

JAN 24 2000

FREEDOM OF INFORMATION SUMMARY

**ZODIAC® FLEATROL™ FLEA CAPS™
HARTZ® FLEA CONTROL CAPSULES™
NADA 141-162**

“for use in dogs, nine weeks of age and older and 4 pounds body weight or greater, for the prevention and control of flea populations. (S)-Methoprene prevents and controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.”

Sponsored by:

**Wellmark International
1000 Tower Lane
Bensenville, IL 60106**

FOIS 1

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I. GENERAL INFORMATION:

NADA Number: NADA 141-162

Sponsor: Wellmark International
1000 Tower Lane
Bensenville, IL 60106

Generic Name: (S)-Methoprene

Trade Names: ZODIAC® FLEATROL™ FLEA CAPS™
HARTZ® FLEA CONTROL CAPSULES™

Marketing Status: OTC (Over-the-Counter)

II. INDICATIONS FOR USE:

ZODIAC® FLEATROL™ FLEA CAPS™ and HARTZ® Flea Control Capsules™ are indicated for use in dogs, nine weeks of age and older and 4 pounds body weight or greater, for the prevention and control of flea populations. (S)-Methoprene prevents and controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND DOSAGE:

Dosage Form: capsule

Route of Administration: oral

Dosage and administration: The capsules are given orally once per week at the recommended minimum dosage of 10 mg (S)-Methoprene per pound of body weight (22 mg/kg) according to the following schedule.

Dog Weight	No. of capsule(s) per week	mg (S)-Methoprene per Capsule	Color
4 to 15 lbs.	1 Capsule	154 mg	Green
16 to 30 lbs.	1 Capsule	308 mg	Red
31 to 45 lbs.	1 Capsule	462 mg	Lavender
46 to 60 lbs.	2 Capsules	308 mg	Blue
61 to 90 lbs.	2 Capsules	462 mg	Brown
91 to 135 lbs.	3 Capsules	462 mg	Brown
136 to 180 lbs.	4 Capsules	462 mg	Brown

IV. EFFECTIVENESS:

(S)-Methoprene is an insect growth regulator (IGR) which breaks the flea life cycle at the egg stage. The adult female flea is exposed to the drug when feeding on a treated dog. The drug, which has no deleterious effect on the adult flea, acts to inhibit the development of flea eggs.

A. DOSE DETERMINATION STUDY:

Title: A Dose Titration Study to Determine the Effective Level of Oral (S)-Methoprene in Dogs for the Inhibition of Cat Flea (*Ctenocephalides felis*) Egg Hatch.

Purpose: To determine the effective level of orally administered (S)-Methoprene for the control of the cat flea (*Ctenocephalides felis*) on dogs.

Investigators/Study Locations:

Dr. Michael Lytwyn
Hartz Mountain Corporation
Bloomfield, NJ

Dr. Marvin L. Sharp
Sharp Veterinary Research
Vernon, TX

Animals: 24 mixed breed dogs (12 males and 12 females)
1 year of age and older, 6 kg-28 kg, 6 groups (4 dogs per group)

Dosage Groupings: placebo (excipients without active ingredients)
10 mg/kg (S)-Methoprene
20 mg/kg (S)-Methoprene
25 mg/kg (S)-Methoprene
50 mg/kg (S)-Methoprene
Initial dose of 40 mg/kg followed by 20 mg/kg once a week

Route of Administration: Oral, mixed into 50 grams of canned dog food

Frequency of Treatment: Once per week

Duration of Study: 35 days for egg collection
64 days for adult emergence

Study Design: Starting on day 0, treatments were administered to all animals once per week until day 28. Each dog was infested with 200 fleas throughout the study and flea eggs were collected on days -7, 2, 7, 9, 14, 21, 28 and 35.

Parameters Measured: The cumulative percent reduction in adult flea emergence from eggs deposited on days 2-28 and 2-35.

Results: The following table shows the cumulative percent reduction in adult flea emergence for days 2 through 28 and days 2 through 35.

**CUMULATIVE PERCENT REDUCTION IN ADULT FLEA EMERGENCE
ON DAYS 2-28 AND 2-35**

TREATMENT GROUP	DAYS 2-28	DAYS 2-35
10.0 mg/kg	74.9%	79.3%
20.0 mg/kg	91.8%	93.3%
25.0 mg/kg	99.6%	99.7%
50.0 mg/kg	99.8%	99.9%
40, 20 mg/kg	99.1%	99.1%

Conclusions: (S)-Methoprene administered at 20 mg/kg provided greater than 90% reduction in adult flea emergence on days 2-28 and 2-35 and was selected as the dosage for further testing.

Adverse Reactions: There were no adverse reactions reported.

B. DOSE CONFIRMATION STUDY:

Title: A Study to Confirm the Efficacy of an Oral (S)-Methoprene Capsule in Dogs for the Inhibition of Cat Flea (*Ctenocephalides felis*) Emergence.

Purpose: To confirm the effectiveness of orally administered (S)-Methoprene in a capsule for the Inhibition of Cat Flea (*Ctenocephalides felis*) egg hatch.

Investigators/Study Locations:

Dr. Michael Lytwyn
Hartz Mountain Corporation
Bloomfield, NJ

Dr. Marvin L. Sharp, DVM
Sharp Veterinary Research
Vernon, TX

Animals: 20 mixed breed dogs (10 males, 10 females)
6 months of age or older, 6 kg-28 kg, 2 groups (10 dogs per group)

Dosage Groupings: placebo (excipients without active ingredients)
22 mg/kg (S)-Methoprene

Route of Administration: Oral, capsules (Days 0, 7)
Mixed into 50 grams of canned dog food (Day 14)

Frequency of Treatment: Once weekly prior to feeding on days 0, 7, and 14

Duration of Study: 42 days

Study Design: Each animal was infested with 200 fleas on days -12, 0, 7, and 14. On day 14, five of the dogs in each treatment group were administered whole capsules after being fed, while the remaining five received their treatment mixed with food. Flea eggs were collected on days 2, 7, 9, 14, 16, 21, and 23.

Parameters Measured: The percent reduction in adult flea emergence.

