Pronefra®

Technical Brochure

All you need to know about our
4 in 1 innovation designed to support
for CKD management in cats and dogs

Shaping the future of animal health

Virbac

Contents

Pronefra®

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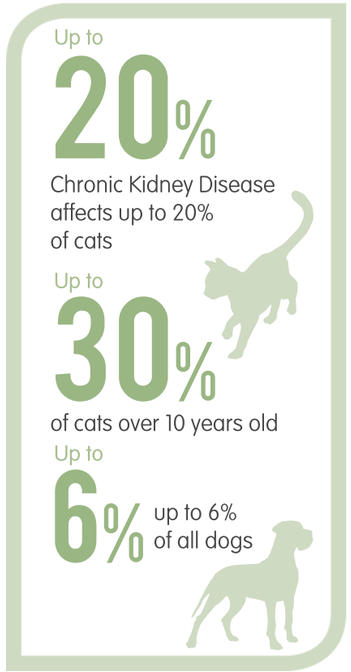
"Many CKD patients live for several years following diagnosis with an excellent quality of life"



Chronic kidney disease (CKD) is one of the most common diagnoses made in veterinary practice and is an important cause of illness in both cats and dogs. CKD is especially common in middle-aged and elderly cats where it is estimated to affect at least 30% of cats over the age of ten years.

It is a progressive illness and affected pets commonly show clinical signs including weight loss, poor appetite, increased thirst and lethargy. Cats in particular are very good at 'hiding' early signs of illness, which is one reason why routine preventive health checks are so important in older animals.

Owner education is vital to encourage owners to attend health screening appointments and report any changes in their pet which might indicate presence of CKD.

Over the last ten years there have been huge advances in our knowledge and understanding of CKD.

Treatment can be very effective and many feline CKD patients live for several years following diagnosis with an excellent quality of life. Successful treatment depends on attention to detail and good teamwork between carer and veterinarian. The treatment plan should be individualised to each pet's specific needs.

Use of renal prescription diets and/or intestinal phosphate binders (IPB), which reduce the amount of phosphate absorbed through the bowel are known to benefit affected cats by helping to prevent hyperphosphataemia. Hyperphosphataemia is very common in pets with CKD and is known to have a negative impact on both quality and length of life primarily through inducing renal secondary hyperparathyroidism. IRIS currently recommends phosphate restriction for all patients in IRIS* Stage 2, 3 and 4 CKD.

Acceptance of phosphate binders can be challenging, especially in pets suffering from a poor appetite due to their CKD. The availability of a palatable phosphate binder in the form of Pronefra is good news for pets with CKD and will hopefully enhance uptake and compliance to phosphate binder therapy.

Additional characteristics of Pronefra may be of benefit in other ways to pets with CKD, helping them to live as long and healthy a life as possible.

* International Renal Interest Society: www.iris-kidney.com

1 CHRONIC KIDNEY DISEASE (CKD) IN DOGS AND CATS

Chronic kidney disease (CKD) is one of the predominant causes of morbidity and mortality in elderly domestic cats and dogs and the most common kidney disease in domestic carnivores. Kidney disease is defined as the presence of functional or structural abnormalities in one or both kidneys.[1]

Regardless of the cause or causes of nephron loss, CKD is characterised by irreversible structural lesions resulting in reduced kidney function.[1] Chronic renal failure (CRF) implies a 75% reduction in glomerular filtration rate (GFR), corresponding to the loss of more than 75% of functional nephrons.[1,2]

CKD is known to affect more than 30% of cats over 10 years of age;[3] the mean age for diagnosis is reported to be close to 13 years of age.[4] The prevalence has been estimated to be up to 7% in dogs and up to 20% in cats for the whole population regardless of age.[1]

The most common signs[5] and markers[1] of kidney damage are:

CLINICAL SIGNS	BLOOD MARKERS	URINE MARKERS
Weight loss	Elevated urea nitrogen concentration	Decreased specific gravity
Reduced appetite	Elevated creatinine concentration	Proteinuria
Polydipsia/polyuria	Hyperphosphatemia	Renal haematuria
Dehydration	Hypo- or hyperkalaemia	Inappropriate pH
Systemic hypertension	Metabolic acidosis	Cylinduria / casts
Vomiting/constipation	Hypoalbuminemia	Cystinuria (dogs)
Anaemia	Increased parathyroid hormone (PTH) levels	
Lethargy/depression		
Mouth ulcers		
Halitosis (uremic breath)		

Table 1: The most common clinical signs and biological markers

Although serum creatinine (SCr) levels are not a precise indicator of GFR, they can still provide an approximate indication of renal filtration capacity and renal health[4] and form the basis of the IRIS staging system.[6]

Current CKD IRIS staging is undertaken following the diagnosis of CKD in order to facilitate appropriate treatment and monitoring of the patient.

