CATS

EFFICACY REVIEW

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DATA ACCESSION NO(S). 456158-01,456281-01,-02 & -03; D282314; S611827; Case# 014261; AC:305

PRODUCT MGR. NO. 03-Layne/Sibold

PRODUCT NAME(S) FRONTLINE® Spray Treatment

COMPANY NAME Merial Limited

SUBMISSION PURPOSE Provide performance data in support of claims for chewing lice and flea allergy dermatitis on cats with standard label rate of subject product.

CHEMICAL & FORMULATION Fipronil 0.29%
(0.859 Sp.Gr. ready-to-use liquid pump spray)

CONCLUSIONS & RECOMMENDATIONS The data presented in EPA Accession (MRID) Number 456158-01, being a summary of data from testing conducted according to requirements of § 95-9(a)(1)-(3) on p. 263 and meeting the standards of § 95-9(b)(2)(i) and (ii) on p. 264 of the Product Performance Guidelines, are adequate to demonstrate the ability of the subject product to kill and control the cat louse, *Felicola subrostratus*, when applied to previously infested cats having been infested by confinement with other infested animals prior to the beginning of testing, at the maximum label rate of 6 ml per kg (approximately 12 pumps per kg) of body weight. There are 3 studies on the efficacy of the subject and closely related products against biting and chewing lice on cats which are summarized in the first third of this volume, namely a pilot efficacy study using a fipronil spot-on, a dose confirmation study using all 3 fipronil formulations including the subject product formulation, and a field study using the subject product in comparison to the fipronil spot-on and a propoxur collar. In the remaining 2/3 of the volume are 2 clinical field studies on the efficacy of fipronil spot-on to control flea allergy dermatitis in the cat by monthly applications, namely a multi-centered clinical (to be continued)

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field study and a single-centered clinical field study. Each of these 5 studies will be discussed in detail below.

Data presented in MRID No. 456281-01, having been obtained from standard clinical testing meeting the same requirements and standard, are adequate to demonstrate the ability of a fipronil spot-on to control cat louse when applied at 0.5 ml per cat according to label directions. The 6 female and 2 male cats were 8 to 13 months old and weighed 1.65 to 2.70 kg on Day -1. The cats were housed in individual cages. On Day -1 each cat was infested with *F. subrostratus* biting lice. The lice were counted and cats were ranked based on the Day -1 count. Four replicates of two consecutively ranked cats were formed. One cat in each replicate was randomly allocated to each of the following two treatment groups: 1) untreated control; 2) fipronil spot-on, 0.5 ml/cat as per label instructions. Treatments were applied twice topically on Days 0 and 28. Lice were counted and animals were clinically assessed on Days 2, 7, 14, 21, 28, 35 and 42. Cats treated with fipronil spot-on were free of lice from Day 2 through trial termination on Day 42. Controls maintained louse infestations through Day 42. No health problems or adverse reactions occurred during this trial. The results of this study indicate that fipronil in a topical spot-on formulation is highly effective for treatment and control of louse infestations (*F. subrostratus*) in the cat.

Data presented in MRID No. 456281-02, having been obtained from standard clinical testing meeting the same requirements and standard, are adequate to demonstrate the ability of the subject product to control cat louse when applied at the maximum label rate. The 14 female and 10 male cross-bred cats in the study were approximately 2.5 to 42 months old, and weighed 0.7 to 3.2 kg on Day -1. The cats were housed in individual cages. Prior to allocation the cats were exposed to *F. subrostratus* through contact with infested donor cats. On Day -1 the number of live lice found in 27 hair coat-partings, located at potential predilection sites for this parasite, were counted. Based on the total count from the 27 partings, the cats were ranked. Six replicates of four consecutively ranked cats were formed. Due to logistical reasons, allocation procedures were performed two separate times in order to form the required number of replicates. One cat in each replicate was randomly allocated to each of the following four treatment groups: 1) untreated control; 2) the subject product, at the maximum label rate of 6 ml/kg; 3) fipronil spot-on at 0.5 ml/cat; and 4) fipronil/(S)-methoprene combination spot-on at 0.5 ml/cat. The treatments were applied topically on Days 0 and 28. Lice were counted in the 27 hair coat partings and animals were clinically assessed on Days 2, 7, and weekly to Day 42. A whole body comb count/search was also conducted on Day 42. No live *F. subrostratus* lice were found on cats treated with the subject product, fipronil spot-on or fipronil/(S)-methoprene combination spot-on product from Day 2 to Day 42. The difference from controls was significant ($p<0.01$) for each product at each time point. Based on the whole body counts at Day 42, the efficacy was 100% in each group. No health problems or adverse reactions occurred during this trial. The results of this study demonstrate that fipronil in three topical formulations are highly effective for treatment (continued)

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and control of louse infestations (*F. subrostratus*) in the cat.