Results: The percent reduction in adult emergence for the (S)-Methoprene treatment group between egg collection days 2 and 14 was 96.1% (See the table below).

% REDUCTION IN ADULT FLEA EMERGENCE

TEST GROUP	TOTAL # OF ADULTS EMERGED/TOTAL # OF EGGS COLLECTED
(S)-Methoprene	37/2379
Placebo	963/2400
Emergence rate*	96.1%

*Emergence rate =
$$\frac{\text{total \# of adults emerged/total \# of eggs collected (placebo group)} - \text{total \# of adults emerged/total \# of eggs collected (treated group)}}{\text{total \# of adults emerged/total \# of eggs collected (placebo group)}}$$

Conclusions: (S)-Methoprene administered at 22 mg/kg provided a 96.1% reduction in adult flea emergence.

Adverse Reactions: There were no adverse reactions reported.

C. CLINICAL FIELD TRIAL:

Title: A Clinical Trial to Determine the Efficacy of a Once a Week Oral (S)-Methoprene Capsule for the Control of Cat Flea (*Ctenocephalides felis*) Populations on Dogs.

Purpose: To confirm the effectiveness and safety of (S)-Methoprene for the control of flea populations under field conditions.

Investigators/Study Locations:

Richard Johnson, D.V.M.
Broadway Animal Hospital
El Cajon, California

Louis Gotthelf, D.V.M.
Animal Hospital of Montgomery
Montgomery, Alabama

Investigators/Study Locations (con't):

David Nielsen, D.V.M.
Animal Medical Group
Manhattan Beach, California

Ted Lamp, D.V.M.
Bellville Veterinary Clinic
Bellville, Texas

George Bailey, D.V.M.
Country Club Animal Hospital
Miami, Florida

Chris Jenkins, D.V.M.
Creature Comfort Animal Clinic
Arlington, Texas

Mark Pelham, D.V.M.
Kelley Animal Hospital
Birmingham, Alabama

Karen Fling, D.V.M.
East Lake Veterinary Hospital
Dallas, Texas

Bob Cartin, D.V.M.
Mission Animal Hospital
Oceanside, California

Michael Shumer, D.V.M.
Beach Boulevard Animal Hospital
Jacksonville, Florida

Stephen Collier, D.V.M.
Parkway Animal Hospital
Panama City, Florida

Animals: A total of 246 (118 males, 127 females) dogs were enrolled in the study (the sex of one animal was not reported). Of these, 165 client owned dogs ranging in age from 6 months to 16 years and weighing between 4 to 130 pounds, were included in the statistical analysis. Sixty-one of the 165 dogs were treated with (S)-Methoprene.

Dosage Groups: positive control (lufenuron tablets: minimum of 10 mg/kg)
minimum of 22 mg/kg (S)-Methoprene

Route of Administration: Oral, lufenuron (in conjunction with or following a meal)
Oral, (S)-Methoprene (by mouth, in a treat or mixed into the food)

Frequency of Treatment: lufenuron: once monthly for five months
(S)-Methoprene: once weekly for five months

Duration of Study: 5 months

Study Design: All dogs enrolled (single and multi-dog households) were harboring natural flea infestations. A burden of at least 20 fleas was required for single dog households and at least one dog in a multi-dog household was required to have at least 20

fleas. Each client received Adams™ Flea and Tick Mist for application once per week for the first eight weeks to eliminate the existing adult flea burdens. The mist was not for use within 5 days before a flea count. Bathing was not permitted within 5 days prior to flea counts and insecticidal shampoos were not allowed. Other treatments and medications commonly used in veterinary practices were allowed.

Parameters Measured: Adult flea counts (months 0, 1, 2, 3, 4, and 5) and percent inhibition of fleas.

Results: Refer to the table below for the geometric mean flea counts and percent inhibition of fleas. The geometric flea counts were used to compute the percent inhibition (PI) of fleas: $PI_t = [(GM_0 - GM_t)/GM_0] \times 100\%$.

GEOMETRIC MEAN FLEA COUNTS AND PERCENT INHIBITION OF FLEAS BY MONTH

Month	GEOMETRIC MEAN FLEA COUNT		PERCENT INHIBITION OF FLEAS	
	Program®	(S)-Methoprene	Program®	(S)-Methoprene
0	74.86	68.18		
1	25.30	18.05	66.2	73.5
2	14.49	8.55	80.6	87.5
3	9.23	9.72	87.7	85.7
4	7.71	6.94	89.7	89.8
5	4.89	4.89	93.5	92.8
1-5	10.75	8.77	85.6	87.1

GM_0 = geometric mean flea count for month 0

GM_t = geometric mean count either for month t (t = 1, 2, 3, 4, or 5) or months 1 to 5 combined.

Conclusions: (S)-Methoprene, administered at a minimum dose of 22 mg/kg body weight at weekly intervals during active flea infestations, effectively controlled the flea populations. (S)-Methoprene, an insect growth regulator (IGR) which has no effect on the adult flea, was used in combination with a topical insecticide to kill the adults for the first 2 months of the study when the pre-existing fleas were at their heaviest. (S)-Methoprene capsules worked as effectively as the positive control.

Adverse Reactions: Vomiting, diarrhea, lethargy/depression and nervousness were observed in the (S)-Methoprene group.

D. LABORATORY SIMULATED HOME ENVIRONMENT TRIAL:

Title: A Study to Determine the Efficacy of a Once a Week Oral (S)-Methoprene Capsule for the Prevention of Cat Flea (*Ctenocephalides felis*) Populations on Dogs.

Purpose: To confirm the effectiveness and safety of (S)-Methoprene for the prevention of flea populations under a laboratory simulated home environment.

Investigator/Study Location: Suzanne Craig, DVM
Stillmeadow Inc.
Sugar Land, TX

Animals: 20 dogs (10 males and 10 females) of various breeds, 8 months to 4 years of age, 14 to 61 pounds body weight

Dosage Groups: negative control (untreated)
22 mg/kg (S)-Methoprene

Route of Administration: oral

Frequency of Treatment: negative control: untreated
(S)-Methoprene: once weekly

Duration of Study: 91 days

Study Design: The dogs were individually housed in cages with partially carpeted runs. Treatment began on day 0 and continued weekly through day 84. Flea populations were established initially by infesting each dog with 100 unfed, adult cat fleas 24 hours after the first treatment (day 1) and maintained by additional infestations on days 5, 8, 12, and 15. The carpeted platform was sprinkled with ground dog food, dried beef blood, and sand on study day 1 to provide a food source for developing fleas.

