

Probable health damage to dogs by intakeing the Bravecto™ Product

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Abstract— *The product based on fluralaner, brand name Bravecto was launched worldwide in 2014 in the form of a chewable tablet whose action on fleas and ticks lasts around three months. Presented by MSD ANIMAL HEALTH as an innovative product, highly safe, and can be ingested by dogs, including puppies, breeders, pregnant and lactating bitches and Collie dogs. In addition, it is indicated as part of the strategy to control allergic dermatitis and reduce the risk of transmitting fatal diseases transmitted by ticks. However, after its launch, numerous cases of development of pathologies and deaths of dogs of various races and ages, coinciding with the intake of the product began to be reported. Later on, the owners whose dogs had adverse effects on the product were organizing and forwarding reports to the manufacturer and entities responsible for product regulation and marketing and consumer support worldwide such as the CVM's Adverse Drug Event (ADE) EMA (European Medicines Agency), various sites on the pathologies developed in different breeds and the signs presented by the animals in the period of product administration. All this data which have become a database available for consultation.*

The European Medicines Agency (EMA) in July 2017 had requested the company to investigate all relevant reports related to various disorders such as neurological, skin and appendage diseases, hypersensitivity or immune-mediated reactions and liver diseases, some of which were fatal. The present review aims to summarize the information and provide a scenario in which, despite the efficacy of the product in the control of ectoparasites, has coincided in the period after its application, with the incidence of several pathologies and even deaths of the canine species

Keywords— *Animal safe, pathologies, drugs, civilservice, data base.*

I. INTRODUCTION

Fluralaner is a novel, recently developed systemically distributed molecule of the isoxazoline class with a highly selective ectoparasitocidal activity achieved through blocking arthropod γ -aminobenzoic acid (GABA) and glutamate-ligand gated chloride channels (1,2).The mode of *action* of fluralaner is the antagonism of the ligand-gated chloride channels (gamma-aminobutyric acid (GABA)-receptor and glutamate-receptor).

American regulators, the US Food and Drug Administration (EMA), Canadian, VDD (Veterinary Drugs Directorate) and Brazilian, MAPA (Ministry of Agriculture, Livestock and Food Supply) have approved the registration of Bravecto™ chewable tablets, from 2014.

MSD Animal Health presented the active ingredient of Bravecto™, fluralaner, as a novel, long-acting systemic insecticide and acaricide belonging to the isoxazoline class of parasiticides marketed in the form of a chewable tablet whose action on fleas and ticks lasts around three months.

Cited as an innovative, highly safe product, it could be ingested by dogs, including puppies, breeders, pregnant and lactating bitches and Collie dogs. In addition, it is indicated as part of the strategy to control allergic dermatitis and reduce the risk of transmitting fatal diseases transmitted by ticks.

After its launch, cases of development of pathologies and deaths of dogs of various races and ages coinciding with the intake of the product began to be reported.

The owners of dogs were organizing and forwarding the reports to the manufacturer or distributor and entities performed in the Civil Service People Survey worldwide, such as the CVM's Adverse Drug Event (ADE), EMA (European Medicines Agency), VMD: Civil Service People Survey, UK Gov and MAPA, Brazil, behong others.

The scientific literature concerned to the compound Fluralaner, the novel isoxazolineparasiticide, reports the effective results of the product in the treatment of dogs in the control of two pests, namely fleas and ticks (3,4,5,6).

All of them agree about the fact that Bravecto is a novel systemic insecticide and acaricide that provides long acting efficacy in dogs after a single oral treatment.

However, research becomes scarce when searching for scientific articles on the mechanisms of action of fluralaner on the non-target species as canine and consequent side effects from its application.

The present study sought, through a search for papers, reports based on the data on the harmful effects of the Bravecto product, based on the fluralaner compound, on animal health, to demonstrate that research is insufficient for the even if it remains in the market, due to the injuries suffered by the animals and their owners.

II. METHODOLOGY

We searched for scientific papers indexed in different databases, databases containing reports of possible side effects of the product in Brazil, the United States and Europe as well as on sites in the same countries.

III. RESULTS AND DISCUSSION

In the article about the Bravecto Technical Dossier (Wengenmayer et al., 2014), we found some of the publications used for product registration, available at: [http://www.parasitesandvectors.com/series/bravecto\(7\)](http://www.parasitesandvectors.com/series/bravecto(7)). published, whose citations and additional information regarding them are presented in Table 1 below.

