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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fipronil Pet Products - Review of Domestic Animal Safety Studies with Spot-on Formulation and Use Information with Spray Formulation

DP Barcode: D221800; D222392
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Action Requested: Review domestic animal safety studies with spot formulation and use information with spray formulation

Recommendation: Toxicology Branch II concludes that the toxicology data base is complete for the spray (0.25%) and spot-on (9.7%) fipronil formulations. See CONCLUSIONS ABOUT ADEQUACY OF DOMESTIC ANIMAL SAFETY STUDIES for a detailed discussion of the data base. See LABEL RECOMMENDATIONS for a recommendations for revisions to the product labels.

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DATA REVIEW

1. Summary of Preliminary Analysis of Adverse Event Incidences During the Frontline® Spray Treatment Clinical Trials

This preliminary report compiles all the adverse event data from the current clinical trials with the Frontline® Spray Treatment treated groups. Veterinarians have been conducting the study and monitoring safety in the animals. Thus far, 96 dogs (45.8% male and 54.2% female) ranging in age from 0.4 years to 15.5 years have been treated once per month for six visits. Seventeen (17) cats (58.8% male and 41.2% female) ranging in age from 0.4 years to 13.0 years have been treated. The dosage rate per application has been 3-6 ml/kg.

Veterinarians were asked to determine if there was a causal relationship between the product and adverse reactions. In the dog, only two events were attributed to the product. In one case, a dog developed a corneal ulceration after the product was accidently sprayed into the animal's face. The ulcer resolved within 7 days with treatment. (The label states "Do not get this product into your pet's eyes or mouth.") In the second case, a dog vomited twice, one time after each transportation home after the initial and one month visit. Four events (lethargy, nausea, pruritus and vomiting) were classified as having an "uncertain association" to the product. No adverse effects have been reported in cats.

2. Summary of Annual Report on Frontline Pharmacovigilance and Toxicovigilance Case Reports

Rhone Merieux estimates that approximately 3 million animals in France were treated with the spray formulation from June 1, 1994 to June 30, 1995. The Centre National d'Informations Toxicologiques Veterinaires, an independent agency, collected calls on cases of adverse effects and prepared this report for the registrant. Only those cases involving a report of an adverse effect will be discussed.

Calls were defined as follows:

emergency - the animal is showing signs after Frontline® application and caller is looking for information regarding treatment

advice - after the case outcome, caller is looking for information to relate the case to the use of Frontline®

A causality assessment was also made on each case using the following categories:

A = probable (chronology and clinical signs observed are compatible with known pharmacological and toxicological features of Frontline)

B = possible (Frontline® is a potential cause, but there is not enough information to classify the case as A)

O = unclassified (reliable data not available or insufficient); generally, the relationship appears poorly compatible

N = unlikely (there is enough information to rule out Frontline®, with "reasonable doubt"

There were 76 emergency and 15 advice calls during this 13 month time period. Sixty-one (61) cases dealt with dogs and cats in which there was an assessment made to determine a causality relationship. The cases were categorized as follows:

Assessment	Number of Dogs	Number of Cats
Probably Associated	0	0
Possibly Associated	6	7
Unlikely Associated	16	9
Unclassified	12	21

The incidence of adverse effects in the 13 dogs and cats with possibly associated adverse effects is 0.00004% of the approximately 3 million animals treated.

Of the six dogs which had adverse effects which were possibly associated with treatment, three dogs presented with ataxia or posterior paresis. The time to onset of signs was 45 minutes to less than 12 hours; the duration was between 1 and 2 hours. Two animals recovered spontaneously; one recovered within 1 hour of treatment with steroids and diuretics. A fourth dog became hyperactive four hours after treatment with Frontline®. The behavior subsided within 6 hours after treatment with a cold bath. Two additional dogs developed "hair modifications" after treatment.

There were 4 deaths with dogs. One case categorized as unclassified was in a poodle which died after an episode of convulsions and aspiration pneumonia. The report states that the dog had been treated for 15 days. It is unclear from the report if the dog was treated with Frontline for 15 days or was treated for the convulsions and pneumonia for 15 days. It is likely the latter since the case was not classified as probably or possibly associated with the product. Three additional cases were classified as unlikely. In one case, a dog was thought to be poisoned by a criminal bait; in the second, the dog died after anesthesia; and in the last, a dog died in convulsive seizures after treatment with another veterinary product.