Parameters Measured: Adult flea counts weekly starting on day 21. Counts were not done the first 2 weeks after treatment to leave the adults undisturbed and to encourage reproduction during the early phases of the study.

Results: (S)-Methoprene capsules demonstrated 93.8% percent reduction of adult fleas by day 49-post treatment. Refer to the table below for the means and percent reductions in adult flea counts.

PERCENT REDUCTION IN ADULT FLEA COUNTS

DAY OF STUDY	CONTROL GEOMETRIC MEANS	(S)-METHOPRENE GEOMETRIC MEANS	PERCENTAGE REDUCTION
21	50.6	42.0	17.0
28	47.2	8.5	82.0
35	56.6	15.8	72.1
42	102.4	17.5	82.9

PERCENT REDUCTION IN ADULT FLEA COUNTS (con't)

DAY OF STUDY	CONTROL GEOMETRIC MEANS	(S)-METHOPRENE GEOMETRIC MEANS	PERCENTAGE REDUCTION
49	123.6	7.7	93.8
56	149.2	7.6	94.9
63	203.1	23.6	88.4
70	218.9	22.7	89.6
77	292.2	23.2	92.1
84	414.9	33.8	91.9
91	499.9	36.5	92.7

Conclusions: (S)-Methoprene capsules administered weekly at 22 mg/kg were effective for the prevention of cat flea (*Ctenocephalides felis*) populations on dogs. There was 93.8% reduction in the adult flea counts by day 49.

Adverse reactions: There were no adverse reactions reported.

V. ANIMAL SAFETY:

A. TARGET ANIMAL SAFETY:

Title: A Target Animal Safety and Tolerance Study of (S)-Methoprene Capsules Administered Orally Once per week to Beagle Dogs.

Purpose: To determine the safety of three dosage levels (1X, 3X and 5X) of (S)-Methoprene following 13 weeks of exposure and to investigate the tolerance effects at 10X for 4 weeks.

Investigator/Study Location: Thomas R. Carpenter, DVM, Ph.D.
Director of Toxicology,
HTI Bio-Services, Inc.,
San Diego, CA

Animals: 32 Beagle puppies (16 males and 16 females), approximately 6-weeks old, 1.62-2.10 kg body weight. Groups 1-4 (6/group) and Groups 5 and 6 (4/group), divided equally by sex

Dosage Groups: Group 1: Negative control (untreated)
Group 2: 1X (22 mg/kg (S)-Methoprene)
Group 3: 3X (66 mg/kg (S)-Methoprene)
Group 4: 5X (110 mg/kg (S)-Methoprene)
Group 5: 10X (220 mg/kg (S)-Methoprene)

Dosage Groups: Group 6: Negative control (untreated)

Route of Administration: orally, followed by a water rinse. The 10X dose was split into two doses, administered within a period of 1 to 2 hours.

Frequency of Treatment: Groups 2, 3 and 4 treated once weekly for 13 weeks
Group 5 treated once weekly for 4 weeks

Duration of Study: 90 days (13 weeks) Groups 1-4
28 days Groups 5 and 6

Parameters Measured: Dogs were observed daily to determine pharmacological and/or toxicological effects. Two physical examinations were performed during the baseline period. Body weights and food consumption were measured weekly. Ophthalmic exams were performed during baseline and the final week of treatment. Blood specimens were collected for hematology, clinical chemistry and coagulation profiles (day -2, 21 and 56), and on the day of necropsy. Animals were euthanized at study completion and organ weights, gross pathology and histology samples were obtained.

Results: There were no adverse effects on body weight, food consumption, ophthalmology, clinical pathology, urinalyses, organ weights, gross pathology or histology. The clinical signs included depression, ataxia (loss of balance) and tremors.

Depression was exhibited as depicted below. All dogs returned to normal by the following observation (next morning). Two dogs in the 3x treatment group and 1 in the 10x group exhibited depression twice on days 0 and 7. By day 14 only 1 dog exhibited mild depression.

DEPRESSION BY DAY AND TREATMENT GROUP

TREATMENT GROUP	DAY 0	DAY 7	DAY 14
1x	2/6		
3x	3/6	3/6	1/6
5x	1/6	3/6	
10x	1/4	3/4	

Ataxia was exhibited as depicted below. All dogs returned to normal by the following observation.

ATAxia BY DAY AND TREATMENT GROUP

	DAY 0	DAY 7	DAY 14	DAY 21	DAY 56
1x	2/6				
3x	2/6	4/6	3/6		1/6
5x	5/6	3/6	2/6		
10x	2/4	4/4	2/4	1/4	

Tremors were exhibited in 1/6 and 1/4 dogs in the 1x and 10x treatment groups, respectively on day 0. All dogs returned to normal by the following observation.

Conclusions: (S)-Methoprene capsules caused clinical signs including depression, ataxia and tremors when administered at 1X, 3X, 5X and 10X the recommended dose in 6 week old puppies. (S)-Methoprene caused depression and ataxia when administered at 3X, 5X and 10X the recommended dose in 7 week old puppies; depression when administered at 3X the recommended dose in 8 week old puppies and ataxia when administered at 3X, 5X and 10X the recommended dose in 8 week old puppies. By day 21 of the study, when the puppies were 9 weeks of age, one puppy in the 10X group experienced ataxia.

(S)-Methoprene capsules (22 mg/kg), administered up to 5X the recommended dose, are safe for administration to puppies, 9 weeks of age and older and 4 pounds body weight or greater.

B. REPRODUCTIVE SAFETY:

Title: A Domestic Animal Safety Study (1-Generation Reproduction) of (S)-Methoprene in the Dog via Capsule Administration.

Purpose: To determine the safety of (S)-Methoprene administration in breeding male and female dogs at 3X the recommended dose.