STAGE 0	At risk of CKD	For patients identified as 'at risk' consider regular screening and taking steps to reduce risk factors
STAGE 1	Non-azotemic	Creatinine <1.6 mg/dL (<140 µmol/l) , but some other renal abnormality present e.g. inadequate concentrating ability, abnormal renal palpation or imaging finding, persistent renal proteinuria.
STAGE 2	Mild renal azotemia	Creatinine levels are 1.6 - 2.8 mg/dL (140-249 µmol/l) Clinical signs usually mild or absent
STAGE 3	Moderate renal azotaemia	Creatinine levels are 2.9 - 5.0 mg/dL (250-439 µmol/l) Systemic clinical signs may be present
STAGE 4	Severe renal azotaemia	Creatinine levels are more than 5.0 mg/dL (>440 µmol/l) Systemic clinical signs are usually present

Figure 1: IRIS CKD staging from www.iris-kidney.com[6]

2 PROGNOSTIC FACTORS OF CKD

As lesions in CKD are irreversible[1], the prevention of their progression after the earliest possible diagnosis is the key objective in the management of this difficult condition.

CKD is a geriatric disease which is very often stable for a long period of time in cats; this period is much shorter in dogs. Cats with stages 2 and 3 commonly survive from 1 to 3 years; dogs with stage 3 CKD will classically survive between 6 months and 1 year.[1] 3 prognostic factors (other than blood creatinine level) have been clearly identified in cats: proteinuria, anaemia and hyperphosphatemia.[4,7,8]

- **Proteinuria** predicts development[2] and progression of feline CKD[7] and survival[8] in patients.
- **Anaemia** predicts progression of feline CKD[7]
- **Hyperphosphatemia** predicts progression of feline CKD with hyperphosphataemic patients having shorter survival times[7]. Management of hyperphosphataemia and secondary hyperparathyroidism results in increased life expectancy[9]

3 MANAGEMENT OF CKD

3.1 Management of **hyperphosphatemia** and secondary hyperparathyroidism

Phosphorus retention is common in renal disease; phosphate balance results largely from the interaction between dietary intake and renal excretion.[10] The kidneys have a pivotal role in the regulation of phosphorus levels because they are the main route of phosphorus excretion.[1]

High levels of serum phosphorus are associated with shorter survival and an increased risk of mortality in CKD cats as well as other species.[7,11] Management of the rise in phosphorus blood levels can dramatically change disease progression. A study in cats has shown that efficient control of hyperphosphatemia and secondary renal hyperparathyroidism could extend life by more than 2 fold.[9]

The majority of dietary phosphorus comes from dietary proteins.[12,11,13] For this reason, three options are currently available for the management of phosphorus in CKD patients:[13] a diet specially restricted in phosphorus (and thus in proteins), IPB or both.

The IRIS guidelines recommend that phosphate restriction should be implemented for all azotemic animals (IRIS stages 2, 3 and 4). Ideally, blood phosphate levels in animals with CKD should be maintained between approximately 1-1.2 mmol/l (3-3.6 mg/dl). The target phosphate levels recommended by IRIS (Table 2) are influenced by the stage of disease.

IRIS STAGE	TARGET PHOSPHATE LEVEL
1	N/A
2	0.9 - 1.5 mmol/l (2.7 - 4.6 mg/dl)
3	0.9 - 1.6 mmol/l (2.7 - 5 mg/dl)
4	0.9 - 1.9 mmol/l (2.7 - 6 mg/dl)

Table 2: Target blood phosphate levels according to the IRIS stage of renal disease: as the renal disease progresses, it tends to be more difficult to maintain phosphate levels in the 'ideal' range of 1-1.2 mmol/l (3-3.6 mg/dl).

