Floege J, et al. Kidney Int, 2014 [Phase III] Kidney Int 2014;86(3):638-47.	1,055 HD and PD pts.	▪ PA21 at 1.0 – 3.0 g/day (2 – 6 tab/d) ▪ Sevelamer carbonate 4.8 – 14.4 g/day (6-18 tab/d)	24 weeks	Serum phosphate level at 12 weeks ▪ ***PA21:*** -0.71 mmol/L (avg: 3 tablets) ▪ ***SEV:*** -0.79 mmol/L (avg: 8 tablets) ▪ Non-inferiority ▪ Lower pill burden ▪ ***S/E:*** diarrhea, discolored feces
Floege J, et al. Nephrol Dial Transplant, 2015 [Phase III – extension study] Nephrol Dial Transplant 2015;30(6):1037-46.	1,055 HD and PD pts.	▪ PA21 at 1.0 – 3.0 g/day (2 – 6 tab/d) ▪ Sevelamer carbonate 2.4 – 14.4 g/day (6-18 tab/d)	28 weeks Extension study	▪ Serum phosphate lowering effect of PA21 was maintained over 1 year (not different from SEV) ▪ Lower pill burden ▪ No evidence of iron accumulation

Sucroferric oxyhydroxide (PA21)

- Velphoro®/P-TOL®: A chewable tablet containing 250 mg, 500 mg (Velphoro®; 500 mg only) iron as polynuclear iron(III)-oxyhydroxide, sucrose and starches



Woodberry flavor

http://www.drugs.com/pro/velphoro.html

- Partially water soluble
- ***Sucrose*** → glucose + fructose → absorbed
- ***Starch*** → glucose + maltose → absorbed
- ***Polynuclear iron(III)-oxyhydroxide*** → nearly insoluble → prevent iron absorption at duodenum

Int J Nephrol Renovasc Dis. 2016; 9: 11–19. 66

Sucroferric oxyhydroxide (PA21)

- Starting dose: 1,500 mg/day (500 mg, t.i.d.)
  Max. 3,000 mg/day
- PA21 must be taken with meals, with the total daily dose divided across the meals of the day to maximize dietary phosphate binding.
- PA21 tablets must be chewed and not swallowed whole.

Drugs 2015;75: 533–542. 69

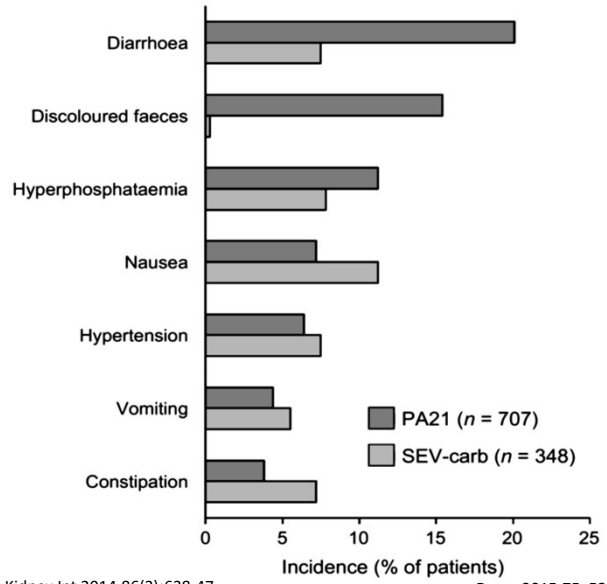
Sucroferric oxyhydroxide (PA21)

- Velphoro®/P-TOL®:
  - A chewable tablet – chewing and disintegration into smaller particles to allow for optimal adsorption.
  - Chewable tablets offer the advantage of more flexibility in not requiring access to water and in the fact that the medication can be more discretely taken.
  - PA21 - *Good benefit for CKD or dialysis patients who require fluid restriction because it can be taken orally without water.*

Drug Dev Ind Pharm. 2014;40(12): 1623-31.

70

Int J Nephrol Renovasc Dis. 2016; 9: 11–19.