Investigator/Study location: Steve Godin, Ph.D., DABT
 Director of Toxicology
 White Eagle Toxicology Laboratories, Inc.
 Doylestown, PA

Animals: 52 Beagle dogs (20 males and 32 females), approximately 2-8 years of age, 9.7-15.6 kg body weight. Groups 1-2 (10 males and 16 females/group)

Dosage Groups: Group 1: Negative control (untreated)
 Group 2: 3X (66 mg/kg (S)-Methoprene)

Route of Administration: orally

Frequency of Treatment: (S)-Methoprene administered weekly through weaning (mated males and 10 females) or up to parturition (unmated males and 6 unmated females)

Duration of Study: approximately 7 months

Study Design: Group 1 (10 males, 16 females) served as the untreated control and received diet only. Group 2 (10 males, 16 females) was administered 3X the recommended dose of (S)-Methoprene weekly for 12 weeks. Following the administration of the test article for 12 weeks, 10 females each from Groups 1 and 2 were mated to 10 males from the same treatment group as they came into estrus. Weekly dosing continued during gestation, parturition and weaning. The 6 unmated females and males in Group 2 were administered (S)-Methoprene at 3X the recommended dose weekly until all of the mated females delivered litters.

Parameters measured:

Adult males and females: Physical examinations prior to mating and at study conclusion. Body weights were measured one week prior to treatment initiation, on the day prior to treatment initiation, and weekly during the study. Observations were made twice daily for pharmacological and/or toxicological effects. Blood specimens were collected for hematology and clinical chemistry at pretest, prior to mating, and at the conclusion of the study.

Pups: Physical examinations within 24 hours of birth and weekly during the 6-week lactation period. Pup weights were recorded within 24 hours after whelping and weekly during the 6-week lactation period. Litters were observed within 24 hours of whelping and twice daily thereafter for pharmacological and/or toxicological effects. The numbers of live and dead pups were recorded weekly starting on day 0 until the end of lactation.

Semen collection and evaluation: Semen was collected and evaluated at pretest and within the female estrous cycle prior to the initiation of mating. The following parameters were recorded: volume, color, motility, total sperm counts, pH, and morphology.

Results: There were no adverse effects on body weight, food consumption, clinical pathology (hematology/serum chemistry) or semen analyses and no reported adult deaths. Nine of 72 pups in Group 1 and 13 of 76 pups in Group 2 died prior to weaning. The puppy deaths in both groups were attributed to other causes (stillborn, maternal neglect, prematurity, peritonitis, and pulmonary edema) and were not considered drug related. One clinical observation was drug related; discolored feces (green), observed in the (S)-Methoprene group, were associated with the gelatin colored capsules administered.

Conclusions: (S)-Methoprene capsules (22 mg/kg), administered up to 3X the recommended dose, are safe for administration to male and female breeding dogs.

C. COMBINATION FLEA ADULTICIDE STUDY

Title: A Study to Determine the Safety of (S)-Methoprene Capsules at 5X the Recommended Dose in Combination with Commercial Flea Adulticides in Beagle Puppies.

Purpose: To determine the safety of (S)-Methoprene administration at 5X the recommended dose in combination with commercial flea adulticides.

Investigator/Study Location: Steve Godin, Ph.D., DABT
Director of Toxicology
White Eagle Toxicology Laboratories, Inc.
Doylestown, PA

Animals: 24 Beagle dogs (12 males and 12 females), approximately 6-10 weeks of age, 2.8-8.6 lbs. body weight. Groups 1-4 (3 males and 3 females/group)

Dosage Groups: Phase I: Group 1: Frontline Top Spot (fipronil)
Group 2: Top Paw shampoo (permethrin/piperonyl butoxide)
Group 3: Derma Dip (phosmet)
Group 4: Zodiac Flea collar (carbaryl)
Phase II: Group 1: Frontline Top Spot and 5X (S)-Methoprene
Group 2: Top Paw shampoo and 5X (S)-Methoprene
Group 3: Derma Dip and 5X (S)-Methoprene
Group 4: Zodiac Flea collar and 5X (S)-Methoprene

Route of Administration: (S)-Methoprene was administered orally and the commercial flea adulticides were applied topically, according to label instructions

Frequency of Treatment: Phase I: Each group received the respective flea adulticide according to label instructions for 2 weeks. A one-week washout period followed Phase I.

Phase II: (S)-Methoprene at a 5X oral dose was administered once weekly for 4 weeks in combination with the flea adulticide.

Duration of Study: 7 weeks

Parameters Measured: Physical examinations were conducted on all animals prior to dosing and at study conclusion. Body weights were measured prior to acclimation, on the day prior to treatment initiation, and weekly during the study. Food consumption was recorded daily starting at acclimation through study completion. Observations were made twice daily for signs of pharmacological and/or toxicological effects. Blood was collected for clinical pathology (hematology/serum chemistry) analyses during phases I and II as illustrated below:

BLOOD COLLECTION DAYS (PHASES I AND II)

Group	PHASE I		Washout Period	PHASE II
	Treatment Type	Clinical Pathology Samples		Clinical Pathology Samples
1	Frontline Top Spot	Days 4 and 9	Days 21-27	Day 50
2	Top Paw	Days 4 and 16	Days 21-27	Day 50
3	Derma-Dip	Days 4 and 16	Days 21-27	Day 50
4	Zodiac Collar	Days 4 and 21	Days 21-27	Day 50

Results: There were no adverse effects on body weight, food consumption, clinical pathology (hematology/serum chemistry) and no reported deaths.

Conclusions: (S)-Methoprene capsules (22 mg/kg), administered up to 5X the recommended dose, are safe for administration in combination with commercially available flea adulticides.

VI. HUMAN SAFETY:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in dogs, which are not food animals.

Human Warnings are provided on the product label as follows: "Not for human use. Keep this and all drugs out of the reach of children."

VII. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that ZODIAC® FLEATROL™ FLEA CAPS™ and HARTZ® Flea Control Capsules™, when used under the labeled conditions of use, are safe and effective.

Because adequate directions for the safe and effective lay use of ZODIAC® FLEATROL™ FLEA CAPS™ and HARTZ® Flea Control Capsules™ could be written, the products have been labeled for over-the-counter distribution.