Oral phosphate binders are therefore an excellent 'Day one' management option upon diagnosis of CKD.

- They provide phosphate restriction to animals in the earlier stages of the disease where protein restriction is not desirable
- They can be helpful whilst transitioning animals onto a renal prescription diet (where appropriate)
- They provide phosphate restriction where renal prescription diets cannot be used for other reasons.

After starting an IPB, or changing the dose, blood phosphate levels should be monitored approximately 4 to 6 weeks later and interpreted according to the IRIS guidelines. If levels remain higher than desired (ie above the IRIS targets) then options which can be considered include:

- Combining an IPB with a phosphate restricted diet (if not already doing so)
- Increase the dose of the IPB: ensure that all of the food that the animal eats contains binder. While the normal recommendation is to split the dose and give the product twice per day, the most important thing is to ensure that all food that the animal eats is phosphate restricted. With Pronefra, it is more appropriate to increase the number of times it is administered than to increase the amount given at each administration.
- Add a second phosphate binder to the regime

3.2 Management of **nitrogen waste**

For practical reasons urea (BUN) could be viewed as a marker of retained uremic toxins representative of water-soluble non-protein nitrogenous components. Vomiting and inappetence are commonly seen in CKD patients and result from the effects of uremic toxins on the medullary emetic chemoreceptor trigger zone with a clear correlation with the magnitude of azotaemia.[1] **The intestinal management of uremic toxins has a direct and practical interest for CKD patients with gastrointestinal complications** (which are common and prominent signs of uremia).[1] It has been suggested that some natural ingredients can reduce intestinal ammonia absorption in CKD cats thus providing a benefit in cats with elevated blood urea nitrogen (BUN) levels.[14]

The benefits of simultaneous use of chitosan and phosphate binders in cats suffering from CKD have been shown previously14 and are an accepted part of the dietary management of this disease.[15]

3.3 Management of **renal fibrosis**

CKD progresses as the result of continuous damage to the renal tissue induced by the disease itself.[1] Inflammation, and then as a result fibrosis, is a final common pathway in CKD that leads to disease progression and ultimately organ failure. In advanced stages of CKD, fibrosis is a major event and these lesions cannot be reversed.

3.4 Management of other disorders

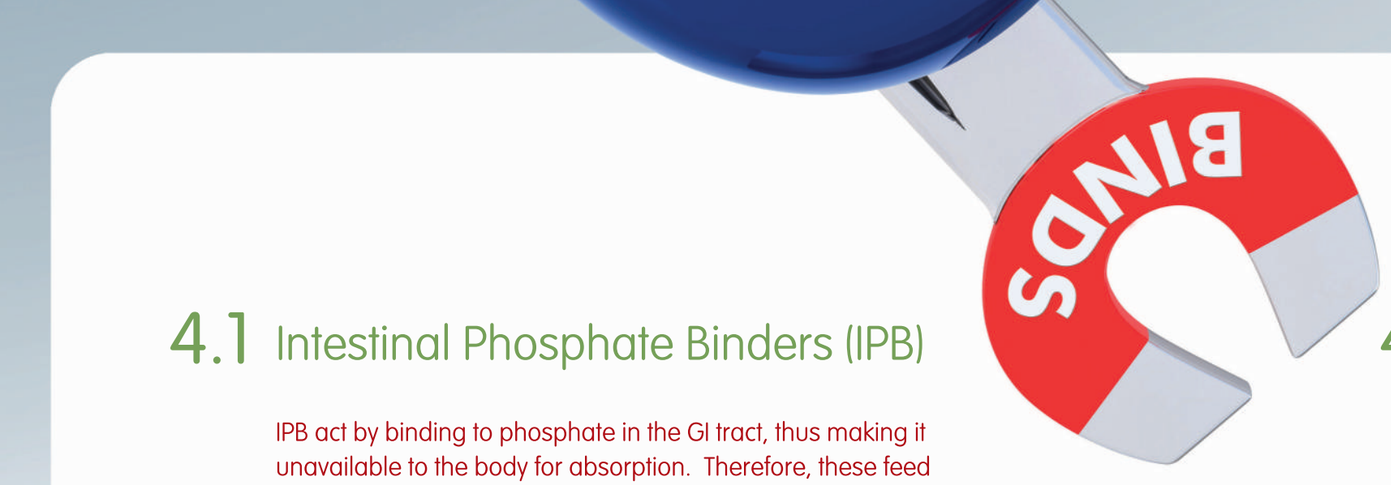
Management of CKD is much more complex than management of only hyperphosphatemia, renal fibrosis and nitrogen waste. Proteinuria, hypertension and various electrolytic disorders should be taken in charge as well as anorexia, vomiting, other digestive troubles: they are not covered in this document.

