EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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8 November 2019
Veterinary Medicines Division

Subject: Responses to Questions raised at the Bravecto petition hand over

Dear Mr van de Sande,

We would like to confirm that further to the meeting at EMA on 4 October 2019, your petition regarding the safety of Bravecto was presented to the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) at its meeting on 8-10 October 2019. The CVMP considered the petition along with the video and the list of questions you provided to us. At the meeting, the CVMP acknowledged your concerns and your feedback.

In response, the CVMP emphasised the fact that information on the observed side effects of Bravecto that are reported after use has been included in updates of the product information since 2017. CVMP also stressed the importance of animal owners in reading the package leaflet and in veterinarians consulting the product's Summary of Product Characteristics (SPC), in order to make an informed decision when prescribing and using Bravecto.

Within its remit, EMA is open to collaborate with stakeholders to raise awareness among veterinarians and animal owners of the potential risks, and the importance of reporting side effects.

Please find attached the CVMP responses as they have been endorsed in the November 2019 meeting. We hope that it adequately addresses your concerns. Please do not hesitate to contact us if you have any further questions.

Yours sincerely,

Dr Ivo Claassen
Head of Veterinary Medicines Division
(authorised signatory)

This letter has been produced electronically and consequently does not bear the signature of the authorised signatory.

cc: All Member States
Committee for Medicinal Products for Veterinary Use

8 November 2019
EMA/553154/2019
Committee for Medicinal Products for Veterinary Use

Responses to the questions raised at the Bravecto petition handover

We would like to begin with some general information, relevant for several of your questions, on the work carried out by the Agency when assessing new veterinary medicines.

The EU has in place one of the most stringent veterinary medicines regulatory systems globally. Well established requirements ensure that the necessary tests to demonstrate the quality, safety and effectiveness of veterinary medicines are performed prior to their authorisation and that these tests conform to a high standard. The data submitted for Bravecto were evaluated according to CVMP's assessment procedures and the committee concluded that the overall benefits for the medicine outweigh the risks and therefore recommended the granting of a marketing authorisation. The requirements include studies on potential toxicity, and for Bravecto these were performed in compliance with relevant safety guidelines and Good Laboratory Practice (GLP) regulations.

In your questions you make reference to hazard classifications for chemical substances as listed in PubChem. It is important to consider that not every hazard, or source of potential harm, results in actual damage or adverse effects. In assessing risk the *likelihood* of an identified harm happening also has to be taken into account.

Risk analysis is an important part of what the Agency's scientific committees do. It is the process where one (a) identifies hazards that have the potential to cause harm (hazard identification), then (b) evaluates the risk associated with that hazard, (c) determines appropriate ways to eliminate the hazard, or control the risk when the hazard cannot be eliminated (risk control) and (d) communicates the risk to those who may be affected.

When assessing new veterinary medicines, CVMP carries out a full benefit-risk assessment. Over and above the hazard identification (which is the basis for the Pub Chem hazard classifications), a multitude of additional studies and clinical trials are required to demonstrate the quality, safety and effectiveness of a new medicine. Any identified risks of the medicine to the treated animal, users of the product, consumers of animal produce and the environment will be weighed against the expected benefits of the product to the target animal.

However, some effects that occur in the field are too rare to be identified in experimental studies or clinical trials and may only become noticeable when a medicine is used in much greater numbers of patients or animals following its authorisation. This is why a very robust pharmacovigilance system has been established to monitor the safety of a product following its introduction to the market place. As discussed at our meeting, side effects that are not observed in studies conducted before authorisation of a product will be captured and reported as a result of this monitoring. In the event that a new risk or new side effect is identified, appropriate actions will be taken, including the possibility to inform prescribers and users of the medicines of that risk/side effect through updates of the product information.

During the meeting on 4 October, we acknowledged that it is important that new information and updated product information reaches all prescribers and users of medicines in a timely manner.