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

Wellmark International patent pending in the U.S.

VIII. LABELING (attached)

I. ZODIAC® FLEATROL™ FLEA CAPS™

- A. Package Insert
- B. Carton
- C. Blister Pack

II. HARTZ® Flea Control Capsules™

- A. Package Insert
- B. Carton
- C. Blister Pack



INTRODUCTION:

Controlling fleas is important to the health of your dog. ZODIAC® FleaTrol™ Flea Caps™ are a weekly medication that works by preventing flea eggs from hatching and developing into biting adults that can harm your dog. We encourage you to read this information thoroughly before administering the ZODIAC FleaTrol Flea Caps to your dog.

DESCRIPTION:

ZODIAC FleaTrol Flea Caps are available in 5 color-coded capsules for dogs and puppies, according to their weight (See DOSAGE section). Each capsule is formulated to provide a minimum of 10 mg per pound (22 mg/kg) body weight of (S)-Methoprene. The active ingredient of ZODIAC FleaTrol Flea Caps is (S)-Methoprene with the following chemical composition: *isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate*. (S)-Methoprene is an Insect Growth Regulator (IGR) which does not kill the adult flea but controls flea populations by breaking the life cycle at the egg stage.

INDICATIONS:

ZODIAC FleaTrol Flea Caps are indicated for use in dogs, 9 weeks of age and older and 4 pounds body weight or greater, for the prevention and control of flea populations. (S)-Methoprene prevents and controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.

HUMAN WARNINGS:

Not for human use. Keep this and all other medications out of reach of children.

PRECAUTIONS:

Do not use in puppies less than 9 weeks of age or in dogs and puppies weighing less than 4 pounds.

ZODIAC FleaTrol Flea Caps have no effect on adult fleas but act to break the flea life cycle by preventing eggs from developing into adults.

However, pre-existing fleas in the dog's environment may continue to develop and emerge as adults after treatment with ZODIAC FleaTrol Flea Caps. Based on results of clinical studies, this emergence generally occurs during the first 30-60 days. Therefore, noticeable control may not be observed until several weeks after dosing when a pre-existing infestation is present. In cooler climates, immature fleas may take longer to complete the life cycle and emerge as adults.

If a ZODIAC FleaTrol treated dog comes in contact with a flea-infested environment, adult fleas may infest the treated animal. These adult fleas are unable to produce viable offspring. Depending on the severity of infestation, the concurrent use of insecticidal products that kill adult fleas may be used.

ADVERSE REACTIONS:

The following adverse reactions have been reported after giving ZODIAC FleaTrol Flea Caps: vomiting, diarrhea, lethargy/depression, nervousness and loss of balance.

DOSAGE:

ZODIAC FleaTrol Flea Caps are administered orally, once a week, at the recommended minimum dosage of 10 mg (S)-Methoprene per pound (22 mg/kg) of body weight. This product is dosed according to your dog's weight. Be sure to weigh your dog before treatment to ensure proper dosage.

RECOMMENDED DOSAGE SCHEDULE

Body Weight	Dose and Capsule Color	(S)-Methoprene per Capsule
4 to 15 lbs.	1 Green Capsule	154 mg
16 to 30 lbs.	1 Red Capsule	308 mg
31 to 45 lbs.	1 Lavender Capsule	462 mg
46 to 60 lbs.	2 Blue Capsules	308 mg
61 to 90 lbs.	2 Brown Capsules	462 mg
91 to 135 lbs.	3 Brown Capsules	462 mg
136 to 180 lbs.	4 Brown Capsules	462 mg

ADMINISTRATION:

ZODIAC FleaTrol Flea Caps can be offered to your dog a variety of ways. Place the entire unopened capsule securely inside a treat. You may also administer ZODIAC FleaTrol Flea Caps without using a treat. Open your pet's mouth wide and place the capsule as far back into the center of the tongue as possible. Gently close your pet's mouth and encourage swallowing through praise and petting underneath the jawline.

1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32" 1-1/32"

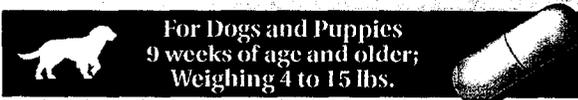
12 Week Supply

ZODIAC.
FLEATROL™
FLEA CAPS™
(S)-Methoprene

For Dogs and Puppies 9 weeks of age and older; Weighing 4 to 15 lbs.



Weekly Treatment for the PREVENTION and CONTROL of Flea Populations



NET CONTENTS: 12 CAPSULES,
154 MG EACH

CONTAINS: (S)-Methoprene: 154 mg per capsule
KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

OPEN OTHER END

Tamper resistant inner unit. If foil seal is broken or torn, do not use.

Expiration Date and Lot #:

OPEN HERE

For Dogs and Puppies 9 weeks of age and older; Weighing 4 to 15 lbs.

ZODIAC.
FLEATROL™
FLEA CAPS™
(S)-Methoprene

ZODIAC.
FLEATROL™
FLEA CAPS™
(S)-Methoprene

For Dogs and Puppies 9 weeks of age and older; Weighing 4 to 15 lbs.



