

Focus on Antiparasitics

Externally applicable drugs like sprays, collars or spot-on preparations against fleas and ticks belong to the standard in veterinary medicine. New to the market are oral applicable drugs whose undesired effects are not very well known and will be briefly summarized in this article.

During the last years the focus was mainly on easy to use spot-on drugs. The disadvantages of those are e.g. the fear of the pet owners of toxicity when in contact with the pet as well as the influence on other externally applicable drugs concerning its effectiveness. Regular shampooing for example, a popular dermatological therapy might significantly reduce the period of the effectiveness, as the active substance is washed off. Besides, there is a number of animals who react to those drugs with e.g. skin irritations.

The new generation of ectoparasiticides are oral applicable preparations which are not influenced by other external therapies, extinguish parasites fast and are effective over a given period.

A short overview about different oral drugs and the feedback received up to now in Germany concerning undesired effects, collected and evaluated by the **Ministry for Food Safety and Consumer Protection (BVL)**, the competent authority for the control of veterinarian medicine after registration:

Some oral drugs have been existing since the 1990`s and possible side effects are known. The new drugs are on the market for quite a short time, only a few years or months, different studies with a limited number of animals proved their harmlessness, but a long time experience is missing.

Oral drugs against fleas

Ectoparasiticides like Program, Program Plus and Capstar are veterinarian medicines which have been on the market for decades. They are only effective against fleas, not against ticks.

Program contains the active substance Lufenuron. Program Plus contains Lufenuron in combination with Milbemycin oxime. They are effective against fleas and Program Plus also against heartworms and other kind of worms. Lufenuron belongs to the benzoyl urea group and is an insect growing regulator. It interrupts the developing cycle of fleas by interfering with the chitin synthesis. Hence, Lufenuron is not effective against adult fleas.

Concerning Program and Program Plus the BVL has only got a low number in reports since its launch (1995). There are 13 reports for Program (2 serious reports and 11 less serious) and 3 reports for Program Plus (2 serious, 2 less serious). The main focus in all reports is on gastrointestinal symptoms, 2 reports were talking about a non sufficient effectiveness on fleas.

Capstar contains Nitenpyram, belonging to the Neonicotinoids, which dock to insect specific Acetylcholin receptors and block them. According to studies this substance kills 100 percent of adult fleas within its active phase of 24 hours.

Concerning Capstar the BVL has received 10 reports since its launch in 2002, 3 were valued as serious, 7 as non serious. The reports were talking about various symptoms like vomiting, lethargy, anaemia as well as neurological symptoms. None of these symptoms were predominant.

New to the market are Comfortis and Trifexis, launched in 2011 and 2013, containing the substance Spinosad or the combination Spinosad / Milbemycin oxime. Spinosad exists of Spinosin and Spinosin D and is made of the Actinomycet *Saccharopolyspora spinosa*. Spinosins belong to the tetracyclic macrolides. The insecticide effect is triggered, beside others, by the activation of nAChRs (Nicotinic acetylcholine receptors), a different mechanism as those of known insecticides. Spinosad kills adult dog fleas within 4 hours, cat fleas within 24 hours and stays effective up to 4 weeks. Spinosad has no repellent effect, as the parasites are killed after contact with the animal. Trifexis is also effective against heartworms as well as against different other kind of worms.

Since its launch in 2013 the BVL has not received any reports. Concerning Comfortis, 29 reports have been received, 23 of them have been valued as serious. Other European countries and the US report significantly more cases. Both, the German and international reports were mainly talking about neurological and gastrointestinal side effects, which were already listed in the description. In four of the German cases shows side effects up to blindness when Ivermectin was taken in addition to Spinosad. There was already a warning about this combination in the description. Both substances dock to the transport protein P-Glycoprotein, which plays an important role in passing the blood-brain barrier. The interaction of these two substances is currently an object of research. Both, Trifexis and Comfortis advise to take caution when applying to animals with known epilepsy.

Oral drugs against fleas and ticks.

In the beginning of 2014 Nexgard and Bravecto have been launched for dogs. They both contain the new active substance group Isoxazoline. According to their description they are effective against fleas and ticks, for 4 weeks (Nexgard) and 12 weeks (Bravecto).

Isoxazoline substances have an insecticide and acaricid effect, as they block the GABA and L Glutamat chloridion channels, which cause the death of the parasites. As with all endoparasiticides they do not have a repellent effect. According to the description, 100 percent of the ticks should be killed within 24 hours after input, 89 percent already after 4 hours.

The BVL has so far received 34 reports concerning Bravecto and 3 reports concerning Nexgard. 30 reports (29 Bravecto/ 1 Nexgard) were valued as serious and 7 (5 Bravecto / 2 Nexgard) were valued as non serious. Symptoms described were diarrhoea and vomiting, also listed in the description. Beside that, effects, not yet listed in the description, were mentioned like pruritus, dermatological and neurological symptoms, e.g. epileptical seizures with dogs who already suffered from it. The European Medicine Agency (Eudravigilance) has received similar reports.

In the German description of Nexgard you will find in the section **side effects**” the text: None Known. In the USA you will find, in the same section, the advice **“Use with caution in dogs with history of seizures”**

Conclusion

These new oral drugs provide advantages for the pet owner as there is no more interference with other external applicable drugs and any contact with drug is impossible. According to the long effective period the compliance of the pet owner will be reduced. While drugs which have been on the market for long years can be listed as save it is not possible to make any statement concerning the new drugs like Bravecto, Nexgard, Comfortis and Trifexis, as there is not enough data. German Reports, concerning the above listed drugs were talking about neurological symptoms and were confirmed by reports from other European and Non European countries.

Neurological symptoms are also reported when applying external drugs and can be explained by the pharmacological effect of ectoparasiticides. Nearly all drugs, with the exception of Lufenuron take influence on the neurotransmitter and therefore on the signal transmission of the neurons of the parasites. This can lead to reactions with sensitive animals. Further monitoring will show if the reports about the new drugs will be confirmed.

Therefore, for a comprehensive assessment reporting all adverse drug reactions – also of approved long-standing veterinary medicines and of already known and in the leaflet mentioned side effects- it is essential that all vets report extensively to the BVL.