Bravecto (fluralaner) chewable tablets have been thoroughly evaluated in multiple countries and are approved as a safe and effective flea, tick and mite treatment for dogs

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***Abstract* —** *Bravecto (fluralaner) is thoroughly tested to international safety standards for veterinary drugs, meeting approval requirements for over 70 countries. This valuable antiparasite (fleas, ticks and mites) treatment contributes to the health of millions of dogs and promotes dog health worldwide by protecting them against dangerous parasite infestations that are known to lead to pathogen transmission, blood loss, local irritation, and skin allergies. In 2017, the European Medicines Agency (EMA) completed an in depth targeted review of all reported adverse events (ADE) related to various potential disorders and confirmed the positive benefit-risk profile of Bravecto. Official records that monitor adverse events are often available online and these reports can be easily misunderstood by people unfamiliar with the procedures and how to interpret monitoring information. For example, many people do not know that the FDA advises "For any given ADE report, there is no certainty that the reported drug caused the adverse event." This means that the cause of a problem reported to this agency has not been determined, and this is typical of drug use reports. Multiple communications from individual dog and cat owners provided photographs showing how their pet has dramatically improved with the help of fluralaner treatment.*

***Keywords*— cat, dog, fluralaner, pharmacovigilance, safety.**

I. INTRODUCTION

Fluralaner is the active ingredient in the Bravecto Chew (MSD Animal Health, Giralda Farms, NJ, USA), a treatment that offers a highly effective way to control external arthropod parasites affecting dogs, including fleas, ticks and mites, for up to 12 weeks following a single dose. This treatment is approved in over 70 countries based on careful review of a comprehensive dossier consisting of multiple field and laboratory studies proving the safety and efficacy of fluralaner. In addition, there are more than fifty peer-reviewed publications available in the scientific literature that provide expert scientific evidence of the safety and efficacy of fluralaner [1-50].

All approved medicines go through an intensive ongoing safety monitoring service to evaluate any potential problems that may become apparent with experience but that did not show up even under intensive pre-approval testing. This monitoring evaluation is called pharmacovigilance and the process follows strict rules that allow experts in the area to detect evidence of any kind of "safety signal". This signal may indicate a previously unrecognized problem with a medicine and be a sign that users should be informed of additional information regarding the profile of the product.

Many regulatory authorities provide access to the public to the reported pharmacovigilance data on approved veterinary products, such as fluralaner. Unfortunately, this information is potentially misinterpreted by some readers, who are uninformed as to how these reports are prepared and assume that every report is an indication that the medicine caused the problem. The careful reader, on the other hand, quickly realizes that this is not the case. In addition to pharmacovigilance, medicines may also be evaluated in other safety studies performed after launch. For example, studies may be conducted because the active ingredient in a veterinary medicine is being reviewed for other uses in other animal species.

Fluralaner belongs to a class of flea and tick treatment drugs called the isoxazolines that distribute systemically in the dog after administration, so that the medicine spreads through the bloodstream to all areas of the skin. These medicines kill the flea or tick when it tries to bite and is then exposed to the active ingredient. Multiple studies on both fleas and ticks have now shown that this approach to controlling these parasites can prevent the damaging effects associated with these bites, including prevention of allergies to biting parasite saliva and reducing the risk of parasite borne disease transmission. The isoxazolines were superior to a topically administered treatment for killing ticks attached to dogs at the time of treatment [28].

II. MATERIALS AND METHODS

All peer reviewed scientific literature and on-line published scientific sources regarding the safety and efficacy of fluralaner were identified and reviewed [1-56]. There are over fifty relevant publications providing in depth review of the mechanism of action, the safety of treating dogs and cats and effectiveness against multiple parasitic infestations. These papers are indexed in multiple scientific databases and are often freely available online to all readers. In addition there are online reports available from government agencies that document the safety of fluralaner, including some unique studies not available for any other isoxazoline approved for treatment of dogs that were reviewed in preparation of this report [57].

III. RESULTS AND DISCUSSION

A unique and comprehensive body of scientific work supports the use of fluralaner against external parasites affecting dogs and cats. Careful and knowledgeable review of the scientific literature confirms the well-documented safety and efficacy profile of fluralaner for dog and cat treatment. Government agency intensive reviews of all adverse event reports from everywhere around the world find that the risk-benefit profile for use of this treatment is positive.

