Date of Approval: December 11, 2017

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-441

IVERHART MAX® Soft Chew

Ivermectin/pyrantel pamoate/praziquantel

Chewable Tablet

Dogs

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).*

Sponsored by:

Virbac AH, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-441

B. Sponsor

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

Drug Labeler Code: 051311

C. Proprietary Name

IVERHART MAX® Soft Chew

D. Product Established Name

Ivermectin/pyrantel pamoate/praziquantel

E. Pharmacological Category

Anthelmintic

F. Dosage Form

Chewable Tablet

G. Amount of Active Ingredient

Soft Chew Size	Ivermectin Content	Pyrantel Pamoate Content	Praziquantel Content	Color Coding on Carton
Toy	34 mcg	28.5 mg	28.5 mg	Purple
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

IVERHART MAX® Soft Chew is available in four dosage strengths for dogs of different weights. Each strength comes in a package of 6 soft chews.

I. Dispensing Status

Rx

J. Dosage Regimen

IVERHART MAX® Soft Chew should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb), 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) and 5 mg of praziquantel per kg (2.27 mg/lb) of body weight, as follows:

Dog Weight Pounds	Soft Chew per Month	Soft Chew Size	Ivermectin Content	Pyrantel Pamoate Content	Praziquantel Content
6.0 to 12	1	Toy	34 mcg	28.5 mg	28.5 mg
12.1 to 25	1	Small	68 mcg	57 mg	57 mg
25.1 to 50	1	Medium	136 mcg	114 mg	114 mg
50.1 to 100	1	Large	272 mcg	228 mg	228 mg

IVERHART MAX® Soft Chew is recommended for dogs 8 weeks of age or older. For dogs over 100 lbs, use the appropriate combination of these soft chews.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

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*).

II. EFFECTIVENESS

A. Dosage Characterization

The minimum dosage of 6 mcg/kg ivermectin, 5 mg/kg pyrantel (as pamoate salt), and 5 mg/kg praziquantel in dogs weighing 6 lbs or greater is supported by data contained in NADA 141-257 for IVERHART MAX® Chewable Tablets (ivermectin/pyrantel pamoate/praziquantel).

B. Substantial Evidence

1. Gastrointestinal Nematodes

   IVERHART MAX® Chewable Tablets (ivermectin/pyrantel pamoate/praziquantel) are approved for the treatment and control of roundworms (*Toxocara canis, Toxascaris leonina*) and hookworms

(*Ancylostoma caninum, Uncinaria stenocephala, Anyclostoma braziliense*) in dogs. Refer to the Freedom of Information (FOI) summary for IVERHART MAX® Chewable Tablets (NADA 141-257) for the effectiveness studies used to support substantial evidence of effectiveness for these indications. To demonstrate that IVERHART MAX® Soft Chew is effective for the same gastrointestinal nematode indications as IVERHART MAX® Chewable Tablets, two studies were conducted with IVERHART MAX® Soft Chew using the dose-limiting parasite (*Toxocara canis*).

a. Laboratory Dose Confirmation Study with an experimental infection of roundworms (*Toxocara canis*) in dogs:

Title: Dose Confirmation Study with Investigational Veterinary Product (IVP) 595.71 (Flavored Ivermectin/Pyrantel Pamoate/Praziquantel Soft Chew) for the Treatment of Experimental Infection with Roundworm (*Toxocara canis*) in Dogs. Study No. U-595.71/60011-10

Study Dates: May 2011 to November 2011

Study Location: Sugar Land, TX

Study Design:

Objective: Confirm the effectiveness of pyrantel pamoate at 2.3 – 4.8 mg/kg of body weight for the treatment of an experimental infection of *T. canis* in dogs when given in combination with ivermectin and praziquantel in a soft chew formulation (IVERHART MAX® Soft Chew).

The study was conducted using the principles of Good Clinical Practices (GCP).

Study Animals: Sixteen mixed-breed mongrels (9 males and 7 females) of varying age and body weight.

Treatment Groups:

Table 1. Treatment Groups

Treatment Group	Treatment	Frequency/ Duration	Number and Gender of Dogs
1	IVERHART MAX® Soft Chew (ivermectin, pyrantel pamoate, praziquantel)	Once on Day 0	8 (5M, 3F)
2	Untreated control group	Untreated	8 (4M, 4F)

Measurements and Observations: On Day -49, all dogs were inoculated with 300 embryonated eggs of *T. canis* per mouth. All dogs had a positive average *T. canis* fecal egg count on Days -3 to -1.