4 PRONEFRA® COMPOSITION AND THE BENEFITS OF THE INGREDIENTS

Pronefra® is a complete solution, ensuring an optimized compliance for dogs and cats with CKD

Pronefra® is a unique proprietary formula, highly palatable and which is based on the association of 4 ingredients:

- **Calcium carbonate** and **magnesium carbonate are well-known intestinal phosphate binders (IPB)**: they decrease dietary availability of phosphorus by intestinal binding.
- **Chitosan** is known to **bind uremic toxins in the intestines.**
- The **marine oligopeptides** contribute to maintenance of a balanced blood pressure



4.1 Intestinal Phosphate Binders (IPB)

IPB act by binding to phosphate in the GI tract, thus making it unavailable to the body for absorption. Therefore, these feed supplements must be taken with or very close to meals in order to bind the phosphate present in the ingested food.[7,18,17,12,20,21]

In Pronefra®, two different IPB are associated which reduces particular concerns regarding eventual adverse effects (in particular hypercalcaemia). Carbonate of calcium is incorporated in Pronefra at a dosage lower than normally recommended (-50 %) as it is associated with magnesium carbonate, according to very recent recommendations.

Despite the fact that there is scientific evidence for the benefits of IPB [10,16,12], market data shows that the majority of pets with CKD are not receiving a phosphorus binding agent [17,18].

Practitioners report a lack of palatability of some supplements[1] and the galenic forms (for example powders) are not always well adapted to cats further contributing to poor compliance.

This problem is even more in evidence when there is a need to provide multiple products to manage the different aspects of the disease. Given the fact that in cats presented with azotaemia the appetite is often variable or may be selective for certain foods, palatability has been cited as one of the major factors that influences the selection of an IPB.[1] **For this reason the palatability of feed supplements designed specifically for CKD cats should be of primary importance in order to avoid inappetence due to the nature of the product.**

Pronefra® provides a daily dose of 18.5 mg/kg of $CaCO_3$ with 5 mg/kg of $MgCO_3$ for cats and 14.8 mg/kg of $CaCO_3$ with 4 mg/kg of $MgCO_3$ for dogs.

Of all recommended management options for CKD, the current consensus is that dietary restriction of phosphorus is the major contributor in slowing the disease progression and improving survival times.[7,18,17,12,20,21]

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4.2 Chitosan

The benefits of simultaneous use of chitosan and phosphate binders in cats suffering from CKD have been shown previously[14] and are an accepted part of the dietary management of this disease.[15]

Chitosan is known in veterinary medicine as a **uremic toxin binder.**[15,14] It is a natural polysaccharide composed of randomly distributed D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine.

It has binding capacities for some soluble nitrogen compounds including ammonia and some molecules containing phosphorus. Acting as an adsorbent inside the gastro-intestinal tract, chitosan combines with acidic nitrogen substances suspected to be uremic toxins, resulting in greater excretion from the body.[15]

The increased blood levels of uremic toxins tend to be correlated with the poor clinical condition of the animal and the severity of vomiting.[1]

Chitosan dosage in Pronefra is 5mg/kg for cats and 4 mg/kg for dogs.

4.3 Protensin vasoactive peptides

These feed supplements could be considered as a nutraceutical ingredient having an overall beneficial effect on the maintenance of normal blood pressure[24], but not as anti-hypertensive compounds.