Kidney Int 2014;86(3):638-47.

Drugs 2015;75: 533–542. 71

Sucroferric oxyhydroxide (PA21)

- Things to be concerned:
  - Some of saccharides contents of PA21 could be metabolized to <u>*glucose, fructose, and maltose.*</u>
  - <u>*Contraindicated*</u> in patients with fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.
  - The use of PA21 in diabetic patients, in particular in those treated with PD, could interfere with capillary glucose tests → induce false results.

Clin Kidney J 2015; 8(2): 161-7.

Drugs 2015;75: 533–542.

Int J Nephrol Renovasc Dis. 2016; 9: 11–19. 72

Sucroferric oxyhydroxide (PA21)

- Things to be concerned:
  - The chemical structure of PA21 prevents iron absorption in the GI tract, but PK study → minimal percentage of iron is actually absorbed.
  - *Contraindicated* in pts with haemochromatosis or any other iron accumulation disorders and iron homeostasis should be monitored.

Clin Kidney J 2015; 8(2): 161-7.

Drugs 2015;75: 533–542.
Int J Nephrol Renovasc Dis. 2016; 9: 11–19.

New Phosphate Binders

Iron-based phosphate binders:

- Ferric citrate (JTT-751, KRX-0502):
  - US FDA approved in September 2014
  - Japanese approval in 2014
  - European Medicines Agency (EMA) in 2015

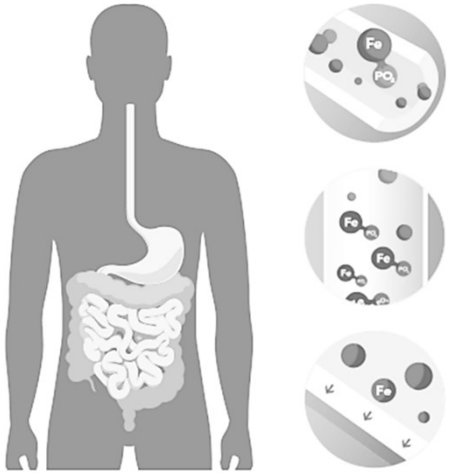
Approved indication:

1. Hyperphosphatemia in patients receiving dialysis. (US)
2. Hyperphosphatemia in all CKD patients. (EU)

Clin Kidney J 2015; 8(2): 161-7.

Semin Nephrol 2016;36(2):130-5.

Ferric Citrate (JTT-751, KRX-0502)



- Ferric iron binds with dietary phosphate in the GI tract.
- Precipitates as ferric phosphate.

- Ferric phosphate is insoluble.
- Excrete via feces

- Iron can be absorbed through the GI tract.

Picture available from: https://www.auryxia.com/mechanism-of-action/

Efficacy, Safety and Tolerability of FC

Table 2. Summary of published trials with ferric citrate

Author/journal year	Study phase	Subjects enrolled	Comparator	Duration	Main results
Yokoyama K Am J Nephrol 2012 [21]	Dose-response	192	Placebo	28 days	Pi decrease is dose dependent up to 6 g/day Pi decreased –2.16 with 3 g/day; Pi < 5.5 in 50% with 3 g/day
Dwyer JP Am J Kid Dis 2013 [22]	Dose-response	151	None	28 days	FC 6 g/day decrease Pi –1.9 ± 1.7 mg/dL and 8 g/day, –2.1 ± 2.0 mg/dL
Yokoyama K Nephrol Dial Transp 2014 [23]	III	230	Sevelamer HC 3-9 g/day	12 weeks	Pi –0.82 mmol/L with FC and –0.78 with sevelamer (non-inferiority) with sig. increase in ferritin and transferrin sat
Lee CT Nephrol 2014 [24]	III	166	Placebo	8 weeks	Pi decrease with 4 and 6 g/day; increase in ferritin and transferrin sat
Lewis JB JASN 2014 [25]	III	441	Active control and Placebo	52 weeks	Pi –2.2 mg/dL compared to Placebo and similar to active control but higher mean iron parameters with less IV iron

Clin Kidney J 2015; 8(2): 161-7.

