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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EFFICACY REVIEW

Date in : 5/5/97 Date out :
Barcodes : D235677, D235670, D235672, D235673, D235675, D235676
Case Number : 005596, 005593, 007500, 005595, 005598, 060705
Chemical : 129099 imidacloprid
Trade Name : Advantage
MRID Number : 442569-01 and 442569-02
Subject : Flea control with dermal applications of imidacloprid
Registration Numbers : 011556-00116, 011556-00117, 011556-00118,
011556-00119, 011556-00120, and 011556-00122
Pests : Fleas
Host : Dogs and cats
Formulation : Liquid
Rate Proposed : 2.5ml of 9.1% w/w solution
Chemical Structure : 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-
imidazolidinamine
Common name : imidacloprid
Purpose of submission : Revise label, change trade names
Branch Chief : Tina Levine
Branch Reviewer : Elizabeth Haeberer
Efficacy reviewer : Paul Schroeder

Proposed changes : Amendment proposals were submitted for six products, two for use on cats; 011556-00116 and 011556-00118 and four for use on dogs; 011556-00117, 011556-00119, 011556-00120, 011556-00122

The proposed changes were essentially the same for each product. Proposed efficacy changes are acceptable. Primary changes in efficacy claims are control of adult fleas within 12 hours of application, control of adult fleas up to four weeks after spraying, control of larvae in areas frequented by treated pets, control of cat fleas on both cats and dogs and good flea control even if pets are shampooed, go swimming or are exposed to rain and sun. In addition name changes were proposed and the registrant requested acceptance of addition of a paragraph on description of allergy dermatitis to the label.

Procedure :

The day before treatment about 100 fleas were placed on each of thirty dogs. The dogs were split into groups of 10, matching individual dogs with others with approximately the same number of fleas. Five male and five female dogs were each given the standard "Advantage" treatment; two males and eight females were given the "Frontline, Top-spot treatment, and six males and four females were given the Advantage Vehicle treatment - called



placebo or control.

Each dog was administered one to 2.5 ml of test material, depending upon weight. Treatments were made to skin on the back of each dog between the shoulder blades and on the back of the neck. Fleas were combed out of the fur of each animal and dead fleas in the pans beneath each dog cage were counted four, eight, twelve, and twenty four hours and six, thirteen, twenty, and twenty seven days post-treatment. The dogs were examined 30 minutes, 1, 3, and 5 hours after treatment for adverse reactions. During the balance of the study the dogs were examined daily. The dogs were infested with approximately 100 adult fleas at specified intervals starting the day before treatment. Two of the dogs in each treatment were examined for dead and live fleas. All fleas were removed and checked to see if they had fed 2, 4, 8, 12, and 24 hours post treatment. This procedure was repeated 6, 13, 20, and 27 days post treatment.

Results :

Imidacloprid applied to the skin between the shoulder blades:

Neither Advantage Nor Top Spot prevented fleas from feeding. By 12 hours after fleas were placed on dogs treated with Advantage or Top Spot, the same day as treatment, both treatments gave 100% control. There was an average of 88.5 live fleas on each check dog reinfested with fleas 12 hours after the treatments were made.

Four hours after fleas were placed on test dogs, 6 and 13 days after treatment, both materials gave virtually 100% of adult fleas. By test day 20 (20 days after the start of the test) flea survival on dogs treated with Top Spot appeared to be somewhat higher than on dogs treated with Advantage.

On test day 27 flea control after two hours exposure on treated dogs was about 50% for each treatment. With four hours to 24 hours exposure, flea control was about 95%. The counts of live fleas on dogs subjected to the two treatments 27 days earlier showed control of adult fleas ranging from 81.5% to 100% after 4 to 24 hour exposure on treated dogs.

In one study in which an imidacloprid topical formulation was used the larvacidal effect of this product against Ctenocephalides felis was measured. Two dogs were treated with a spot treatment between the shoulder blades. Two other dogs served as untreated checks. The dogs were placed in individual cages. Five to ten milligrams of debris was collected from the tray beneath each dog cage and put into petri dishes along with 10 mg. of dried bovine blood and 22 unhatched flea eggs. Five or six replicate samples from each dog were prepared the same way. The petri dishes were placed in an incubator at 23.5 to 26.5 degrees centigrade and 75 to 92% relative humidity. The dishes were examined at 4 hours and then daily for nine days to determine the effect of the debris on the viability of larvae hatching from the

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flea eggs.

Inclusion of the debris from imidacloprid treated dogs collected 1, 7, 14, and 28 days after treatment gave an overall inhibition of larval development of more than 99% (788/795 larvae killed over all periods). No pupae developed in any sample from treated dogs whereas pupation occurred in control samples. Most larvae were dead or affected within four hours.

In a second study, an enclosed concrete area was divided into two identical rooms, each measuring 1.6 meters by 2.5 meters (approximately eight feet by five feet) and separated by a 2.5 meter high wall. The temperature in both rooms varied from 16 to 26.5 degrees C and relative the humidity varied from 67 to 91%. Four kilograms (8.8 pounds) of untreated sawdust was spread over the floor of each room. Two dogs infested with fleas were confined to each room for two hours on Mondays, Wednesdays, and Fridays for three weeks. Three other dogs infested with fleas and treated with imedacloprid were placed in one room for one hour, five days a week, starting one day after the untreated dogs first were placed in the test rooms.

After 18 days from the first introduction of infested dogs, a composite sample of sawdust from each room was placed in separate petri dishes with 500 mg of bovine blood and 100 flea eggs. Two additional samples of sawdust were collected and placed in petri dishes with 2500 unhatched flea eggs plus 500 mg of bovine blood and 100 mg dried yeast powder. The petri dishes were examined microscopically seven and eleven days later looking for immature fleas. Twenty three days after the start of incubation of the eggs in petri dishes they were examined for presence of pupae. Failure of eggs to hatch plus larval mortality resulted in 97.7% control of fleas in the sawdust from the room where the treated dogs were confined. No pupae were found in the floor sawdust samples from the room in which treated dogs were confined. However, after 23 days of incubation 83 pupae were found in a comparable sample of sawdust from the room in which only untreated dogs were confined.

On day 29 no pupae were found from litter from the room where treated dogs had been confined. At 42 days, 94 adult fleas were counted on the white overalls of a technician within 14 seconds of entering the room where only untreated dogs had been confined. Only three fleas were detected in 12 minutes of search in the room where treated dogs had been confined.

Discussion:

In a complex set of studies conducted in Australia, imidacloprid gave excellent control of adult fleas, flea eggs and flea larvae. Changes on the label claiming flea control in 12 hours are acceptable.

Advantage, active ingredient imidacloprid, activity,

speed of activity, effectiveness when challenged by periodic exposure to additional adult fleas was equal to the standard, Top Spot, active ingredient fipronil. Neither material was toxic to the test animals and neither material prevented fleas from feeding.

Products containing imidacloprid are effective against adult cat fleas. The efficacy requirement is satisfied.