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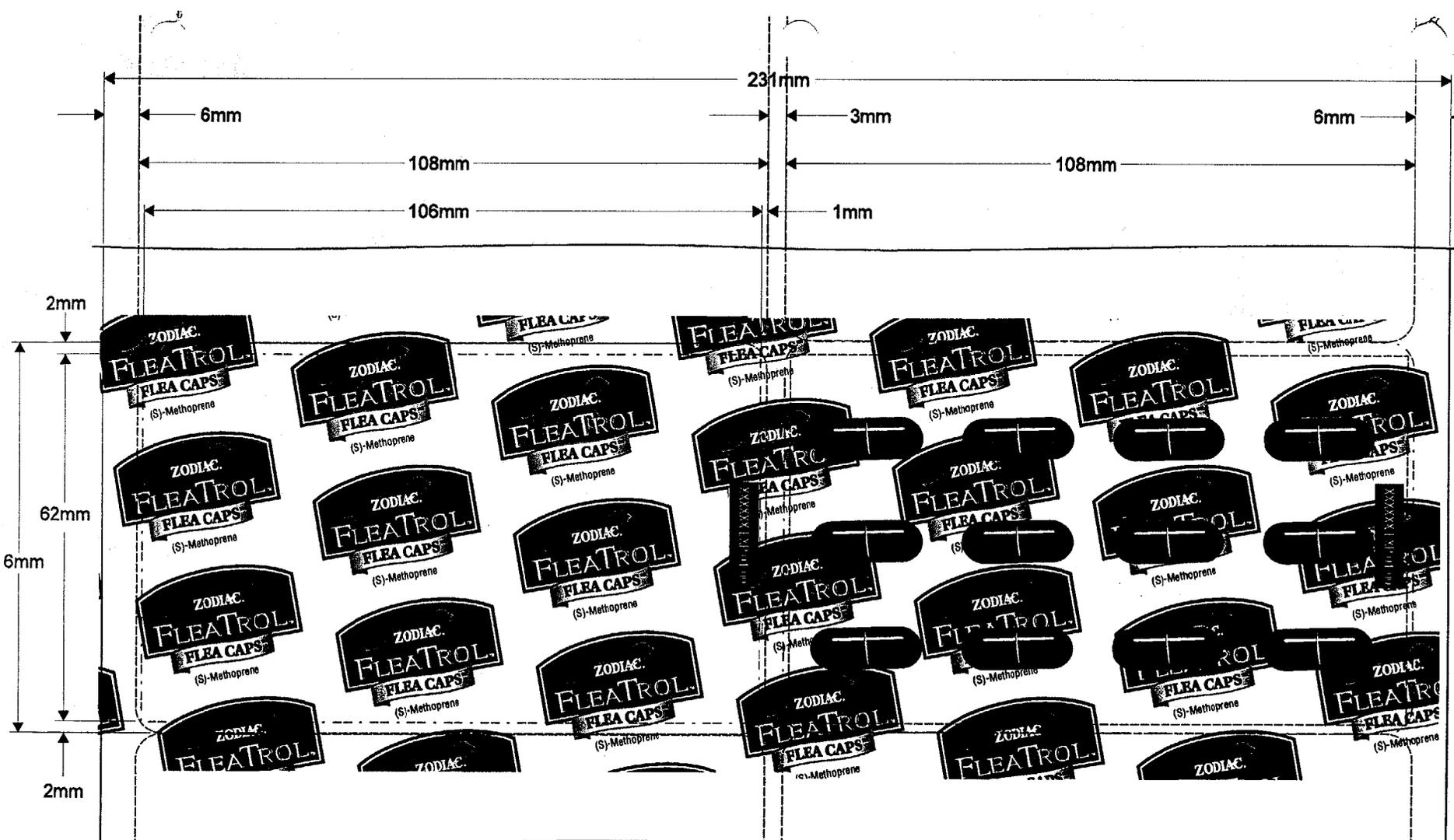


Manufactured for Wellmark International, Bensenville, IL 60106. Visit our Web site, www.zodiapet.com. To report adverse reactions or for additional information call 1-800-950-4783.

IMPORTANT DIRECTIONS FOR USE
• ZODIAC® Fleatrol™ Flea Caps™ should be administered directly or wrapped with your dog's favorite treat. If your dog will not swallow the capsule, gently pull apart the capsule to open it, and mix the contents from the capsule into a small amount of wet food.
• ZODIAC Fleatrol Flea Caps have no effect on adult fleas, but control flea populations by breaking the flea life cycle at the egg stage.
• Treatment may begin at any time of the year. In geographic regions where fleas are seasonal, treatment should begin several weeks before the flea season and continue until the end of the flea season. In regions with year-round fleas, treatment should be given all year, without interruption.
* It is important to treat all dogs and/or puppies in the household according to the dosing schedule provided on the enclosed insert. Each animal should be treated separately to ensure they each receive the proper dosage. For other pets in the household, treat with flea control products appropriate for their species.
*ZODIAC Fleatrol Flea Caps must be administered weekly, preferably on the same day each week, to maximize benefits.
* If you miss a dose, administer capsules immediately and then resume your weekly dosing schedule.
The enclosed insert provides more specific directions to follow when administering ZODIAC Fleatrol Flea Caps.
To report adverse reactions or for additional information call 1-800-950-4783.
Visit our Web site, www.zodiapet.com

Weekly Treatment for the PREVENTION and CONTROL of Flea Populations





016 OF 072

SPOT COLOR	
	PMS 2765
	

HARTZ® Flea Control Capsules™

(S)-Methoprene

Introduction:

Controlling fleas is important to the health of your dog. Hartz® Flea Control Capsules™ are a weekly medication that works by preventing flea eggs from hatching and developing into biting adults that can harm your dog. We encourage you to read this information thoroughly before administering the Hartz® Flea Control Capsules™ to your dog.

Description:

Hartz® Flea Control Capsules™ are available in 5 color-coded capsules for dogs and puppies, according to their weight (See DOSAGE section). Each capsule is formulated to provide a minimum of 10 mg per pound (22 mg/kg) body weight of (S)-Methoprene. The active ingredient of Hartz® Flea Control Capsules™ is (S)-Methoprene with the following chemical composition: *isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate*. (S)-Methoprene is an Insect Growth Regulator (IGR) which does not kill the adult flea but controls flea populations by breaking the life cycle at the egg stage.

Indications:

Hartz® Flea Control Capsules™ are indicated for use in dogs, 9 weeks of age and older and 4 pounds body weight or greater, for the prevention and control of flea populations. (S)-Methoprene prevents and controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.

Human Warnings:

Not for human use. Keep this and all other medications out of reach of children.

Precautions:

Do not use in puppies less than 9 weeks of age or in dogs and puppies weighing less than 4 pounds.

Hartz® Flea Control Capsules™ have no effect on adult fleas but act to break the flea life cycle by preventing eggs from developing into adults. However, pre-existing fleas in the dog's environment may continue to develop and emerge as adults after treatment with Hartz® Flea Control Capsules™. Based on results of clinical studies, this emergence generally occurs during the first 30-60 days. Therefore, noticeable control may not be observed until several weeks after dosing when a pre-existing infestation is present. In cooler climates, immature fleas may take longer to complete the life cycle and emerge as adults.