In the following pages please find additional details addressing your questions:

1. **"On the website Pubchem (US Department of Health) "fluralaner" is classified as: "suspected of damaging fertility or the unborn child" (warning reproductive toxicity, code H361), "very toxic to aquatic life" (warning hazardous to the aquatic environment, acute hazard, code H400), and "very toxic to aquatic life with long lasting effects"(code H410). For this reason "fluralaner" should never have been allowed on the market as a "medication" for animals. And now that this is a know fact, we think that this drug should be withdrawn from the market immediately. What is your response to this?"**

Reproductive toxicity is assessed by CVMP when evaluating new medicines. Studies to investigate reproductive toxicity of fluralaner were performed in rats. As described in the European Public Assessment Report (EPAR) for Bravecto, reproductive effects were not seen in the studies provided, including a study in pregnant dogs when the product was administered at twice the recommended dose.

Specific studies investigating the safety of Bravecto in dogs and cats and the safety for people applying the medicine were carried out to ensure that when used as intended the benefits of the medicine still outweigh its risks.

Many substances used in veterinary anti-parasitic medicines are very toxic to aquatic life due to the way they work, but do not affect the treated animals to the same degree. Regarding toxicity of Bravecto to aquatic life, I can confirm that a relevant environmental impact assessment was performed. It is concluded that the potential environmental exposure to the medicine is considered very low when the product is used in accordance with the authorised conditions of use.

As a group, these medicines are considered essential for the benefit they provide of parasite control in most companion and production animals, and they have been safely used for many years.

2. **"What is your opinion as CVMP / EMA about the fact that vets are world wide structurally denying the possibility of side effects from Bravecto, referring to the "proven safety" as determined by EMA? And are the CVMP and EMA aware of the fact that - partly due to this attitude of veterinarians, only about 1 % of the side effects and deaths with animal medication is actually reported? Many vets don't even inform their customers about the possibility of reporting. Do you acknowledge that this is blocking a correct, transparent and complete registration of side effects and deaths?"**

EMA and CVMP fully agree that to enable effective safety surveillance it is important that animal owners, veterinarians and others who observe a side effect, report all details to the regulatory authority in a Member State or to the marketing authorisation holder, which is obliged under EU legislation to forward this information to the relevant regulatory authority. All reports received are evaluated as part of the continuous assessment of authorised medicines to ensure that the benefits of the medicines continue to outweigh the risks, with the addition of new safety warnings and side effects to the product information if needed.

Underreporting is indeed one of the known reporting biases. A publication in the Veterinary Record by the Federation of European Veterinarians[1] from 2017 outlines some of the reasons for underreporting. The paper concluded that in order to increase reporting the process needs to be made easier (such as by developing mobile apps, or incorporating reporting via the practice management system software) and that veterinarians' awareness of the value of reporting needs to be increased. Member States are making

[1] Veterinary pharmacovigilance in Europe: a survey of veterinary practitioners, http://vetrecordopen.bmj.com/content/4/1/e000224

continued efforts to improve reporting. Experts evaluating the incidence of side effects take account of known underreporting when deciding on actions.

For the future, and as part of the implementation of the new veterinary regulation in January 2022, a key priority will be to improve reporting by veterinarians and the public. We will continue to work on improving communication of information on important changes in product literature so that veterinarians and animal owners are kept fully informed.

To enable the continuous monitoring of authorised veterinary medicinal products, it is important that veterinarians report suspected adverse events (side-effects) to medicines. Considering your negative experience in this respect, the EMA will bring your concern to the attention of the Federation of Veterinarians of Europe (FVE).

3. "The EMA indicates that it is in favor of "transparancy". Many vets are not at all aware of the figures of reported serious side effects and deceased animals with animal medications. Don't you think it should be the task of the EMA to officially publish a list of medication side effects every year, open to both veterinarians and their customers, the animal owners?"

