

## TOP TEN AZODYL QUESTIONS (and counting)

1. **How does it work?** A: This is a mixture of three viable bacteria that are strongly urease positive. This means they actively utilize the uremic toxins that diffuse into the bowel from the circulatory system thereby reducing the uremic toxic load.
2. **How long will it take?** A: Depending on the overall health state of the animal the reduction in BUN and creatine can occur as soon as two weeks but certainly we can see a reduction by the time of the next re-check (usually 1 month).
3. **Can I use it with Epakitin?** A: Certainly, in fact it can be used with any CKD treatment the patient is presently receiving. Epakitin is used primarily for reduction of serum phosphorous. We see that in IRIS stages 2 to 4. In about 10-15% of the azotemic patients we see elevated serum phosphorous (serum hyperphosphatemia).
4. **How long can it be non-refrigerated?** A: As these are viable organisms we recommend that it be kept refrigerated at all times. We store under refrigerated conditions and ship using coolers and freezer packs. Our distributors keep it stored under those conditions. A clinical study showed that the bacterial counts were stable at -20, 4 and 25 degrees Centigrade (C) for up to 14 days. The counts decreased at 37, 45 and 55 degrees C. The urea hydrolytic activity remained at least at 50% even under the 45 degree conditions. We recommend refrigeration as we are concerned that there may be a cumulative effect of temperature elevations over time. These temperatures are: 4C= 39.2 Fahrenheit (F), -20C=-4 F, 25C=77F, 37C=99F, 45C=113F, 55C=131F.
5. **Is there any way that one can tell if the Azodyl capsule cultures are still active?** (Since the capsules must be kept refrigerated, how does the consumer know that somewhere along the line from the time it left the company, either due to someone's neglect or forgetfulness, that the capsules have been left out too long and destroyed the cultures?) We make every effort to make sure our product is stored and shipped to keep bacteria alive, We also have trusted distributors we work with that knows the requirements of this product. The veterinarians are also educated in the proper storage. We also know there is a time frame that it can be kept out of the refrigerator and still be active. Vetoquinol works very hard at maintaining high quality products and regularly doing quality assurance tests. The one place we have no control over is if you buy this product off the internet as we do not sell to companies on the net. There is no way once they send it out to the consumer to know if they are active. If you buy it off the net it means the drug has been diverted out of our normal distribution chain and we have no idea how it has been maintained.

6. **What are the side effects?** A: We have no reported side effects except for a case of vomiting and two cases of diarrhea. These may be attributed to the concurrent CKD effects on the body. Re-establishing the normal gut microflora may have accounted for the upsets. If AZODYL is suspected we recommend reducing the dose and continue observing the patient.
7. **Can I open the capsules?** A: The capsules are intended to be administered as presented. Anecdotal evidence suggests that there is efficacy in BUN and creatinine reduction when the product is administered on the food. We are investigating: reduction of counts and BUN reduction if administered other than directed. These results should be available in a couple of months. Best results are observed when administered whole.
8. **Why a capsule?** A: The bacteria in Azodyl work best in the colon region of the intestine. The harsh environments of the stomach and small intestine are detrimental to the bacteria. Consequently, we have to encapsulate them to ensure the maximum number of viable bacteria reach the colon.
9. **Do you have any studies?** A: There are a number of studies. BUN and creatinine reduction has been observed in a pig model study. The results of clinical evaluation in client owned cats were recently reported in "The Journal of Veterinary Holistic Medicine". Additional studies are underway.
10. **Do you have any literature?** A: We have sales aids for detailing the product to the veterinarian as well as client brochures. We offer reminder cards for the veterinarian to use with the client. We can provide the abstracts of the studies mentioned above.
11. **I didn't think BUN and creatinine were toxic?** A: BUN and creatinine are not toxic per se. They are indicators of kidney function. They also serve as markers for the hundreds of other non-protein nitrogen and other metabolic byproducts that are toxic. Azodyl reduces these toxins as is evidenced by the reduction in BUN and creatinine
12. **How do the toxins get into the gut?** A: The toxins are normally produced from protein metabolism and muscle breakdown. In a healthy animal the kidneys filter these toxins out and they are eliminated in the urine. As kidney function diminishes these toxins build up in the blood and diffuse into and out of the gut by simple diffusion across the blood gut barrier. This is where Azodyl is effective. The bacteria engulf the toxins and they are eliminated through fecal formation. Thus the term Enteric Dialysis.
13. **What is the bioactivity of the organisms?** A: We don't measure "bioactivity" instead we measure their activity through BUN and creatinine reduction.
14. **What is the biokinetics?** A: Again as above we are not concerned with the biokinetics. These are GRAS, Generally Recognized As Safe items, listed in the American Association of Feed Council Officials (AAFCO) handbook. They have been found safe to use as feed additives.

