

The FDA Issues Warning about Flea and Tick Products

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The US Food and Drug Administration (FDA) issued a warning on September 20, 2018 about the isoxazoline flea and tick products fluralaner for dogs and cats (Bravecto®), afoxaloner for dogs (Nexgard®), and saroloner for dogs (Simparica®). The recently introduced isoxazoline, lotilaner (Credelio®) for dogs falls into this same class.

Dogs and cats with no known prior medical history of muscle tremors, ataxia, and seizures have experienced those adverse reactions to this class of flea and tick preventive pesticides. While the FDA is not pulling the four flea and tick preventatives off the market at this time, they will all have to carry an FDA warning on their packaging.

Clinical, evidenced-based reports have been coming forward for the past several years and many studies are currently percolating about the reported adverse reactions to isoxazolines, synthetic pesticides. Dr. Jean Dodds is currently on a privately convened expert committee researching this topic and their report should be issued soon.

Oftentimes when information such as this is brought to light, veterinarians and researchers can point to certain breed characteristics, age, drug interactions, or genetic mutations. For instance, dogs that are epileptic or prone to seizures should not have spinosads – a natural substance made by a soil bacterium that can be toxic to insects – that is also for treatment or prevention of fleas. Two of the most well-known spinosad products are Trifexis® and Comfortis®.

Another example is the MDR1 gene mutation. This gene undergoes one or more mutations that allow a higher absorption of drugs and toxic substances to enter the central nervous system and then can breach the blood-brain barrier and create adverse reactions. Plus, we know that this gene mutation is most commonly found in dog breeds of herding breed ancestry. According to the Washington State Veterinary Clinical Pharmacology Lab, nearly three of every four Collies in the US have the mutant MDR1 gene. The frequency is about the same in France and Australia, so it is likely that most Collies worldwide have the mutation. The MDR1 mutation has also been found in Shetland Sheepdogs (Shelties), Australian Shepherds, Old English Sheepdogs, English Shepherds, German Shepherds, Long-haired Whippets, Silken Windhounds, and a variety of mixed breed dogs.

This is where this can get tricky with the MDR1 gene mutation. FDA-approved antiparasitic drugs such as ivermectin (Heartgard), selamectin (Revolution), milbemycin oxime (Interceptor) and moxidectin (Advantage Multi; Proheart 6) have been tested and found safe for MDR1-affected dogs when given at the prophylactic heartworm preventative dosage level. Despite this commentary, the present author does not recommend several of these products, especially for toy and small breeds and puppies or those with or at familial risk for autoimmune disorders, including vaccinosis.

Further, if a heartworm preventative is given with a spinosad, isoxazoline, ketoconazole, itraconazole, fluconazole or related antifungals, then serious drug-drug interactions can occur in dogs that have the MDR1 mutation.

While we have known about the MDR1 mutation situation before, **the scary part now about the isoxazoline class of drugs is that researchers and veterinarians thus far cannot point to breed characteristics, age group, drug interactions or genetic mutations as contributing factors to the latest**

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findings that prompted the FDA warning. These adverse reactions to the isoxazoline class appear to be affecting pets randomly.

As of May 4, 2018, 420 reports of worldwide adverse reactions to these pesticides in humans have been given to the European Medical Agencies (EMA). These reactions include breathing problems, skin conditions, and even seizures and the onset occurred after handling the chewable or spot-on treatment of fluralaner. Causality assessment at that time was placed at: 37 as probable, 13 as possible, 4 unclassifiable, 3 inconclusive, and the rest have not been assessed.

What is possibly most concerning is the introduction of Exzolt[®], which curbs red poultry mites. Red poultry mites can cause anemia, disease susceptibility and higher mortality rates in chickens. Exzolt[®] is made of the same isoxazoline (fluralaner), which is sold as Bravecto[®] for dogs and cats. The EMA recommended to the European Union to approve Exzolt[®] use through water treated with the product. As of September 2017, the product was being marketed in Europe. The withdrawal period for meat from chickens treated with Exzolt[®] is 14 days. The withdrawal period for eggs from chickens treated with Exzolt[®] is zero days, which means there is no mandatory waiting time.

We have written extensively about the use of medications in livestock and how many of them can be passed up the food chain. We do not know definitively whether Exzolt[®] is passed up the food chain. Clearly, we believe that the EMA needs to reconsider its use.

After a search on the FDA's website for fluralaner, afoxolaner, sarolaner and lotilaner, the use of these isoxazoline drugs is not approved for use in livestock or food producing animals.

If your companion dog or cat is not prone to fleas or you do not live in a tick-infested area, there is no reason to give flea and tick medications as preventatives. If these bugs attach themselves, you can use flea shampoos and combs, or specially designed tick removers. It is a little bit more work, but your companion pet's health is worth it.

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