The EU's surveillance system assesses suspected adverse event reports and takes actions, as necessary, to protect animals such as updating the information on possible side effects in the package leaflet. Whenever package leaflets are updated this information is published on EMA's website. The updated leaflets are also available to veterinarians and animal owners. For example, for Bravecto, the product information was updated in 2017 to include convulsions as a new side effect that is reported very rarely, i.e., less than one animal out of 10,000 animals treated. The update at the time also included advice to veterinarians and pet owners to use Bravecto with caution in dogs with epilepsy.

EMA releases an annual pharmacovigilance bulletin[2] which highlights all agreed actions for EU centrally authorised products, i.e. products authorised after evaluation by the EMA's CVMP. This publication includes information that has not yet led to action being taken, however, it is released to alert veterinarians and to encourage reporting.

Under the new regulation, EMA will have a legal obligation to provide access to the public to data collected in the central EU database called EudraVigilance. A project is ongoing to provide direct access to the data through a dedicated portal (similar to the portal already available for the reports on human medicines (http://www.adrreports.eu/en/index.html)) in advance of the new regulation becoming applicable.

4. "In the case of approval (authorization) of a medicine / product, the EMA conclusion is based on the research results supplied by the manufacturer. What guarantees does EMA have that the research results have not been "adjusted" to the advantage of the manufacturer, since there is hardly any control during their own research procedure?"

The procedures and testing requirements for new veterinary medicines are set out in detailed guidelines. There are checks and balances in place that guarantee collection of appropriate scientific data to regional or internationally agreed standards.

The marketing authorisation application dossier includes access to raw data and trial protocols. The EU has a system of inspections of applicants for marketing authorisations, marketing authorisation holders and manufactures in place that allows direct checking of relevant information including of studies. Any potential fraud is treated very seriously. Pharmaceutical companies are well aware of the reputational damage that this may cause and so have their own quality control systems in place to prevent fraudulent data.

This is the way medicines regulation is established worldwide in the different regions.

[2] https://www.ema.europa.eu/en/documents/newsletter/public-bulletin-veterinary-pharmacovigilance-2018_en.pdf

5. **"While so many complaints about Bravecto were reported, EMA gave market authorisation for "Bravecto plus", and for the drug Exzolt (against blood lice in chickens) for the European market. A "medication" containing the same toxic substance (Fluralaner) as in Bravecto. Exzolt is used in chickens that lay our eggs for consumption. And that while there were already so many signals that Fluralaner can cause serious health problems! Why didn't EMA apply the precautionary principle here?"**

The EU's procedures for approving medicines for use in food-producing animals includes the setting of maximum residues levels (MRLs) for residues of the active substance that may be present in food of animal origin. MRLs are set so that any residues remaining in food below these levels are without effect on the consumer.

CVMP has set MRLs for fluralaner in chicken tissues and eggs. Based on these levels and information provided for Exzolt, withdrawal periods (the time between last use of the medicine and first possible slaughter time point or time point for egg collection) have been established for the product ensuring that residues will be well below these limits. CVMP concluded that the overall benefits to chickens from the use of Exzolt use outweigh the risks, and recommended that a marketing authorisation be granted.

6. **"Do CVMP and EMA understand that there is more and more mistrust towards the organization, when animal owners see that their complaints are not being taken seriously, and very few side effects (and death risk) are actually added to the package leaflet as a warning?"**

We take stakeholders' feedback and concerns very seriously. For side effects to be included in the package leaflet, data must first be assessed to determine the potential causal effect of the treatment considering other concomitant treatments, disease or circumstances which may also lead to the events seen. For rare events or events linked to the continued or repeated use of a medicine, it is often difficult to establish potential causality since there are no controlled reference data with which to compare. For medicines used extensively with high sales across a species population, it needs to be considered whether rare observations are linked to the occurrence of an event in a normal population (without treatment) or whether this is an event linked to the use of a medicine.

Even if a side effect is seen shortly after a specific medicine was given, it does not always mean that the reaction was caused by the medicine. Pet owners should discuss any treatment and effects they see with their veterinarian who has the full clinical history of the animal, the knowledge to investigate potential causes of any effects seen, and is best placed to discuss both the benefits and the risks in each particular case with the pet owner.