CLINICAL RESEARCH www.jasn.org

Ferric Citrate Controls Phosphorus and Delivers Iron in Patients on Dialysis

Julia B. Lewis,* Mohammed Sika,* Mark J. Koury,† Peale Chuang,‡ Gerald Schulman,* Mark T. Smith,§ Frederick C. Whittier,‖ Douglas R. Linfert,¶ Claude M. Galphin,** Balaji P. Athreya,†† A. Kaldun Kaldun Nossuli,‡‡ Ingrid J. Chang,§§ Samuel S. Blumenthal,‖‖ John Manley,¶¶ Steven Zeig,*** Kotagal S. Kant,††† Juan Jose Olivero,‡‡‡ Tom Greene,§§§ and Jamie P. Dwyer,* for the Collaborative Study Group

- 441 subjects on dialysis (HD, or PD) were randomized to
  - Ferric citrate (FC)
  - Active control (AC): sevelamer or calcium acetate
- Duration: 52-week

Results: Serum Phosphate Levels (mg/dL)

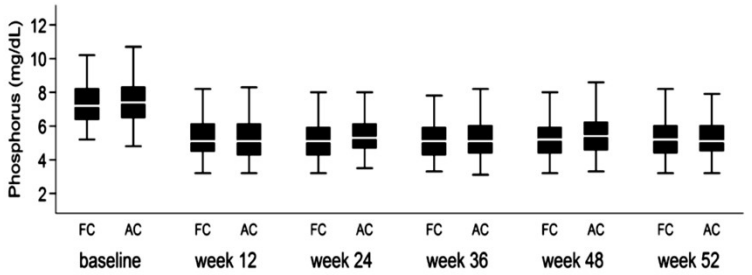


Figure 2. Serum phosphorus levels (milligrams per deciliter) by study time point during the 52-week active control period, with missing values imputed using the last follow-up observation carried forward. Box plots display 5th, 25th, 50th, 75th, and 95th percentiles. Under the repeated measures mixed effects model, the mean difference in serum phosphorus between the ferric citrate and active control groups over weeks 12, 24, 36, 48, and 52 was −0.0127 mg/dl (95% confidence interval, −0.056 to 0.030 mg/dl). AC, active control; FC, ferric citrate.

AC: Sevelamer or calcium acetate or combination

Results: Iron parameters (serum ferritin, TSAT)

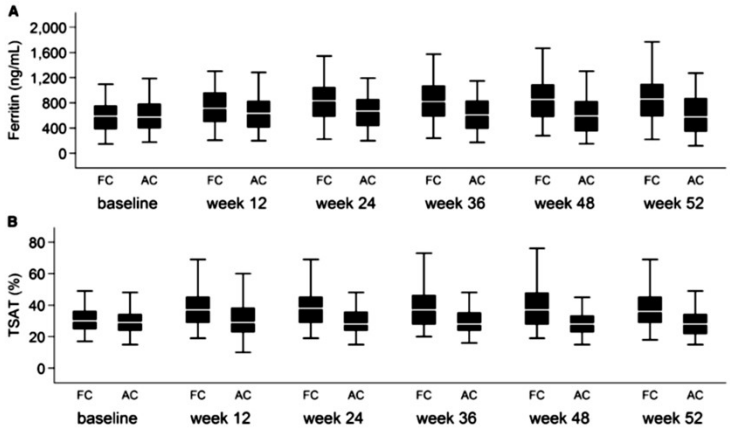


Figure 3. Iron parameters by study time point during the 52-week active control period. (A) Serum ferritin and (B) serum TSAT, with missing values imputed using the last follow-up observation carried forward. Box plots display 5th, 25th, 50th, 75th, and 95th percentiles. AC, active control; FC, ferric citrate.