TABLE 1
PAPERS ABOUT ASPECTS OF SEGURANCE AND EFFICACY OF BRAVECTO™

Paper citation	Interest conflites	Number of health dogs receiving Fluraner
Meadows et al.: A randomized, blinded, controlled USA field study to assess the use of fluralaner tablets in controlling canine flea infestations. Parasites & Vectors 2014 7:375.	Drs. Meadows, Guerino, e Sun are hired by pela Merck Animal Health.	118
Walther et al.: Safety of the concurrent treatment of dogs with Bravecto™ (fluralaner) and Scalibor™ protectorband (deltamethrin). Parasites & Vectors 2014 7:105.	FMW, PF, MJA, RKAR e MCN are hired by Merck/MSD Animal Health.	24
Kilp et al.: Pharmacokinetics of fluralaner in dogs following a single oral or intravenous administration. Parasites & Vectors 2014 7:85.	All the authors except DR, are hired by Merck / MSD Animal Health.	24
Rohdich et al.: A randomized, blinded, controlled and multi-centered field study comparing the efficacy and safety of Bravecto™ (fluralaner) against Frontline™ (fipronil) in flea- and tick-infested dogs. Parasites & Vectors 2014 7:83.	All the authors except DR, are hired by MSD Animal Health.	108
Walther et al.: Safety of fluralaner, a novel systemic antiparasitic drug, in MDR1(-/-) Collies after oral administration. Parasites & Vectors 2014 7:86.	FMW, MJA, RKAR e MCN are hired by Merck / MSD Animal Health. AJP is hired by IllinoisUniversity.	8
Walther et al.: The effect of food on the pharmacokinetics of oral fluralaner in dogs. Parasites & Vectors 2014 7:84.	FMW, MJA, RKAR e MCN are hired by Merck / MSD Animal Health.	12
Taenzler et al.: Onset of activity of fluralaner (BRAVECTO™) against Ctenocephalidesfelis on dogs. Parasites & Vectors 2014 7:567.	JF is haired by ClinVet and all the others authors are MSD Animal Health..	44
Walther et al.: Safety of concurrent treatment of dogs with fluralaner (Bravecto™) and milbemycin oxime - praziquantel. Parasites & Vectors 2014 7:481.	FMW, PF, MJA, RKAR e MCN are hired by Merck/MSD Animal Health.	20

As common points among the publications it is quoted that all of them are published in an the open access publication, all in the year of 2014.. Another point to be considered is that in all studies healthy dogs were used as quoted in the Technical Dossier, aiming the registration of the product. Being a free-marketing product offered by pet shop attendants, in the case of Brazil, it would be impossible to know if the dog that will receive the product is healthy or if it presents a genetic predisposition or of another nature that would restrict the use of the same one .

Regarding the form of commercialization, in Europe and the United States, the law restricts this drug to use by or on the order of a licensed veterinarian (8,9).

In Brazil, there is a free commercialization of the product, without the order of a veterinarian licensed, including by e-commerce although there are many cases of administration of the product under the guidance of veterinarians who seem to ignore or ignore the harmful effects of the drug.

On the website <http://www.seubuldoguefrances.com.br/2016/03/a-polemica-do-bravecto.html> founded by CamilliChamone (10), geneticist and molecular biologist, on 08/14/2008 that became the first and largest blog in Latin America on French bulldogs, a post was published in March 2016 whose comments on the product insert highlighting the fact that:

In the leaflet of the medication, the first sentence of Indications is already quite elucidative: For the treatment of infestations by ticks and fleas ..." That is, there is no indication of use of this product for prevention.

This is still reiterated and very well explained when the manufacturer himself says: "Fleas and ticks should be attached to the dog and already started feeding [dog's blood] to be exposed to the active principle."

"I may be mistaken, but logic tells me that if fleas and ticks are not prevented from stinging an animal, the risks of transmission or manifestation of disease (DAPP, erlichiosis, babesiosis) are not eliminated."

The author completes her comments regarding the systemic action of the product with little known effects on the animal organism.

Demonstrating a return to claims from organized civil society, the European Medicines Agency (EMA) after 11 February 2014; it has granted a marketing authorization valid throughout the European Union for the veterinary medicinal product Bravecto. The full EPAR for Bravecto can be found on the Agency's website at: ema.europa.eu/Find medicine / Veterinary medicines / European public assessment reports. Last updated in March 2016, it presented in July 2017 some questions and new requirements regarding the maintenance of the product in the market.

The European Medicines Agency (EMA) concluded in July 2017 that" Bravecto, a medicine that treats tick and flea infestations in dogs and cats, continues to have an acceptable safety profile. However, the company that markets the product will have to update the package leaflet and include convulsions as a new side effect that is reported very rarely, i.e., less than one animal out of 10,000 animals treated. Veterinarians and pet owners will also be advised to use Bravecto with caution in dogs with epilepsy.

EMA's Committee for Medicinal Products for Veterinary Use (CVMP), following a regular but inconclusive analysis of limited data on serious side effects, had requested the company to investigate all relevant reports related to various disorders such as neurological, skin and appendage diseases, hypersensitivity or immune-mediated reactions and liver diseases, some of which were fatal. The investigation had to take into account the age and breed of animals, the number of treatments, underlying disease conditions and concomitant treatments.