Recent investigations into the safety of fluralaner use in dogs present new evidence for the safety profile of fluralaner following administration [57]. Fluralaner was administered to dogs daily at up to 4 mg/kg for one year (52 weeks) without report of a serious adverse event. The same reference also reports no adverse events in dogs receiving very high fluralaner doses (up to 750 mg/kg) daily for 28 consecutive days [57].

Additional evidence and testimonials from pet owners, while anecdotal, further confirm the often dramatic effect that fluralaner treatment can produce in parasite-infested dogs (Figures 1-7). The illustrations below were provided by pet owners who documented the dramatic improvement seen in their formerly parasite-affected animals following fluralaner treatment. In at least one case, the owner was so desperate for an effective treatment and concerned about the discomfort their dog was in that they were considering euthanasia.

FIGURE 1. Head on and lateral view of a dog with a severe skin parasitic infestation just before treatment with Bravecto (fluralaner).

FIGURE 2. The same dog as in fig. 1 photographed 8 weeks later. (Photo credit Emma O'Brien, used with permission)

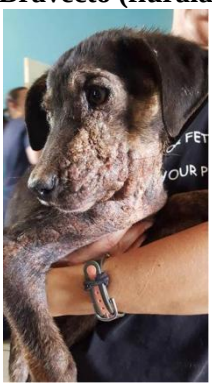

FIGURE 3. Another untreated dog with a severe skin parasitic disease

FIGURE 4. The same dog as in fig. 3 photographed 8 weeks after fluralaner treatment

FIGURE 5. A puppy presented with severe parasitic skin disease (on the left) and the same puppy 8 weeks later following treatment with fluralaner (on the right).

FIGURE 6. Heavy tick infestation in the ear of a dog before treatment with fluralaner.

FIGURE 7. The same dog as in Fig. 6 one week following fluralaner treatment

One frequent source of information regarding potential adverse events associated with treatments is the US FDA adverse drug event database. The US FDA provides clear statements for this database to help readers correctly interpret the report numbers, but these guidelines may be ignored or misunderstood by individuals who review information from the database and then present these numbers in their published work. It is helpful to review the recommendations the US FDA makes to help readers understand these reports and to consider their meaning:

- "For any given ADE report, there is no certainty that the reported drug caused the adverse event. The adverse event may have been related to an underlying disease, using other drugs at the same time, or other non-drug related causes. The clinical detail listing does not include information about underlying diseases, other drugs used at the same time, other non-drug related causes, or the final outcome of the reaction.
- The accuracy of information regarding the ADE is dependent on the quality of information received from the reporting veterinarian or animal owner.
- Accumulated ADE reports should not be used to calculate incidence rates or estimates of drug risk, because there is no accurate way to determine how many animals were given the drug, which is needed as the denominator in calculations of incidence and relative risk.
- It is inappropriate to make use of adverse event data to compare the safety of different products. For example, if a drug is widely used to treat certain conditions, there may be more ADEs for that drug than another product that is not used as often. This would not mean that the first drug was more unsafe than the second.

- The number of reports simply represents the number of ADEs received for a particular drug and should not be used for any type of comparison purposes.
- Underreporting occurs with most adverse event reporting systems. The frequency of reporting for a given drug product varies over time, and may be greater when the drug is newly marketed, or when media publicity occurs.
- Information on how the drugs were used (for indications on the product label or in an extra label manner) is not provided in the clinical detail listing."

These cautionary statements make it clear that the ADE database information needs to be interpreted by people who understand how summarized reports can be used to look for evidence of safety signals. These reports should not be presented as evidence of lack of drug safety and this would be an incorrect conclusion without more background details. Those who have the expertise to assess such reports – namely the global regulatory agencies – have concluded that the benefit-risk profile of Bravecto remains favorable.

IV. CONCLUSION

The scientific literature contains convincing data showing that Bravecto (fluralaner) offers a unique combination of long lasting efficacy and safety for dogs and cats and provides multiple benefits for pet owners of pets by helping them to prevent dangerous parasite skin infestations with fleas, ticks and mites.

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