The primary variable was effectiveness against adult *T. canis* in experimentally-infected dogs, based on comparing post-treatment worm count reduction between the treated and control groups. Animal health observations made once daily during the treatment period (Day 0 to Day 7) and treatment day observations hourly for the first four hours post-dosing were used to evaluate the occurrence of adverse reactions associated with treatment.

Statistical analysis: For each dog, the total count of *T. canis* was transformed to the natural logarithm of (counts+1). A percent effectiveness was calculated using the geometric means. In addition, an unequal variance and two-sided t-test with $\alpha = 0.05$ was used to test the difference of the natural-log-transformed total count of *T. canis* between the two groups.

Results:

All sixteen dogs completed the study and were euthanized and necropsied on Day 7. Seven of the eight dogs in the control group had at least five adult *T. canis* worms present at necropsy (range = 1 – 21), confirming adequacy of infection. The IVERHART MAX® Soft Chew treated groups demonstrated a significant reduction ($p < 0.0001$) in the number of *T. canis* adults when compared to the control group. Dogs in the control group had a geometric mean adult worm count of 11.8 compared to 0.2 in the IVERHART MAX® Soft Chew treatment group. The combination product demonstrated 98.4% post-treatment effectiveness against *T. canis.*

Adverse Reactions:

There were no adverse reactions during the study.

Conclusions:

A single dose of IVERHART MAX® Soft Chew was effective against experimental infections of adult *T. canis* in dogs.

b. Laboratory Dose Confirmation Study with a natural infection of roundworms (*Toxocara canis*) in dogs:

Title: Dose Confirmation Study with IVP 595.71 (Flavored Ivermectin/Pyrantel Pamoate/Praziquantel Soft Chew) for the Treatment of Natural Infection with Roundworm (*Toxocara canis*) in Dogs. Study No. U-595.71/60010

Study Dates: October 2010 to June 2012

Study Location: Stanwood, MI

Study Design:

Objective: Confirm the effectiveness of pyrantel pamoate at 2.3 – 4.8 mg/kg of body weight for the treatment of a natural infection of *T. canis* in

dogs when given in combination with ivermectin and praziquantel in a soft chew formulation (IVERHART MAX® Soft Chew).

The study was conducted using the principles of Good Clinical Practices (GCP).

Study Animals: Twenty healthy dogs (12 males and 8 females) of varying breeds, age, and body weight.

Treatment Groups:

Table 2. Treatment Groups

Treatment Group	Treatment	Frequency/ Duration	Number and Gender of Dogs
1	IVERHART MAX® Soft Chew (ivermectin, pyrantel pamoate, praziquantel)	Once on Day 0	10 (4M, 6F)
2	Untreated control group	Untreated	10 (8M, 2F)

Measurements and Observations: All dogs had a natural infection with *T. canis*. All dogs had a positive average *T. canis* fecal egg count on Days -3 to -1.

The primary variable was effectiveness against adult *T. canis* in naturally-infected dogs, based on comparing post-treatment worm count reduction between the treated and control groups. Animal health observations made twice daily during the treatment period (Day 0 to Day 7) and treatment day observations hourly for the first four hours post-dosing were used to evaluate the occurrence of adverse reactions associated with treatment.

Statistical Analysis: For each dog, the total count of *T. canis* was transformed to the natural logarithm of (counts+1). A percent effectiveness was calculated using the geometric means. In addition, an unequal variance and two-sided t-test with $\alpha = 0.05$ was used to test the difference of the natural-log-transformed total count of *T. canis* between the two groups.

Results:

All twenty dogs completed the study and were euthanized and necropsied on Day 7. Six of the ten dogs in the control group had at least five adult *T. canis* worms present at necropsy (range = 1 – 32), confirming adequacy of infection. The IVERHART MAX® Soft Chew treated groups demonstrated a significant reduction (p= 0.0001) in the number of *T. canis* adults when compared to the control group. Dogs in the control group had a geometric mean adult worm count of 6.9 compared to 0.37 in the IVERHART MAX®

Soft Chew treatment group. The combination product demonstrated 94.6% post-treatment effectiveness against *T. canis.*

Adverse Reactions:

There were no adverse reactions during the study.

Conclusions:

A single dose of IVERHART MAX® Soft Chew was effective against natural infections of adult *T. canis* in dogs.