Vasoactive oligopeptides have been known for over fifteen years in human medicine; the first reports started to appear in the 1990s. Much more work has been done in the last ten years in understanding the nature of these compounds and how they work. They have been isolated from several food sources, mostly milk or fish products[24], and biochemically characterised. These products have also been proposed as supplements in humans.[24]

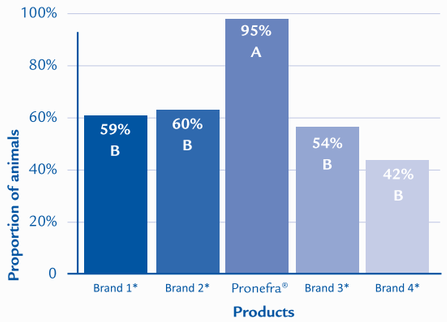
5 PALATABILITY DATA IN CATS

5.1 External and independent palatability study

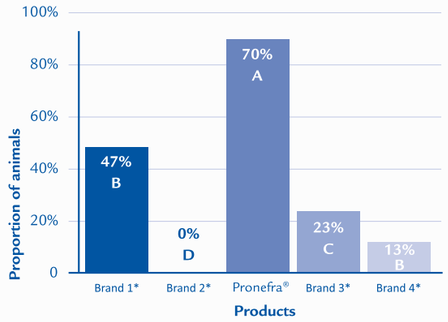
Study objectives:

The aim of the present study[27] was to investigate the palatability of four commercially available feed supplements designed for cats suffering from CKD: Ipakitine® (Vetoquinol, France), Azodyl® (Vetoquinol, USA), Renalzin® (Bayer, France), Rubenal® (Vetoquinol, France) and an additional recently developed feed supplement: Pronefra® (Virbac, France).

Spontaneous prehension of CKD supplements in cats



Useful consumption (≥50%) of CKD supplements in cats



Bars indicate the percentage of cats which consumed more than 50% of the product in each group

Columns not bearing a similar letter are significantly different

Study conclusion: This study has shown that most of the existing presentations of feed supplements designed for CKD (Azodyl®, Ipakitine®, Renalzin® and Rubenal®) have rather low prehension and consumption levels in healthy cats.

One product in this study (Pronefra®) was clearly demonstrated to have superior prehension, total consumption and useful consumption rates along with the lowest refusal rate.

* Data on file

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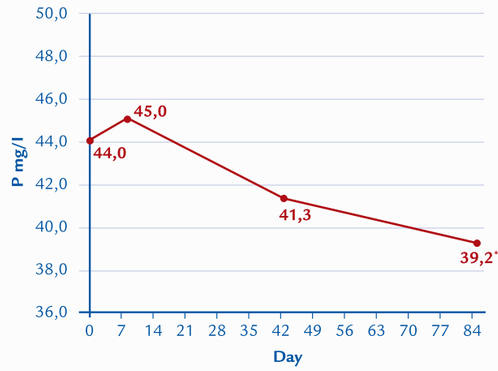
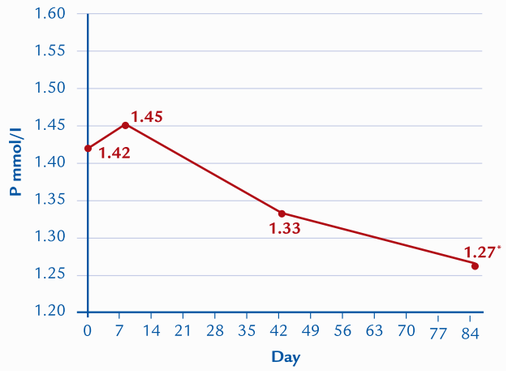
6 EFFICACY DATA

6.1 In cats

Study objectives:

The goal of this experimental study[26] was to assess the ability of Pronefra® to reduce serum phosphorus levels and to follow its impact on other renal biochemical parameters.





Results obtained during a 12 week study in cats*

Figures 2 . Mean serum inorganic phosphorus concentrations (with standard error of the mean) over the course of the study in all cats (n=10) (* p<0.05 compared to the beginning of the study at day 0),

Results: Over the study period, supplementation with Pronefra® resulted in a statistically significant decrease of inorganic phosphorus levels.

- A significant decrease of SCr levels was also observed during supplementation with Pronefra®.
- Fractional excretion of phosphorus was significantly reduced by supplementation.

6.2 In dogs

Pronefra® has been shown to be efficient in P binding in dogs which have been nutritionally stabilised.

