Date of Approval: February 15, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-257

IVERHEART MAX Chewable Tablets

Ivermectin, pyrantel pamoate, praziquantel
Chewable Tablet
Dogs

This supplement provides for removal of the following statement from the Precautions section of the package insert: "The effective use of this drug for the treatment and control of tapeworms has not been evaluated in dogs less than 15 pounds."

Sponsored by:

Virbac AH, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-257

B. Sponsor: Virbac AH, Inc.
3200 Meacham Blvd.
Ft. Worth, TX 76137

Drug Labeler Code: 051311

C. Proprietary Name(s): IVERHEART MAX Chewable Tablets

D. Established Name(s): Ivermectin, pyrantel pamoate, praziquantel

E. Pharmacological Category: Antiparasitic

F. Dosage Form(s): Chewable Tablets

G. Amount of Active Ingredient(s):

Tablet Size	Ivermectin Content	Pyrantel Pamoate Content	Praziquantel Content	Color Coding on Carton
Toy	34 mcg	28.5 mg	28.5 mg	Magenta
Small	68 mcg	57 mg	57 mg	Blue
Medium	136 mcg	114 mg	114 mg	Green
Large	272 mcg	228 mg	228 mg	Brown

H. How Supplied: Each of the four dosage strengths comes in boxes of 6 and 12 chewable tablets packed 10 boxes per display box.

I. How Dispensed: Rx

J. Dosage(s):

Weight (lbs)	Tablet Size	Tablet per Month
6.0 to 12	Toy	1
12.1 to 25	Small	1
25.1 to 50	Medium	1
50.1 to 100	Large	1
Greater than 100	Use the appropriate combination of tablets	

K. Route(s) of Administration: Oral

L. Species/Class(es): Dogs

M. Indication(s): For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of roundworms *(Toxocara canis, Toxascaris leonina)*, hookworms *(Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense)*, and tapeworms (*Dipylidium caninum*, *Taenia pisiformis*).

N. Effect(s) of Supplement: This supplement provides for removal of the following statement from the Precautions section of the package insert: "The effective use of this drug for the treatment and control of tapeworms has not been evaluated in dogs less than 15 pounds."

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The FOI Summary for the original approval of NADA 141-257 dated October 13, 2006, contains dosage characterization information for dogs.

The minimum dose of 5 mg/kg praziquantel for dogs weighing 25 pounds or greater is supported by published literature[1,2]. The minimum dose of 5 mg/kg praziquantel for smaller dogs is supported by the laboratory effectiveness and dose confirmation study listed under Substantial Evidence.

B. Substantial Evidence:

1. Laboratory Effectiveness and Dose Confirmation Study

<u>*D. caninum* Dose-confirmation study in dogs weighing less than 15 pounds:</u>

1 Georgi JR. Tapeworms. *Veterinary Clinics of North America: Small Animal Practice* 1987;17(6):1285-1305.

2 Dey-Hazra A. The efficacy of DRONCIT (Praziquantel) against Tapeworm Infections in Dog and Cat. *Vet Med Rev* 1976;2:131-141.

a) Purpose:	Confirm the effectiveness of the three-way combination of ivermectin, pyrantel pamoate, and praziquantel for the treatment of tapeworm (*D. caninum*) infection in dogs weighing less than 15 pounds.
b) Investigator:	Dawie J. Kok, D.Sc.
c) Study location:	ClinVet International (Pty) Ltd Bloemfontein Republic of South Africa
d) Animals:	5 male and 11 female dogs, of various breeds, weighing 5.61 to 11.77 pounds, naturally infected with *D. caninum*
e) Groups:	Group 1 (n = 8): placebo Group 2 (n = 8): ivermectin 6 mcg/kg, pyrantel pamoate 5 mg/kg and praziquantel 5 mg/kg
f) Statistical methods:	Log worm counts for the treatment group were compared to log worm counts for the control group by means of an analysis of variance contrast. Percent effectiveness was computed as: $\frac{\text{(control GM - treated GM)}}{\text{control GM}} \times 100$ where GM = geometric mean worm count
g) Study design:	Day -10: applied flea adulticide to all dogs to prevent re-infection with *D. caninum* Day -2: allocation to a treatment group Day 0: treatment Day 14: necropsy (worm counts)
h) Study results:	Group 1: 8 dogs with *D. caninum* GM = 10.27 (range: 1-164) Group 2: 0 dogs with tapeworms GM = 0 Group 2 Vs. Group 1* - Effectiveness: 100% *statistically significant, $\alpha = 0.05$
i) Conclusion:	Effectiveness of the three-way combination against *D. caninum* infection in dogs weighing less than 15 pounds was demonstrated.

j) Adverse reactions: Six dogs (four from the treated group) had diarrhea before treatment, and 7 dogs (four from the treated group) had isolated episodes of diarrhea up to 7 days after treatment.

One dog treated with IVERHEART MAX Chewable Tablets developed diarrhea on Day 5. Following a post-mortem examination on Day 10, a diagnosis of canine distemper virus infection was made. Immunoperoxidase stain was positive for canine distemper viral antigen in the brain, lung, pancreas, and lymph node tissue sections examined by the pathologist. The infection was not treatment-related.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-257 dated October 13, 2006, contains a summary of target animal safety studies for dogs.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to IVERHEART MAX Chewable Tablets:

Human Warnings are provided on the product label as follows: "**For use in animals only. Keep out of reach of children.** In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a poison control center for advice concerning cases of ingestion by humans."

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that IVERHEART MAX Chewable Tablets, when used according to the label, are safe and effective for preventing canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of roundworms (*Toxocara canis*, *Toxascaris leonina*), hookworms

(*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*), and tapeworms (*Dipylidium caninum*, *Taenia pisiformis*).

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise and proper diagnosis are required to determine the existence of heartworm infections and to monitor the safe use of the product.

B. Exclusivity

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the removal of the following label statement: "Precaution: The effective use of this drug for the treatment and control of tapeworms has not been evaluated in dogs less than 15 pounds," for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(1)).

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:
Package insert

cc: Document Control Unit, for the administrative file of:
N-141257-C-0004-B1
Courtesy copy for the sponsor
HFV-12, FOI Staff
HFA-305, Division of Dockets Management

Other administrative information: Not applicable

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