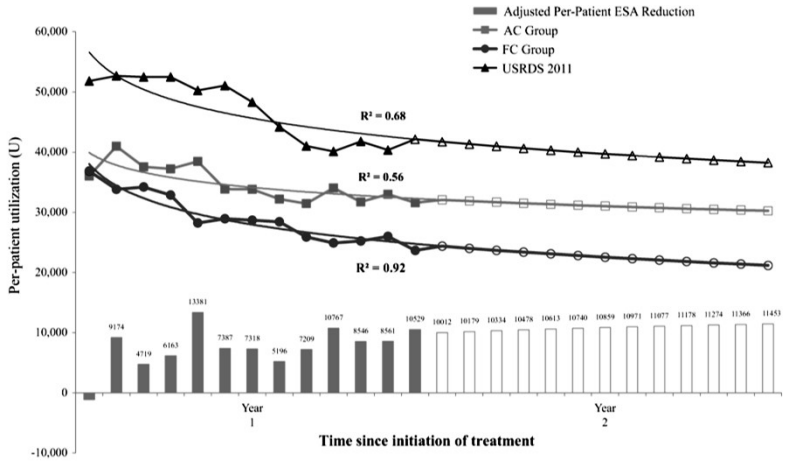


Fig. 1 Phase III trial-based and projected ESA utilization with USRDS-standardized differences. *AC* active control, *ESA* erythropoiesis-stimulating agent, *FC* ferric citrate, *USRDS* United States Renal Data System

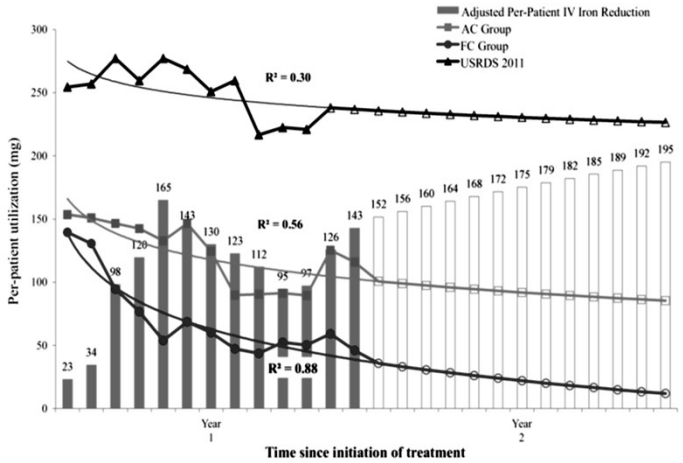


Fig. 2 Phase III trial-based and projected IV iron utilization with USRDS-standardized differences. *AC* active control, *FC* ferric citrate, *IV* intravenous, *USRDS* United States Renal Data System

Drugs R D 2015;15:271–279

Ferric Citrate (JTT-751, KRX-0502)

- AURYXIA®(ZERENEX®): U.S.
- FEXERIC®: European Union
- RIONA®: Japan

210 mg of ferric iron equivalent to 1 g of ferric citrate.

AURYXIA 210 MG TABLET

Identification

Color: peach
Shape: oval
Imprint: KX52

Starting dose: 2x3 w/ meal
Swallow NOT chew

This medicine is a peach, oval, film-coated tablet imprinted with "KX52".

Picture available from: http://www.webmd.com/drugs/2/drug-167468/auryxia-oral/details#images

Ferric Citrate (JTT-751, KRX-0502)

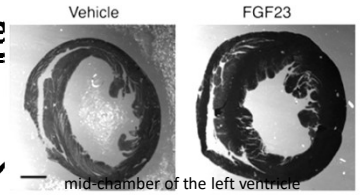
- Adverse Drug Reaction:

  Mostly GI adverse events:

  - Diarrhea (21%)
  - Discolored feces (17%)
  - N/V
  - **IRON OVERLOAD:** *Contraindicated* in pts with haemochromatosis or any other iron accumulation disorders and iron homeostasis should be monitored.

J Am Soc Nephrol 2015;26(2):493-503. Clin Kidney J 2015; 8(2): 161-7.