This data was generated during a safety study. Although it was not the primary goal of the study, and 4 weeks is normally too short to see a significant drop in blood phosphorus levels in healthy dogs eating a standard diet, Pronefra® was shown to be effective in phosphorus binding at the recommended dosage in dogs (p=0.017).

7 SAFETY DATA

7.1 In cats

The product was tested at three different dosages: normal dosage (ND), 2 times ND, and 5 times ND.

The total duration of the study was 112 days

The data has shown that Pronefra® is well tolerated and has an excellent safety profile at the recommended posology

7.2 In dogs

Pronefra was tested at normal dosage[25] and two times normal dosage.

The total duration of the study was 56 days

This study has shown that Pronefra® is safe and very well tolerated in dogs for continuous use over 8 weeks.

8 USE IN PRACTICE

How often should Pronefra® be given?

Pronefra® should be given twice daily **with food or close to mealtime**.

Indeed, Pronefra® contains IPB that act by binding to phosphate in the GI tract, thus making it unavailable to the body for absorption.

How could Pronefra be given?

It can be mixed with food or directly given into the mouth by using the provided syringe. Water should be available at all times.

What is the dosage for Pronefra®?

Pronefra® is available in 2 presentations:

1 ml / 4 kg / twice a day

1 ml / 5 kg / twice a day

60 ml for cats
1 month administration for a 4 kg cat

180 ml for cats and dogs

3 month administration for a 4 kg cat

1 month administration for a 15 kg dog

Storage and conservation

Shelf life of the closed bottle is 24 months.

Once open, it can be used for 3 months.

Keep at room temperature (preferably below 30°C), no fridge conservation is requested. Pronefra® is a suspension and for this reason should be shaken before each use.

How long can I give Pronefra®?

Pronefra® could be initially administered up to 6 months. However, the use of phosphate binders could be required lifelong in CKD patients to obtain efficient control of phosphorus and the decision to use Pronefra® longer than 6 months should be taken according to the patient condition.

Can Pronefra be combined to a renal phosphate diet?

Yes, Pronefra® can be combined to a renal prescription diet, which is already phosphorus reduced, if this is required to obtain an efficient control of phosphorus.

At which stages should Pronefra® be used?

It is recommended to use Pronefra® from the early stages of the CKD when an increase in phosphorus blood levels and/or in parathormon blood levels are detected.

IRIS currently recommends phosphate restriction for all patients in IRIS stages 2, 3 and 4.