Data presented in MRID No. 456281-03, having been obtained from standard field testing meeting the same requirements and standard, are adequate to demonstrate the ability of the subject product to control cat louse when applied at the maximum label rate. The efficacy of a single topical application of fipronil in two topical formulations against natural infestations of lice was compared to an approved reference product (a propoxur collar) in cats under field use conditions. From a total of six locations distributed in northern Italy, the investigator could enroll eighteen crossbred cats, 7 females and 11 males, in the study over a recruitment period of 5 months. At the six locations, owners kept three to six cats together. The cats lived inside with access to the outside or entirely outside before inclusion in the study. Cats were 4 months to 8 years of age and weighed 0.5 to 3.8 kg at study start. Three cats naturally infested with biting lice on Day 0 were enrolled at each location. Replicates of three cats were formed in strict order of presentation. The order of presentation corresponded to the order in which animals were searched for the presence of lice. The sponsor provided an allocation table that was prepared by means of the 'random number' function in MS-Excel 97. Within replicates, one cat each was randomly allocated to each treatment group: 1) propoxur collar, 12.5 g, cut to the correct length to fit the animals neck; 2) the subject product at approximately 6 ml/kg body weight; and 3) fipronil spot-on, 0.5 ml pipette. After treatment, animals were kept individually with no contact to other cats and no access to the outside. On Days 0, 2, 28 and 42, each animal was searched approximately 20 minutes for the presence of lice using the coat parting technique (*i.e.* fingerpartings). Cats in replicate 1 were searched on Days 26 and 41 instead of Days 28 and 42. Individual counts on Day 0 ranged from 3 to 156 lice on individual animals. Louse counts of cats treated with either the subject product or fipronil spot-on were not different than those of cats receiving the propoxur collar at all post-treatment counts. The efficacy of the latter was 100% on each occasion when compared to the pre-treatment count. The efficacy of fipronil was 98.3% and 98.8% on Day 2 for spray and spot-on, respectively. The efficacy was 100% for both formulations at the following counts on Days 28 and 42. No health problems related to treatment were observed. Standardized louse counts in this field trial provided a quantitative evaluation of the louse burden of cats which is more accurate than subjective and qualitative estimates often used in the field. With this technique in place, fipronil demonstrated to be highly effective (100%) for the treatment and elimination of an existing louse infestation (*F. subrostratus*) under field use conditions following a single topical application.

Data in MRID Nos. 456281-04 and -05 which present results of clinical testing for the purpose of treating flea allergy dermatitis were not included in the data attached to the current submission, but they were summarized in MRID No. 456158-01 previously mentioned above. The results of the two studies were similar and the use of short acting corticosteroids was limited (to be cont'd)

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to a few cases. Fipronil spot-on effectively reduced the flea burden on the allergic cats as determined by flea scores or counts, flea feces and flea egg scores (Tables 4, 5, 6, 7 and 8). At the initial visit, all cats (except four animals in CLI277/ASR 19012) exhibited mild or intense pruritis. By Day 28 in study CLI277 (ASR 19012), pruritis scores were significantly improved in fipronil treated cats compared to the vehicle treated animals, and in PR&D 0012701-04, pruritis scores improved significantly from Day 14 onward. At the time of final evaluation, more than 70% of cats no longer exhibited pruritis (Table 1). The prevalence of military dermatitis at the Day 0 visit was also high (80%-93%) in both studies. Military dermatitis scores were significantly improved at most visits after fipronil spot-on treatments in both studies, and the prevalence of the condition was reduced to 35 to 40% of cases by the final evaluations (Table 1). The prevalence of alopecia on Day 0 ranged between 57 and 78%. The change from baseline alopecia scores was significantly higher in fipronil treated cats compared to vehicle treated animals from Day 28 onwards in CLI277 (ASR 19012). Similar significant improvement was recorded in PR&D 0012701-04, with prevalence of alopecia reduced to 17.5% by the Day 90 visit (Table 1). Other parasitological and fungal infections, also causes of dermatitis, were excluded in these studies. However, allergic inhalant dermatitis (atopy) and food allergy which may also be commonly responsible for the production of military dermatitis in cats, were not ruled out with certainty in those studies. Therefore, the possible involvement of those conditions concomitantly to FAD could have accounted for some of the treatment failures. A significant improvement in pruritis and in the most important clinical signs associated with feline FAD was substantiated following monthly treatment of flea allergic cats and other pets in the households with fipronil spot-on. Based on overall assessment of efficacy at the final visit, the clinical condition of 73.2% of cats in the one study and 85% in the other was rated as "excellent" or "good". These data support the conclusion that, by eliminating fleas, monthly applications with fipronil spot-on of flea allergic cats and their congeners (dogs and cats) in the household are effective for the treatment and control of flea allergy dermatitis.

These data collectively support the following label claims for the subject product: "Kills fleas which may cause flea allergy dermatitis"; "Treats and controls flea allergy dermatitis"; "Rapidly eliminates infestations with chewing lice"; "...provides effective flea...and chewing lice control for adult...cats and for ...kittens 8 weeks of age or older"; "...residual activity prevents reinfestation by killing fleas...and chewing lice for at least 30 days"; "To prevent flea build-up or reinfestation, use...prior to the onset of flea season and monthly thereafter."

RL Vern L. McFarland, IB

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