New Phosphate Binde



- Iron-based phosphate
  - Hyperphosphatemia → ↑
  - ↑FGF23 → ↑ Progression of CKD
    ↑FGF23 → ↑ LVH, Cardiovascular events (MI, amutation, stroke, death).
  - Iron status is an independent negative predictor of plasma FGF23 concentration and *iron supplementation is associated with a significant decrease in FGF23 values.*

J Clin Invest. 2011 Nov;121(11):4393-408.
Kidney Int 2012;82(7):737-747.
Int J Nephrol Renovasc Dis. 2016; 9: 11–19.

New Phosphate Binders

- Iron-based phosphate binders and FGF23:
  - Iron administration per se and also treatment with iron-based phosphate binders → ↓ FGF23 both directly and by reducing phosphate intestinal absorption.
  - PA21, FC → ↓ FGF23.
  - PA21 (dialysis patients)
  - FC (non-dialysis CKD patients)

Kidney Int 2012;82(7):737-747.

Int J Nephrol Renovasc Dis. 2016; 9: 11–19.

Iron-Based Phosphate Binders

- Both sucroferric oxyhydroxide and ferric citrate are effective phosphate binders, ↓ FGF23 :
  - Sucroferric oxyhydroxide may be more suited for hyperphosphatemic CKD patients not requiring iron supplementation.
  - Sucroferric oxyhydroxide → low pill burden
  - Ferric citrate: more suited to treat hyperphosphatemia in CKD patients who require iron supplementation.
  - Monitoring: Serum phosphate, iron status

Clin Kidney J 2015; 8(2): 161-7. [87]

Ferric oxide adipate (PT20)

At a glance

Highest Development Phases

Phase II	Hyperphosphataemia

Most Recent Events

07 May 2015	Phosphate Therapeutics plans a phase III study in Hyperphosphataemia
07 May 2015	Adverse events data from a phase IIb trial in Hyperphosphataemia released by Phosphate Therapeutics
29 Apr 2015	Phosphate Therapeutics completes a phase IIb trial in Hyperphosphataemia (In adults, In the elderly) in USA (NCT02151643)

Data available from: http://adisinsight.springer.com/drugs/800036595 [88]

Management of Hyperphosphatemia

The important aspects that should be considered in phosphate binders therapy

- GI absorption of the active moieties.
- Phosphate binders also bind harmful or useful substances in the gut.
- The compliance to phosphate binders
- The effect of different phosphate binders on FGF-23 serum levels.

Clin Kidney J 2015;8: 161–167

Management of Hyperphosphatemia

New Phosphate binders:

- Iron-based phosphate binders:

  Sucroferric oxyhydroxide:
  Approval: US FDA 2013, EMA 2014, JP 2015

  Ferric citrate:
  Approval: US FDA and JP 2014, EMA 2015

NOW IRON-BASED PHOSPHATE BINDERS ARE NOT AVAILABLE IN THAILAND

Clin Kidney J 2015; 8(2): 161-7.

ยาจับฟอสเฟต	ขนาดเริ่มต้นที่ใช้ในการรักษา	การปรับขนาดยา	อาการไม่พึงประสงค์ทั่วไปที่อาจพบได้	หมายเหตุ
แคลเซียมคาร์บอเนต (ประกอบด้วย elemental calcium ร้อยละ 40)	500 มก. elemental calcium รับประทานวันละ 3 ครั้ง พร้อมมื้ออาหาร ควรเคี้ยว หรือบดยาให้ละเอียด รับประทานพร้อมอาหาร	ปรับขนาดยาเพิ่มหรือลดครั้งละ 500 มก. (คิดเป็น elemental calcium 200 มก.) ขนาด elemental calcium สูงสุดไม่เกิน 1,500 มก./วัน	- คลื่นไส้ อาเจียน - ท้องอืด - ท้องผูก - ระดับแคลเซียมในเลือดเพิ่มสูงขึ้น - เกิดการสะสมของตะกอนแคลเซียมฟอสเฟตในร่างกาย	- เป็นยาทางเลือกแรกในผู้ป่วยโรคไตเรื้อรังที่ไม่มีภาวะแคลเซียมในเลือดสูง - ราคาไม่แพง และสามารถจับฟอสเฟตได้ดี - ควรหลีกเลี่ยงการใช้แคลเซียมร่วมกับยา levothyroxine และยาต้านจุลชีพในกลุ่ม fluoroquinolone และ tetracycline
แคลเซียมอะซิเตต[a] (ประกอบด้วย elemental calcium ร้อยละ 31.625 Thai RDI)	1,000 มก. (คิดเป็น elemental calcium 253 มก.) รับประทานวันละ 3 ครั้ง พร้อมมื้ออาหาร	ปรับขนาดยาเพิ่มหรือลดครั้งละ 1,000 มก. (คิดเป็น elemental calcium 253 มก.) ขนาด elemental calcium สูงสุดไม่เกิน 1,500 มก./วัน		