Of the seven cats classified as possibly associated, the most

prominent clinical signs were central nervous system depression in 5 cases (with or without other neurologic/digestive problems). Behavior disorders and digestive disorders were mentioned in one case each. Ataxia, sedation, weakness and tremors were the most common neurological signs mentioned, however one cat was reported to be hyperactive after being sprayed with Frontline®.

Ten cats died during this time period. Two cases categorized as unclassified involved 2 kittens which developed an acute episode thought to be organophosphate poisoning and a Siamese cat euthanized after 4 days of "clinical troubles" which developed 12 hours after Frontline® application. Four cases were classified as unlikely. In the first, four 15-day old kittens died in 24 hours with coma, keratitis, ascites and hepatitis which occurred 30 minutes after Frontline® application. Another cat was found dead two days after Frontline® application and was not necropsied. In another case, death in a Persian cat was attributed to urinary stones. In the last case, a cat developed hypothermia and vomiting less than 30 minutes after Frontline application; death was attributed to renal impairment.

Twelve cases of adverse effects were noted in humans; only one was classified as possibly related to Frontline treatment. A woman applied the product to her dog while wearing gloves. After she was done, she took off the gloves and patted the dog. Two to three days later, she developed brownish spots on the convex part of her hands.

3. Domestic Animal Safety Study in Cats with Spot-on Formulation

"Domestic Animal Safety Study by Topical Administration to Cats" - MRID #4386801

Material Tested: RM1601E/62 (9.7% fipronil)

In this domestic animal safety study, 4 male and 4 female domestic short hair cats (approximately 12 weeks of age) were administered a single topical treatment of RM1601E/62 (9.7% fipronil) of either 0.25 ml/kg (1x), 3x or 5x that dose once every month for a total of six treatments. A group of 4 male and 4 female kittens served as a control group and were treated with the formulation vehicle at 5x the 1x dose. A similar group served as an untreated control. The following parameters were evaluated: clinical observations, body weight, food consumption, water consumption, hematology and clinical chemistry. As there was no ante-mortem evidence of any treatment-related effects, necropsy examinations were only of the application sites. The study was not conducted in accordance with the protocol design. The label recommended dose is 0.5 ml, regardless of the animal's weight. This dose was not achieved until the fourth treatment for most animals when they were approximately 24 weeks old. However, since three treatments at this dose were applied, Toxicology Branch II judges that the study is adequate.

The study demonstrated that RM1601E/62 (9.7% fipronil) has at least a 5x margin of safety in cats greater than 24 weeks of age.

Classification: Acceptable

4. Domestic Animal Safety Study in Dogs

"Domestic Animal Safety Study by Topical Administration to Dogs" - MRID # 43863802

Material Tested: RM1601E/62 (9.7% fipronil)

In this domestic animal safety study, 4 male and 4 female pure-bred beagle dogs (approximately 10 weeks of age) were administered a single topical treatment of RM1601E/62 (9.7% fipronil) of either 1x, 3x or 5x the recommended dose (0.133 mg/kg/spot) once every month for a total of six treatments. A group of 4 male and 4 female dogs served as a control group and were treated with the formulation vehicle at 5x the recommended dosage. A similar group served as an untreated control. The following parameters were evaluated: clinical observations, body weight, food consumption, water consumption, hematology and clinical chemistry. As there was no ante-mortem evidence of any treatment-related effects, necropsy examinations were only of the application sites. There was an increase in the number of animals in the vehicle control and treated groups which were observed to scratch and rub at the treated areas after application. On microscopic examination of the skin at the application sites, there was an increase in the number of females in the 3x and 5x groups which had superficial dermal inflammatory cells as compared to the untreated controls. The study demonstrated that RM1601E/62 (9.7% fipronil) has at least a 5X margin of safety in dogs greater than 10 weeks of age. The product label should state that there may be temporary irritation after application.

