What are isoxazoline drugs?

The isoxazoline class of drugs includes afoxolaner (Nexgard), fluralaner (Bravecto), suralaner (Simparica), and lotilaner (Credelio). These are a highly effective class of FDA-approved flea/tick preventives available in a oral chew or in some cases, a topical liquid.

What is all the hype about?

The FDA carefully reviewed studies and other data on Bravecto, Credelio, Nexgard and Simparica prior to approval, and these products continue to be safe and effective for the majority of animals. **The agency is asking the manufacturers to make the changes to the product labeling in order to provide veterinarians and pet owners with the information they need to make treatment decisions for each pet on an individual basis.**

The FDA monitors adverse drug event reports received from the public or veterinarians, other publicly available information (such a peer-reviewed scientific articles), and mandatory reports from the animal drug sponsor (the company that owns the right to market the drug). Drug sponsors must report serious, unexpected adverse events within 15 days of the event. In addition, they must submit any events that are non-serious, plus any laboratory studies, in vitro studies, and clinical trials that have not been previously submitted to the agency, on a bi-annual basis for the first two years following product approval and annually thereafter.

The FDA continues to monitor adverse drug event reports for these products and encourages pet owners and veterinarians to report adverse drug events. You can do this by reporting to the drugs' manufacturers, who are required to report this information to the FDA, or by submitting a report directly to the FDA.

To report suspected adverse drug events for these products and/or obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, contact the appropriate manufacturers at the following phone numbers:

Merck Animal Health (Bravecto): 800-224-5318

Elanco Animal Health (Credelio): 888-545-5973

Merial (Nexgard): 888-637-4251

Zoetis (Simparica): 888-963-8471

Why are flea/tick preventives important?

Fleas are not only a nuisance in the home (an infestation can take up to several months to effecitvely clear from your home and yard), but pose a health hazard to your pets as well. Fleas can be carriers of tapeworm larvae, which are then transmitted to your pets when a flea is accidentally ingested while grooming. Fleas can also cause severe skin allergic reactions from their saliva. While not all flea preventives stop fleas from biting, they do control the flea population making bites less likely.

Ticks can also be carriers of serious parasites such as Babesia, Ehrlichia, and Anaplasma which may cause pets to have fever, painful joints, decreased platelet counts and subsequent bleeding disorders, and kidney dysfunction. Recent studies have shown that pets exposed to some of these parasites (Lyme and Ehrlichia) and in areas endemic for these conditions have an increased risk of chronic kidney disease even if your pet is not currently infected.

Counterfeit medications

Any time pet medications or products are purchased online through an unapproved distributor, the potential for counterfeit exists. These products may not contain the active ingredient stated on the packaging, and therefore may be ineffective or even harmful. Counterfeit products can be extremely convincing and may not be easily established as such. If you have concern that your pets' products may be counterfeit, please contact the manufacturer at the numbers listed below.

EPA recommendations for identifying counterfeit products:

There is no single characteristic that will identify all counterfeit products. Some of the issues that have been found include:

Differences in weight between the outer package and the product inside

Lack of directions in English

Products not packaged in child-resistant packaging

Missing directions for use

Product in the container is not appropriate for the animal or size of animal pictured on the outside

Stickers on the box to hide the foreign labeling

EPA registration number is missing

Foreign labeled product with stickers containing some U.S. information

Foreign-labeled products.

Consumer affairs recommendations for purchasing products online:

So how can you tell if you're dealing with an illegitimate online pharmacy? Here are a few tip-offs:

The website doesn't end in ".Pharmacy." You might be used to looking for the Vet-VIPPS seal on your pharmacy's website, but as of August 2017, consumers should look for pharmacy websites ending in ".Pharmacy." Websites that end in ".Pharmacy" are trustworthy, as they have met strict standards for enrollment.

It doesn't require a vet's prescription. If the site claims that it will prescribe a drug after one of its on-staff veterinarians "evaluates" the pet after looking over a form filled out by the pet owner, it may be an illegitimate site.

Not state-licensed. To ensure the pet medicine you're buying online is safe, order from an outsourced prescription management service that your veterinarian uses. These state-licensed internet pharmacy services work directly with the veterinarian, require that a prescription be written by the veterinarian, and support the veterinarian-client-patient relationship.

Product Safety Labeling

Bravecto Chew: The most common adverse reactions recorded in clinical trials were vomiting, decreased appetite, diarrhea, lethargy, polydipsia, and flatulence. Bravecto Topical Solution for Dogs: The most common adverse reactions recorded in clinical trials were vomiting, hair loss, diarrhea, lethargy, decreased appetite, and moist dermatitis/rash. **Use with caution in dogs with a history of seizures. Seizures have been reported in dogs receiving fluralaner, even in dogs without a history of seizures.**

Nexgard: **Afoxolaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.** In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded.

The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in

both groups. Five treated dogs experiencedanorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

Post-Approval Experience (July 2018):

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. <u>It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.</u>

The following adverse events reported for dogs are listed in decreasing order of reporting frequency for NexGard: Vomiting, pruritus, lethargy, diarrhea (with and without blood), anorexia, seizure, hyperactivity/restlessness, panting, erythema, ataxia, dermatitis (including rash, papules), allergic reactions(including hives, swelling), and tremors.

What is the bottom line?

Some neurological abnormalities have been observed with flea and tick preventives in general, including the isoxazoline class of drugs. However, these medications have been used frequently without incident in pets with history of seizures. If your pet has a condition causing seizures and has difficulty attaining control even with appropriate treatment, this class of drug and flea/tick prevention in general may not be in the pet's best interest, a decision best made in conjunction with a veterinarian.