Calcium based phosphate binders should not be use in patients with:
- Hypercalcemia
- Arterial calcification
- iPTH < 100 pg/mL

ดาราพร รุ่งพราย. การจัดการภาวะฟอสเฟตในเลือดสูง: จากแนวทางการรักษาสู่การปฏิบัติ. ใน: บุษบา จินดาวิจักษณ์, ธนรัตน์ สรวลูเสน่ห์, ปรีชา มนทกานติกุล, บรรณาธิการ. Connecting Pharmaceutical Care and Outcomes. กรุงเทพฯ: ประชาชน; 2558, หน้า 97 – 113.

ยาจับฟอสเฟต	ขนาดเริ่มต้นที่ใช้ในการรักษา	การปรับขนาดยา	อาการไม่พึงประสงค์ทั่วไปที่อาจพบได้	หมายเหตุ
อะลูมิเนียมไฮดรอกไซด์ 	300 – 600 มก. รับประทานวันละ 3 ครั้ง พร้อมมื้ออาหาร เคี้ยว	ไม่มีคำแนะนำในการปรับขนาดยา เนื่องจากไม่แนะนำให้ใช้สำหรับการรักษาในระยะยาว	- คลื่นไส้ อาเจียน - ท้องผูก	- ราคาไม่แพง และสามารถจับฟอสเฟตได้ดีมาก - ในระยะยาวเพิ่มความเสี่ยงต่อการเกิดพิษจากอะลูมิเนียม
เซเวลาเมอร์คาร์บอเนต 	800 – 1,600 มก. รับประทานวันละ 3 ครั้ง พร้อมมื้ออาหาร ห้ามเคี้ยว	ปรับขนาดยาเพิ่มหรือลดครั้งละ 800 มก. ต่อมื้ออาหาร	- คลื่นไส้ อาเจียน - ท้องอืด - ท้องเสีย หรือ ท้องผูก	- ราคาแพง แต่ความสามารถในการจับฟอสเฟตค่อนข้างน้อย - ลดความเสี่ยงในการเกิดโรคหัวใจและหลอดเลือดได้
แลนทานัมคาร์บอเนต 	1,500 มก./วัน โดยแบ่งให้รับประทานวันละ 3 ครั้ง พร้อมมื้ออาหาร Chewable tab. (เคี้ยว)	ปรับขนาดยาเพิ่มหรือลดครั้งละ 750 มก./วัน	- คลื่นไส้ อาเจียน - ปวดท้อง - ท้องผูก	- ราคาแพง แต่มีความสามารถในการจับฟอสเฟตได้ดีมาก - ลดการสะสมของแคลเซียมฟอสเฟตที่ผนังหลอดเลือด

ดาราพร รุ่งพราย. การจัดการภาวะฟอสเฟตในเลือดสูง: จากแนวทางการรักษาสู่การปฏิบัติ. ใน: บุษบา จินดาวิจักษณ์, ธนรัตน์ สรวลเสน่ห์, ปรีชา มนทกานติกุล, บรรณาธิการ. Connecting Pharmaceutical Care and Outcomes. กรุงเทพฯ: ประชาชน; 2558, หน้า 97 – 113.

THANK YOU FOR YOUR ATTENTION