If a Hartz® Flea Control Capsules™ treated dog comes in contact with a flea-infested environment, adult fleas may infest the treated animal. These adult fleas are unable to produce viable offspring. Depending on the

severity of infestation, the concurrent use of insecticidal products that kill adult fleas may be used.

Adverse Reactions:

The following adverse reactions have been reported after giving Hartz® Flea Control Capsules™: vomiting, diarrhea, lethargy/depression, nervousness and loss of balance.

Dosage:

Hartz® Flea Control Capsules™ are administered orally, once a week, at the recommended minimum dosage of 10 mg (S)-Methoprene per pound (22 mg/kg) of body weight. This product is dosed according to your dog's weight. Be sure to weigh your dog before treatment to ensure proper dosage.

Recommended Dosage Schedule

Body Weight	Dose and Capsule Color	(S)-Methoprene per Capsule
4 to 15 lbs.	1 Green Capsule	154 mg
16 to 30 lbs.	1 Red Capsule	308 mg
31 to 45 lbs.	1 Lavender Capsule	462 mg
46 to 60 lbs.	2 Blue Capsules	308 mg
61 to 90 lbs.	2 Brown Capsules	462 mg
91 to 135 lbs.	3 Brown Capsules	462 mg
136 to 180 lbs.	4 Brown Capsules	462 mg

Administration:

Hartz® Flea Control Capsules™ can be offered to your dog a variety of ways. Place the entire unopened capsule securely inside a treat. You may also administer Hartz® Flea Control Capsules™ without using a treat. Open your pet's mouth wide and place the capsule as far back into the center of the tongue as possible. Gently close your pet's mouth and encourage swallowing through praise and petting underneath the jaw line.



HARTZ[®] Flea Control Capsules™

((S)-Methoprene)



Another alternative is to place a small amount of moist food into your dog's bowl, gently pull apart the capsule to open it and pour the contents directly onto the food. Mix well and serve to your dog. If you use this method, make sure that your dog consumes all of the food that you have mixed with the medication. If you have multiple dogs or puppies, make sure that each pet is fed separately to ensure they each receive the proper dosage. You may notice a change in the color of your dog's feces due to the coloring in the capsules. This has no effect on the safety and efficacy of the product.



Hartz[®] Flea Control Capsules™ must be administered weekly, preferably on the same day each week, to maximize benefits. If you miss a weekly dose, administer Hartz[®] Flea Control Capsules™ immediately and resume your weekly schedule. To maximize results, it is important to treat all dogs and/or puppies in the household. Untreated animals may develop fleas, which reduce the overall flea control within a given household.

Fleas on Your Dog:

Fleas can live on your dog and develop in your home and in your yard. They feed on your dog's blood, mate with other fleas, and lay thousands of eggs that fall off your dog and survive in their surroundings. The eggs hatch and grow into biting adults within just a few weeks. The bite of the flea may cause intense itching that causes your dog to scratch incessantly. Flea allergy dermatitis can develop from flea bites and can cause darkening and crusting of the skin and lead to hair loss and skin abrasions. Additionally, fleas transmit tapeworms and severe cases of fleas can lead to life-threatening anemia.

The Flea Life Cycle:

It is important to understand the life stages of the flea life cycle in order to control and prevent flea populations on your dog. One of the most difficult aspects to controlling fleas is the flea's capacity to reproduce. A single female flea may lay over a thousand eggs in a lifetime. Here is how (S)-Methoprene breaks the flea life cycle:



ADULT FLEAS:

After biting a Hartz[®] Flea Control Capsules™ treated dog, the female adult flea ingests a blood meal containing (S)-Methoprene which is deposited in her eggs.

FLEA EGGS:

(S)-Methoprene prevents those flea eggs from hatching.

FLEA LARVAE:

By preventing flea eggs from hatching, larvae production is stopped.

FLEA PUPAE:

By preventing flea eggs from hatching, pupae production is stopped. Over a period of time, you will find that flea populations in your home are controlled.

When a dog or puppy that is being treated with Hartz[®] Flea Control Capsules™ enters a flea-infested area, the dog may become temporarily reinfested. You may need to treat your dog and home with other flea control products to kill existing adult flea populations.

How do you know if your dog has a flea problem?

Adult fleas are about the size of a dark brown sesame seed and flattened from side to side. Their hind legs are extremely powerful and they use this jumping ability to leap onto a passing dog.

The "Flea Dirt" Test: You can easily check your dog for fleas:



1 Put white paper towels on the floor, under your pet. Have your dog sit or lay down.

2 Vigorously scruff up the hair on the neck, stomach area and the rump just above the tail.

3 Remove your dog and look for what appears to be "black pepper".

4 Dampen the paper towel containing the "black pepper". If it turns to a dark red color, your dog probably has fleas. This black pepper-like substance is "flea dirt" (which is actually dried blood), left by fleas biting your dog. Live fleas can often be spotted on the inside fold of the back legs where the body temperature is warmest.

Storage Conditions:

Store at room temperature; avoid excessive heat (40° C; 104° F).

How Supplied:

Hartz[®] Flea Control Capsules™ are available in five packages (see dosage section), formulated and color-coded according to weight of the dog. Each dose is available in color-coded packages of 8 or 16 capsules each.

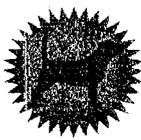
Manufactured by ©The Hartz Mountain Corporation, 400 Plaza Drive, Secaucus, NJ 07094 and St. Thomas Ontario, N5P 3W7, Canada.

NADA #141-462, Approved by FDA

RM136879 555118

For Dogs and Puppies
9 Weeks of Age or Older;
Weighing 4 to 15 lbs.

HARTZ® Flea Control Capsules™
(S)-Methoprene



HARTZ®

Flea Control Capsules™
(S)-Methoprene

Weekly treatment for
the **PREVENTION** and
CONTROL of Flea Populations

For Dogs and Puppies 9 Weeks of Age or Older;
Weighing 4 to 15 lbs.