BIBLIOGRAPHY

1. S. Ettinger and E. Feldman, Textbook of Veterinary Internal Medicine, Volume 2, St.Louis: ELSVIER SAUNDERS, 2005.
2. R. E. Jepson, "Evaluation of predictors of the development of azotemia in cats.," J. Vet. Intern. Med., p. 806–813, 2009.
3. J. P. Lulich, C. A. Osborne, T. D. O'Brien and D. Polzin, "Feline renal failure:Questions, answers, questions.," Compend Contin Educ Pract, no. 14, p. 127–152, 1992.
4. L. Boyd, C. Langston, K. Thompson, K. Zivin and M. Imanishi, "Survival in Cats with Naturally Occurring Chronic Kidney Disease," J Vet Intern Med, no. 22, pp. 1111-1117, 2008.
5. S. Caney, "Caring for a cat with chronic kidney disease", Cat Professional, 3rd Edition, 2012.
6. IRIS (Internation Renal Interest Society), "Staging System for Chronic Kidney Disease (CKD)," 2013. [Online]. Available: http://www.iris-kidney.com/guidelines/en/staging_ckd.shtml. [Accessed 30 July 2013].
7. S. Chakrabarti, H. Syme and J. Elliott, "Clinicopathological Variables Predicting Progression of Azotemia in Cats with Chronic Kidney Disease," J Ver Intern Med, no. 26, pp. 275-281, 2012.
8. H. Syme, P. Markwell, D. Pfeiffer and J. Elliott, "Survival of Cats with Naturally Occurring Chronic Renal Failure Is Related to Severity of Proteinuria," J Vet Intern Med, no. 20, pp. 528-535, 2006.
9. J. Elliott, J. Rawlings, P. Markwell and P. Barber, "Survival of cats with naturally occuring chronic renal failure: effect of dietary management.," Journal of Small Animal Practice, no. 41, pp. 235-242, 2000.
10. A. Kidder and D. Chew, "Treatment options for hyperphosphatemia in feline CKD: what's out there?," J Feline Med Surg., vol. 11, no. Nov;11, pp. 913-924, 2009.
11. K. Kalantar-Zadeh, "Patient education for phosphorus management in chronic kidney disease," Patient Preference and Adherence, no. 7, p. 379–390, 2013.
12. P. Barber, J. Rawlings, P. Markwell and J. Elliott, "Effect of dietary phosphate restriction on renal secondary hyperparathyroidism," Journal of Small Animal Practice, no. 40, pp. 62-70, 1999.
13. B. H. Schmidt, U. Dribusch, P. C. Delport, J. M. Gropp and F. J. van der Staay, "Tolerability and efficacy of the intestinal phosphate binder Lantharenol® in cats," BMC Veterinary Research, pp. 8-14, 2012.
14. E. Wagner, I. Schwendenwein and J. Zentek, "Effects of a dietary chitosan and calcium supplement on Ca and P metabolism in cats," Berl. M nch.Tier rztl.Wschr., no. 117, pp. 310-315, 2004.
15. A. Zatelli, M. Pierantozzi, P. D'Ippolito, M. Bigliati and E. Zini, "Effect of Dietary Supplements in Reducing Probability of Death for Uremic Crises in Dogs Affected by Chronic Kidney Disease (Masked RCCT)," The Scientific World Journal, 2012.
16. S. Caney, "Pet owner insights: importance of phosphorus control.," in ISFM Proceedings, Barcelona, 2013.
17. J. Markovich, L. Freeman, M. Labato and C. Heinze, "Survey of the Dietary and Medication Practices of Owners of Cats with Chronic Kidney Disease," J Vet Intern Med, no. 27, pp. 735-736, 2013.
18. Vetpanel, "Vet Omnibus Survey," CM reasearch, 2012.
19. E. Garabed, "Salivary Phosphorus Binding:A Novel Approach to Control Hyperphosphatemia," J Am Soc Nephro, vol. 20, pp. 460-462, 2009.
20. H. Wang, J. Li, L. Yu, Y. Zhao and W. Ding, "Antifibrotic effect of the Chinese herbs,Astragalus mongholicus and Angelica sinensis, in a rat model of chronic puromycin," Life Sci., no. 74, pp. 1645-58, Feb 2004.
21. G. Zhang and A. M. Nahas, "The effect of rhubarb extract on experimental renal fibrosis.," Nephrol Dial Transplant., pp. 186-90, Jan 1996.
22. S. Li, Y. Zhang and J. Zhao, "Preparation and suppressive effect of astragalus polysaccharide in glomerulonephritis rats.," Int Immunopharmacol., vol. 7, no. 1, pp. 23-28, Jan 2007.
23. X. Li, D. He, L. Zhang , X. Cheng , B. Sheng and Y. Luo, "A novel antioxidant agent, astragalosides, prevents shock wave-induced renal oxidative injury in rabbits.," Urol Res., vol. 4, no. 34, pp. 277-282, Aug 2006.
24. A. H. Pripp, "Effect of peptides derived from food proteins on blood pressure: a meta-analysis of randomized controlled trials.," Food Nutr Res., no. 52, Jan 2008.
25. N. Bernachon, H. Gatto, P. Monginoux and D. McGahie, "Safety evaluation in dogs of a feed supplement containing a combination of calcium and magnesium carbonate intestinal phosphate binders, associated with natural reno-protectant substances (Pronefra®)," in BSAVA, Birmingham, 2014.
26. N. Bernachon, S. Fournel, H. Gatto, P. Monginoux and D. McGahie, "Effect of a product containing the dietary phosphate binders calcium and magnesium carbonate associated with other reno-protectant substances (Pronefra®) on blood parameters and mineral balance in adult cats," JARVM, 2014.
27. N. Bernachon, S. Fournel, H. Gatto, P. Monginoux and D. McGahie, "Comparative palatability of five feed supplements designed for cats suffering from chronic renal disease.," 2014.

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