15. **Can you send me a sample?** A: A sample is not sufficient to prove the efficacy of this product. We rather you purchase the product, try it for a month reevaluate the patient, notice the startling reduction in BUN and Creatinine. Then if you are not satisfied request a full 100% refund, as offered with all Vétoquinol USA products. A single sample used for a month to evaluate the efficacy will prevent using this in additional CKD patients that will otherwise benefit from BUN and creatinine reduction during your investigational period.
16. **Can Azodyl be given with simultaneous administration of antibiotics?** We commonly see UTI's with CKD. Primarily due to altered quantity and pH of the urine. It is suggested that you space the administration out by 6 hours. The antibiotics will be fully absorbed by then and the  $\frac{1}{2}$  life will be reduced sufficiently that any return to the gut will be negligible.
- a. Can you tell me the interaction between Azodyl and Clavamox. Does Clavamox destroy the active bacteria in Azodyl? If so is there another antibiotic compatible with Azodyl?
    - i. We have not yet performed tests with this combination. Most antibiotics commonly used in renal failure are rapidly absorbed and have a short half life as they are excreted unchanged in the urine. There should be little to no interaction with the antibiotics as they are absorbed in the small intestine. These bacteria remain in the gut using the non-protein nitrogen uremic toxins as a nutrition source. The capsule is enteric coated to be dissolved in the large intestine/colon.
17. **How can your recommended dosing have the same effect for a 20 pound dog as it would on a 170 pound dog?** With bacteria therapy the dose is not truly dependant on size alone but many other factors including the uremic toxin load. The bacteria are very specific in that they only use non-protein nitrogen molecules (NPNM) as a source of nutrition. Once the NPNM are consumed the bacteria are not able to reproduce. That is why we give twice daily doses. They will reproduce to the limit of the environmental influences. It is not necessary to set a dose strictly based on the size of the animal.

18. “Doesn’t AZODYL confuse our interpretation of renal function?” Let’s look at this in full. AZODYL reduces the BUN and Creatinine values. This occurs because the bacteria consume non-protein nitrogen molecules found in the gut. BUN and Creatinine are the markers used for evaluation of renal function. Uremic toxins build up during renal failure as the kidneys are unable to remove them. It does stand to reason that if we reduce the levels of BUN and Creatinine we may develop a false sense of increased renal function. BUT, does anything improve renal function? NO, once we lose the nephron (the functional element of the kidney) it is not replaced. Early on, a compensatory mechanism occurs whereby the remaining nephrons “pick-up the slack”. Soon they “burn themselves out”. This compensatory mechanism is detrimental. We recommend administration of AZODYL once the kidneys display signs of Azotemia. We define azotemia as persistent increases in BUN and creatinine. Clinically, azotemia is an indication that we have lost 75% of the functional nephrons. With 25% or less of the nephrons remaining we know we are on the downward slide. We can continue to monitor the decreased renal function as the BUN and Creatinine rise and offer no systemic support to the animal or we can try to improve the quality of life. We have opted to improve the quality of life. If we remove these uremic toxins we help to minimize or possibly prevent the effects of a uremic crisis. With all that said let’s look at it another way. In human medicine we offer dialysis. This procedure eliminates toxins that build up in the body, thereby improving the quality of life. Without the elevation of these toxins and the markers of renal function we could assume the kidneys are doing better. NOT THE CASE. We already know that renal function is so compromised that the animal (or human) will suffer the effects from a uremic crisis. We can prevent that by reducing the effects of the uremic toxin build up.