2. Gastrointestinal Cestodes and the Prevention of Heartworm Disease:

IVERHART MAX® Chewable Tablets are approved for the treatment and control of tapeworms (*Dipylidium caninum* and *Taenia pisiformis*) and to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection in dogs. Refer to the FOI summary for IVERHART MAX® Chewable Tablets (NADA 141-257) for the effectiveness studies used to support substantial evidence of effectiveness for these indications. To provide a bridge to the tapeworm (*Dipylidium caninum* and *Taenia pisiformis*) and prevention of heartworm disease (*Dirofilaria immitis)* effectiveness studies conducted with IVERHART MAX® Chewable Tablets, a bioequivalence study was conducted with IVERHART MAX® Soft Chew and IVERHART MAX® Chewable Tablets.

a. Bioequivalence Study of IVERHART MAX® Soft Chew and IVERHART MAX® Chewable Tablets Formulations.

Title: Collection and Analysis of Plasma Samples for Determination of the Pharmacokinetics of Ivermectin and Praziquantel in Healthy Male Beagle Dogs Following Crossover Oral Administration of IVERHART MAX® Flavored Chews[1] and IVERHART MAX® Chewable Tablets. Study No. 963-008.

Study Dates: January 2014 to June 2014

Study Location: Mattawan, Michigan

Study Design:

Objective: This study was conducted to evaluate and characterize the pharmacokinetics of ivermectin and praziquantel in healthy male Beagle dogs following oral administration of IVERHART MAX® Soft Chew (test product) and IVERHART MAX® Chewable Tablets (reference product). The secondary objectives of the study were 1) to assess bioequivalence with respect to ivermectin and praziquantel exposure between the Reference Product (IVERHART MAX® Chewable Tablets, medium size) and Test Product 1 (IVERHART MAX® Soft Chew, medium size), and 2) to assess bioequivalence with respect to ivermectin and praziquantel exposure

[1] Note: During development, the IVERHART MAX® Soft Chew was referred to as IVERHART MAX® Flavored Chews and IVERHART MAX® Semi-Moist Chewable Tablets.

between Test Product 1 (IVERHART MAX® Soft Chew, medium size) and Test Product 2 (IVERHART MAX® Soft Chew, toy size).

The study was conducted in accordance with Good Laboratory Practices (GLP).

Study Animals: Sixty healthy male, Beagle dogs weighing 8.4 - 10.9 kg and approximately 7.5 - 8.5 months of age, were selected for the study.

Drug Administration: The study was a three-period, six-sequence (groups), three-treatment study with two crossovers and a washout period of two weeks separating dosing for each period. Each period consisted of dosing and blood collection associated with that dose. Each dog was administered one medium size IVERHART MAX® Chewable Tablets (reference), one medium size IVERHART MAX® Soft Chew (test), and one toy size IVERHART MAX® Soft Chew (test).

Measurements and Observations: Blood samples were collected from each dog pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 14, 18, 24, 36, and 48 hours post-dose. Plasma was harvested and assayed for ivermectin and praziquantel using validated analytical methods.

Determination of Bioequivalence: The extent of product bioavailability was estimated by the area under the blood concentration vs time curve ($AUC_{0\text{-}Last}$). The rate of absorption was estimated by the maximum observed drug concentration (C_{max}) and the corresponding time to reach this maximum concentration (T_{max}).

Bioequivalence for ivermectin or praziquantel was demonstrated if the 90% Confidence Interval for the ratio of the test and reference $AUC_{0\text{-}Last}$ and C_{max} fell between 0.80 to 1.25.

Results:

Tables 3 and 4 list descriptive statistics for ivermectin and praziquantel systemic exposure and pharmacokinetics parameters. The $AUC_{0\text{-}Last}$ and C_{max} are corrected for dose and body weight. T_{max} was a secondary outcome variable.

Table 3. Summary Statistics for $AUC_{0\text{-}Last}$, C_{max}, and T_{max} Pharmacokinetic Parameters for Ivermectin (Dose Corrected Values)

Parameter	Treatment	N†	Mean*	Std Dev+	Minimum	Maximum
$AUC_{0\text{-}Last}$, ng*hour/mL	Chewable tablet, medium	60	7.2	2.1	1.1	12.8
$AUC_{0\text{-}Last}$, ng*hour/mL	Soft chew, medium	60	9.5	2.1	2.2	13.8
$AUC_{0\text{-}Last}$, ng*hour/mL	Soft chew, toy	60	7.9	2.2	0.8	13.1
C_{max}, ng/mL	Chewable tablet, medium	60	0.5	0.2	0.1	1.1
C_{max}, ng/mL	Soft chew, medium	60	0.7	0.2	0.1	1.1
C_{max}, ng/mL	Soft chew, toy	60	0.6	0.2	0.1	1.0
T_{max}, hours	Chewable tablet, medium	60	2.7	0.7	1.5	4.0
T_{max}, hours	Soft chew, medium	60	3.4	1.0	1.5	6.0
T_{max}, hours	Soft chew, toy	60	2.4	0.9	1.0	6.0