As stated before, we will seek to improve the communication of information on relevant changes to product information to prescribers and end users.

7. **"Contradiction in regulations for puppies and kittens: On the USA medication leaflet (and on the website of the manufacturer) we found the following text: "BRAVECTO has not been shown to be effective for 12-weeks' duration in puppies or kittens less than 6 months of age." How can CVMP / EMA defend that the European medication leaflet indicates: "Because there is no information available, the veterinary medicinal product should not be used in puppies under 8 weeks of age and / or dogs under 2 kg in weight." / "As no information is available, this veterinary medicinal product should not be used in kittens under 11 weeks of age and / or cats under 1.2 kg in weight." Conclusion: It does not make sense to expose such young puppies / kittens to the poisonous drug fluralaner when the USA medication leaflet indicates that *the product has not shown to be effective* at this young age. In our opinion (and for the sake of credibility of the CVMP) the**

medication leaflet should be adapted to the american version, so that puppies and kittens are no longer burdened with the poisonous drug".

Two studies investigating the effectiveness of Bravecto in the field (under conditions of normal use) were submitted to the EMA , one European study and one from the US; in addition one field palatability study was available. In these studies the age range of Bravecto-treated dogs was 0.2 to 15.0 years and weights ranged from 2 to 69 kg. CVMP concluded that fluralaner was well tolerated and that the effectiveness in the treated range of dogs in terms of age and weight was proven. The statements on the European package leaflets mentioned by you indicate the age and weight groups for which no data were available.

The FDA is a separate regulatory authority and will have received data matching its legal requirements on which its own decisions will have been based.

8. **Quote (medication leaflet Bravecto): "Parasites must have begun feeding on the host to be exposed to fluralaner; therefore, the risk of transmission of parasite-related diseases cannot be excluded."**
   Quote website Pubchem: Source:
   https://pubchem.ncbi.nlm.nih.gov/compound/Fluralaner * H361: Suspected of damaging fertility or the unborn child
   [Warning Reproductive toxicity].
   *** H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard].**
   *** H410: Very toxic to aquatic life with long lasting effects.**
   So we have a product that is poisonous to the environment with long lasting effect, may cause epileptic seizures, may harm the unborn child, and doesn't actually prevent against tick born diseases, as it was supposed to do…. So why was this product allowed on the European market in the first place?!

Please refer to the introduction to our responses and the specific response to question 1, explaining the studies assessed by the CVMP in relation to reproductive toxicity.

The package leaflet contains the statement on the risk of transmission of parasite-related diseases because prevention of transmission of parasite-related diseases was not specifically studied, as this is not the indication for using Bravecto. Bravecto kills ticks within 12 hours. In principle, disease transmission can occur at any time once ticks have begun feeding, but the likelihood of diseases transmission increases the longer a tick remains attached. For example, in order to transmit Lyme disease the American tick species *Ixodes scapularis* needs to be attached 36 to 48 hours. The individual dog or cat will nevertheless benefit from freedom from ticks and fleas, including clinical cure from flea allergy dermatitis.

"Claims on the EMA (Angelika Angie Schön)

BVL (= Bundesamt für Verbraucherschutz und Lebensmittelsicherheit = German Federal Office for Consumer Protection and Food Safety

UAW = Unerwünschte Arzneimittel Wirkung (ADE, adverse drug event / ADR, adverse drug reaction)

1) **"Producers and veterinarians should be prohibited from claiming that BRAVECTO is "safe"."**
2) **"Veterinarians must be required to provide package leaflets and fully and truthfully inform of possible adverse reactions."**
3) **"No veterinarian may claim that he does not know of any UAW´s. Both the BVL (Germany) and the FDA (USA) have issued warnings in this regard. Every veterinarian has the possibility to request the reports of the EMA."**

In response to the above three questions, we note that Bravecto should be used in accordance with the authorised conditions outlined in the package leaflet, which legally should be available to the end user. The package leaflet includes all relevant information, including possible side effects. Veterinarians are best placed to advise and decide on the best available treatment for a particular dog or cat.