Contains: (S)-Methoprene: 154 mg per capsule
KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.
8 WEEK SUPPLY; NET CONTENTS: 8 CAPSULES, 154 MG EACH



HARTZ® Flea Control Capsules™
(S)-Methoprene
For Dogs and Puppies 9 Weeks of Age or Older; Weighing 4 to 15 lbs.

HARTZ®
Open Here

Tamper resistant inner unit.
If foil seal is broken or torn, do not use.
Open other end

EXP. MM/YY
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EXPIRATION DATE
& LOT CODE WILL
BE EMBOSSED ON
THE MANUFACTURING LINE

HARTZ® Flea Control Capsules™
(S)-Methoprene
For Dogs and Puppies 9 Weeks of Age or Older;
Weighing 4 to 15 lbs.

Manufactured by
The Hartz Mountain Corporation
400 Plaza Drive, Secaucus, NJ 07094
Canada
NADA #141-462, approved by FDA

VISIT OUR WEBSITE
WWW.HARTZ.COM
HARTZ® Every Pet's Best Friend™

To report adverse reactions
or for additional information
call 1-800-275-1414

For Dogs 4 to 15 lbs.
Most Popular Breeds
(at maturity)
Chihuahua
Yorkshire Terrier
Pekingese
Maltese
Pomeranian
Toy Poodle
Puppies of other breeds
Be sure to weigh your dog or puppy
to ensure proper dosage.
Also available in additional package
sizes for other weight ranges.

IMPORTANT DIRECTIONS FOR USE

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● Hartz® Flea Control Capsules™ have no effect on adult fleas, but control flea populations by breaking the flea life cycle at the egg stage.

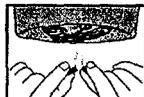
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● Hartz® Flea Control Capsules™ must be administered weekly, preferably on the same day each week, to maximize benefits.

● If you miss a dose, administer capsules immediately and then resume your weekly dosing schedule.

The enclosed insert provides more specific directions to follow when administering Hartz® Flea Control Capsules™.



For Dogs and Puppies
9 Weeks of Age or Older;
Weighing 4 to 15 lbs.

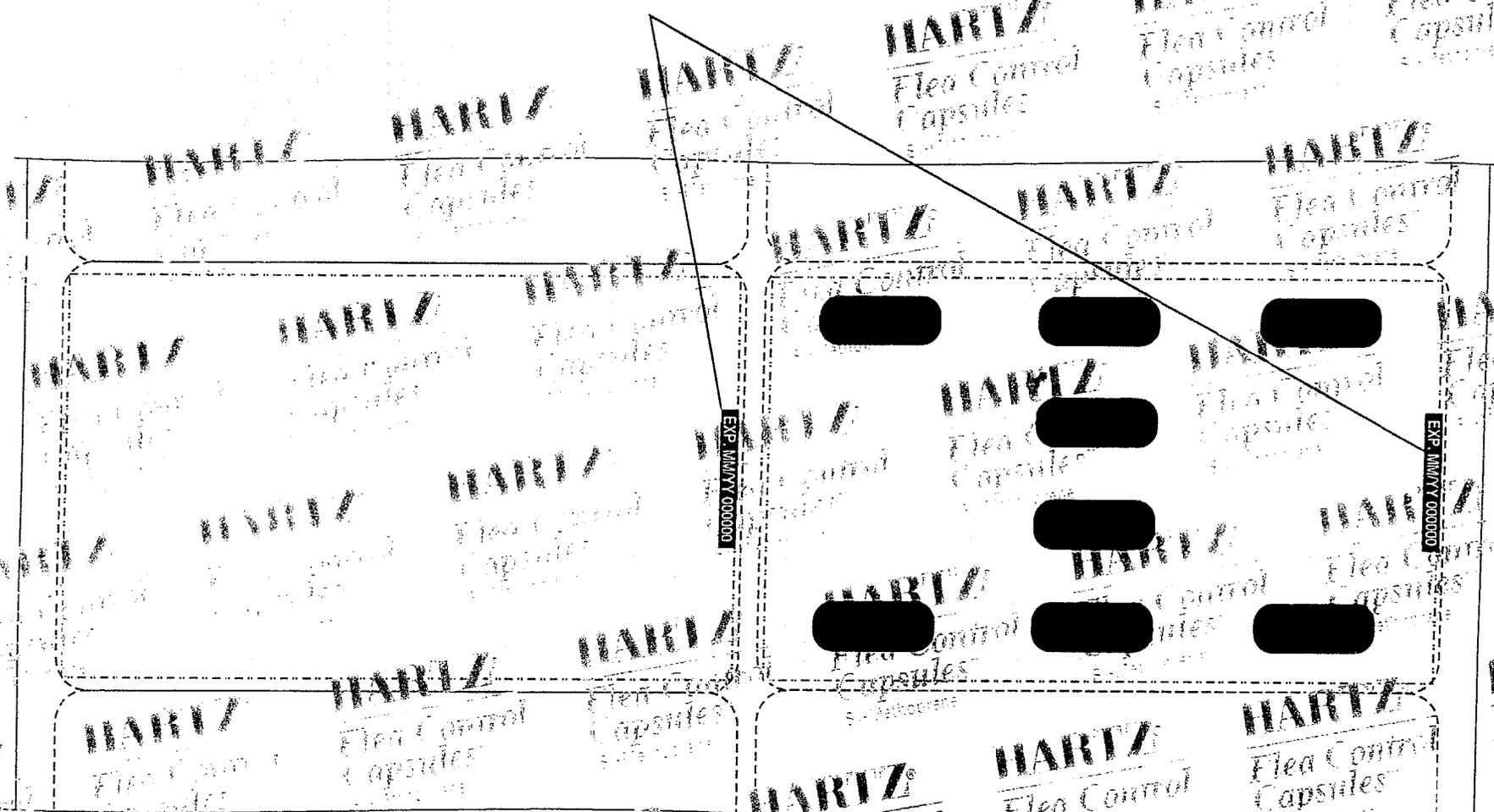
Weekly treatment for the **PREVENTION**
and **CONTROL** of Flea Populations

Flea Control Capsules™
(S)-Methoprene

HARTZ®

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EXPIRATION DATE
& LOT CODE WILL
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THE MANUFACTURING LINE



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