Classification: Acceptable

CONCLUSIONS ABOUT ADEQUACY OF DOMESTIC ANIMAL SAFETY STUDIES

The administrative history of the proposed fipronil pet products is convoluted and confusing. The following is a summary of the domestic animal safety studies reviewed to date for both the spray and spot-on formulation. In a January 24, 1996 memo from Virginia Dobozy to Rick Keigwin/Ann Sibold, PM Team 10, Toxicology Branch II agreed that data generated with either formulation could be applied for the individual product's regulatory requirements. The basis for this decision was the comparability of doses received by animals regardless of the product used.

The data base is complete for both the spray and spot-on formulations for adult and juvenile dogs and cats. The studies cited are as follows:

1) MRID #43444905 - Domestic Animal Safety Study in Puppies

Material Tested: 0.25% fipronil spray formulation
Age of Animals: ≈ 8 weeks old at initiation of treatment
Dosages Tested: Control (Vehicle at 5x), 1x and 5x once per month for 3 months
Findings: No treatment related effects

2) MRID # 43444904 - Domestic Animal Safety Study in Kittens

Material Tested: 0.25% fipronil spray formulation
Age of Animals: ≤ 8 weeks old at initiation of treatment
Dosages Tested: Control (Vehicle at 5x), 1x and 5x once per month for 3 months
Findings: No treatment-related effects

3) MRID # 4386802 - Domestic Animal Safety Study in Dogs

Material Tested: 9.7% fipronil spot-on formulation
Age of Animals: 10 weeks at initiation of treatment
Dosages Tested: Untreated Control, Vehicle Control (at 5x), 1x, 3x and 5x once per month for six months
Findings: No systemic treatment-related effects, however animals in the vehicle control and treated groups were observed to scratch and rub at application sites

MRID # 4386801 - Domestic Animal Safety Study in Cats

Material Tested: 9.7% fipronil spot-on formulation
Age of Animals: 12 weeks at initiation of treatment
Dosages Tested: Untreated Control, Vehicle Control (at 5x), 1x, 3x and 5x once per month for six months
Findings: There were no treatment-related effects. The study was not conducted in accordance with the protocol design and animals were not treated at the above dosages until the fourth treatment when they were approximately 24 months old. Toxicology Branch II judged that the study was adequate since three treatments were applied at these dosages.

Three domestic animal safety studies in dogs (MRID #43121110), puppies (MRID #43121111) and cats (MRID #43121112) were unacceptable due to various deficiencies including lack of GLP compliance, failure to test at 5x the recommended dose and low numbers of animals.

LABEL RECOMMENDATIONS

1. The label for the spot-on formulation should state that pets may experience some temporary irritation at the site of product application. The basis for this recommendation is the increased incidence of scratching and rubbing at the site in the domestic animal safety study in dogs (MRID #4386802).

2. The spot-on label states, "Fipronil is not absorbed into the body, but rather collects in the oils of the skin and hair follicles. Fipronil continues to be released from hair follicles onto the skin and fur, resulting in long residual activity." A previously submitted study (MRID #43577715) in which radiolabeled fipronil was administered to dogs at a high dose (10 mg/kg) demonstrated that the chemical is absorbed systemically. Plasma levels of radioactivity were detected from day 2 to day 30 post-treatment. These statements should be deleted from the label for dogs. A similar study in cats determined that systemic absorption was insignificant.

3. The spray formulation label states, "Following use, if you notice changes in your pet's behavior or appearance, consult a veterinarian or call 1-800-934-4447 for 24 hr. assistance. It is advisable to consult a veterinarian before using this product with other pesticides or drugs." It is recommended that these instructions also appear on the spot-on formulation label. Although the incidence of adverse reactions in the French use experience data was very small, the reports of central nervous system effects in both cats and dogs is of concern. Neurological signs were also seen in the toxicology studies in laboratory animal studies after ingestion of the technical chemical.

4. The spray formulation label contains instructions for pet owners to wear latex gloves and wash hands and exposed skin thoroughly with soap and water after use. It is recommended that these instructions also appear on the spot-on formulation label.

5. The information supplied under Statement of Practical Treatment for the spray formulation label and under First Aid on the spot-on formulation label should be consistent.