The company that markets the medicine is expected to implement the changes to the package leaflet within six months of the CVMP conclusion.

According to the company, about 41.6 million doses had been distributed worldwide, of which approximately 18 million were in the European Union (EU) between February 2014 and December 2016. By 15 August 2017, suspected side effects had been reported electronically for 5,326 dogs, of which 2,144 were in the EU. Between February 2014 and 15 August 2017, deaths had been reported in 1,265 dogs worldwide and 342 in the EU. Each report relates to dogs under different health conditions, often receiving multiple medicines, therefore these figures may or may not be related to the use of Bravecto in dogs"(11).

Another survey conducted by the European Medicines Agency (EMA) reports all races that suffered side effects coincident with the post-administration period and were reported to MSD and MERK. About 89 breeds were reported involving about 870 dogs. It was observed that many cases reported were of crossed and unlisted races (12).

Numerous petitions are under way and some have already been forwarded. The recent petition with 40,000 signatures from the Netherlands: the anti bravecto petition with 40,000 signers has been delivered at the Ministry of Agriculture, Nature and Food quality), released by social media around the world.

IV. CONCLUSIONS

Bravecto™ product, an insecticide acaricide, based on the fluralaner compound, has its administration coincided to the occurrence of serious pathologies leading to death of dogs in all the countries in which it is in commercialization.

Strong evidences that the product not only targets flea and tick, but compromises the health of the non target species like dogs, its recommendation as oral treatment in the form of chewable tablets, should be carefully reviewed.

CONFLICT OF INTEREST

The author has no interest involved besides contributing to the safety of animals, in the present case dogs.

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To Nix, wishing his sacrifice was not in vain.

REFERENCES

- [1] OZOE Y, ASAHi M, OZOe F, NAKAHIRA K, MITA T. The antiparasitic isoxazoline A1443 is a potent blocker of insect ligand-gated chloride channels. *BiochemBiophys Res Commun*. 2010;391:744–749. doi: 10.1016/j.bbrc.2009.11.131.
- [2] KILP S, RAMIREZ D, Allan MJ, Roepke RK, Nuernberger MC. Pharmacokinetics of fluralaner in dogs following a single oral or intravenous administration. *Parasite & Vectors*. 2014;7:85.
- [3] MEADOWS et al.: A randomized, blinded, controlled USA field study to assess the use of fluralaner tablets in controlling canine flea infestations. *Parasites & Vectors* 2014 7:375.
- [4] WALTHER et al.: Safety of the concurrent treatment of dogs with Bravecto™ (fluralaner) and Scalibor™ protectorband (deltamethrin). *Parasites & Vectors* 2014 7:105.
- [5] GASSEL, M1; WOLF .C1; Noack, S; WILLIAMS, H; ILG,T. The novel isoxazoline ectoparasiticide fluralaner: Selective inhibition of arthropod g-aminobutyric acid- and L-glutamate-gated chloride channels and insecticidal/acaricidal activity. *Insect Biochemistry and Molecular Biology* 45 (2014) p.111-124
- [6] ROHDICH, N; ROEPKE; R.K.A.; ZSCHIESCHE E. A randomized, blinded, controlled and multi-centered field study comparing the efficacy and safety of Bravecto™ (fluralaner) against Frontline™ (fipronil) in flea- and tick-infested dogs. *Parasit & Vectors*. 2014;7:83.
- [7] WENGENMAYER et al. Dossiê Técnico Bravecto. (licenciado por BioMed Central Ltd. Este é um artigo de acesso livre distribuído sob os termos da Licença Atribuída a Creative Commons (<http://creativecommons.org/licenses/by/4.0>) 2014. Disponível em: https://www.bravecto.com.br/sou_vet/DOSSIE_TECNICO_BRAVECTO. Acesso em 06/12/2017.
- [8] Flavoured chews for dogs. Caution: FEDERAL (USA)- Bravecto. Disponível em: https://us.bravecto.com/pdfs/bravecto_pi_mah.pdf. Acesso em 07/12/2017.
- [9] Bravecto, INN- Fluralaner- Europa EU Disponível em: https://ec.europa.eu/health/documents/community-register/.../anx_127740_pt.pdf. Acesso em 07/12/2017.
- [10] Camilli Chamone. Disponível em: <http://www.sebuldoguefrances.com.br/2016/03/a-polemica-do-bravecto.html>. Acesso em 07/12/2017.
- [11] EUROPEAN MEDICINE AGENCY. Tick and flea control agent Bravecto continues to be acceptably safe to use. **New adverse reaction to be included in** package leaflet. Disponível em: <http://www.ema.europa.eu/ema/acesso> em 07/12/2017.
- [12] FDA-CVM FOIA. Response 2016-96 January 2016A. Disponível em : yourpetsneedthis.com/.../Bravecto-fluralaner-ADE-report-Jul201. Acesso em 11/12/2017.