As mentioned above, EMA will work with the Federation of Veterinarians of Europe (FVE) to ensure that veterinarians are effectively informed of changes in the product information for products like Bravecto.

4) **"The notification and registration of UAW´s should be regulated in Europe by a uniform procedure."**

The requirements for marketing authorisation holders and the regulatory authorities in the EU for notification and recording of adverse events related to veterinary medicines use are organised through a uniform procedure. The procedure allows for initial reports to be sent through different possible routes, to increase likelihood of reporting. Most Member States have on-line reporting forms available in the local language. In some Member States there are steps towards adding a module to veterinary practice management software to help electronic reporting by veterinarians directly from a patient's file, since one of the reasons for underreporting is the time taken by veterinarians to report.

5) **"In particular, the BVL cannot reject symptoms that have occurred as a side effect as UAW if a drug has been administered several times."**

EU regulatory authorities follow the agreed uniform procedure in the EU and will record and send all reports that they receive, including all reported potential adverse reactions, to the central EU database for further analysis.

6) **"It is not justified for veterinarians to deny the suspicion of a UAW and for owners of damaged animals to be laughed at and made insecure."**

Veterinarians are best placed to provide advice and make the decision for a particular treatment for a given animal and should follow their local code of conduct which is regulated at Member State level.

Veterinarians in general take their obligation to provide best possible advice to animal owners very seriously. In cases where side effects are reported, it falls to the veterinarian to consider and investigate all possible causes for an animal's clinical signs.

In each Member State there are statutory bodies for the veterinary profession to which animal owners can turn, should they feel that they did not receive proper treatment from the veterinarian.

7) **"Veterinarians should be obligated to report each suspicion on UAW´s."**

Requirements for the reporting of adverse events (side-effects) by veterinarians are regulated at individual Member State level and in some countries reporting is mandatory. However, recent published research[3] has indicated that such legal requirements do not necessarily make a significant difference in the relative reporting rates.

8) **"Bravecto should not be prescribed for animals with chronic diseases such as neurological problems such as epilepsy or a known MDR-1 defect."**

EMA takes the safety of medicines very seriously. Like all medicines, the safety of Bravecto is tightly and continuously monitored by the Agency to ensure that it can be safely used in dogs and cats.

In 2017, following a review of serious adverse events, including deaths, associated with Bravecto chewable tablets, EMA requested Intervet International B.V. to update the product information to include a new

[3] Veterinary pharmacovigilance in Europe: a survey of veterinary practitioners, http://vetrecordopen.bmj.com/content/4/1/e000224

adverse reaction and information on its occurrence: "convulsions have been reported very rarely in spontaneous (pharmacovigilance) reports" and a new special precaution for use in animals: "use with caution in dogs with pre-existing epilepsy". This change was implemented before the end of 2017.

With the initial application for marketing authorisation for Bravecto tablets, studies with MDR1-deficient Collies were submitted. These studies used a dose that was 3 times the recommended dose and showed that the product can be safely used in dogs with a MDR1 defect.

In addition, following review of periodic safety update reports (PSURs) and/or serious adverse events, updates to the product information for Bravecto spot-on were recommended in March 2018 (on special precautions to be taken by the person administering the veterinary medicine to animals), for Bravecto tablets in October 2018 (hypersensitivity reactions in humans) and for Bravecto tablets in September 2019 (adding information on the potential adverse reactions 'muscle tremors' and 'ataxia').

9) "In the future no nerve poisons should be certified as medicament for animals, for which no antidote is available".

The management of animal health, in particular for parasite control relies heavily on active substances that act directly on the parasite's nervous system. Such medicines are stringently tested before authorisation to ensure their quality, safety and effectiveness. There are years of experience with antiparasitic products, and the medicines, when used within the limits of the authorised conditions, are considered safe and effective. In case of overdose, there are supportive treatments available and veterinarians should always be consulted.