*Arithmetic means, values are corrected for dose and body weight
+Std Dev = Standard Deviation
†N = Number of dogs

Table 4. Summary Statistics for $AUC_{0\text{-}Last}$, C_{max}, and T_{max} Pharmacokinetic Parameters for Praziquantel (Dose Corrected Values)

Parameter	Treatment	N†	Mean*	Std Dev+	Minimum	Maximum
$AUC_{0\text{-}Last}$, ng*hour/mL	Chewable tablet, medium	60	424.5	178.9	155.0	890.0
$AUC_{0\text{-}Last}$, ng*hour/mL	Soft chew, medium	60	531.6	213.1	163.0	1030.0
$AUC_{0\text{-}Last}$, ng*hour/mL	Soft chew, toy	60	438.8	180.2	182.0	843.0
C_{max}, ng/mL	Chewable tablet, medium	60	104.1	43.1	18.6	209.0
C_{max}, ng/mL	Soft chew, medium	60	177.0	60.4	67.2	329.0
C_{max}, ng/mL	Soft chew, toy	60	236.3	91.6	100.0	446.0
T_{max}, hours	Chewable tablet, medium	60	1.7	1.1	0.5	8.0
T_{max}, hours	Soft chew, medium	60	1.5	0.6	0.5	3.5
T_{max}, hours	Soft chew, toy	60	1.1	0.6	0.5	3.5

*Arithmetic means, values are corrected for dose and body weight
+Std Dev = Standard Deviation
†N = Number of dogs

Tables 5 through 7 define the bioequivalence comparisons of interest for both ivermectin and praziquantel.

Mean ivermectin systemic exposure ($AUC_{0\text{-}Last}$/Dose and C_{max}/Dose) values were similar across treatments (test product to reference product ratios ranged from 1.03 to 1.35) following administration of IVERHART MAX® Chewable Tablets, medium size; IVERHART MAX® Soft Chew, medium size; or IVERHART MAX® Soft Chew, toy size. The IVERHART MAX® Soft Chew, toy size was bioequivalent to the IVERHART MAX® Chewable Tablets, medium size. The IVERHART MAX® Soft Chew, medium size was not bioequivalent to IVERHART MAX® Chewable Tablets, medium size (ratios of test/reference $AUC_{0\text{-}Last}$ and C_{max} were 1.35 and 1.33, respectively). Based on the $AUC_{0\text{-}Last}$ ratio, ivermectin was approximately 35% more bioavailable in the IVERHART MAX® Soft Chew, medium size.

Mean praziquantel $AUC_{0\text{-}Last}$/Dose was similar across treatments (test product to reference product ratios ranged from 1.04 to 1.26) following administration of IVERHART MAX® Chewable Tablets, medium size;

IVERHART MAX® Soft Chew, medium size; or IVERHART MAX® Soft Chew, toy size. Mean C_{max}/Dose values for praziquantel appeared to increase (test product to reference product ratios ranged from 1.74 to 2.30) for dogs treated with IVERHART MAX® Soft Chew, medium size, and IVERHART MAX® Soft Chew, toy size. The IVERHART MAX® Soft Chew, toy size was bioequivalent to the IVERHART MAX® Chewable Tablets, medium size in extent of absorption (ratio of test/reference $AUC_{0\text{-}Last}$ 1.04), but had a faster rate of absorption (ratio of test/reference C_{max} 2.30, mean T_{max} 1.1 hours for IVERHART MAX® Soft Chew, toy size versus 1.7 hours for IVERHART MAX® Chewable Tablets, medium size). The IVERHART MAX® Soft Chew, medium size was more bioavailable (ratio of test/reference $AUC_{0\text{-}Last}$ 1.26) and also had a faster rate of absorption than the IVERHART MAX® Chewable Tablets, medium size (ratios of test/reference C_{max} 1.74, T_{max} 1.5 hours for IVERHART MAX® Soft Chew, medium size versus 1.7 hours for IVERHART MAX® Chewable Tablets, medium size).

The bioavailability of ivermectin and praziquantel from IVERHART MAX® Soft Chew, toy size was less than the IVERHART MAX® Soft Chew, medium size.

Table 5. Ivermectin and Praziquantel Comparative Bioavailability Parameters for IVERHART MAX® Soft Chew, Toy Size (Test) versus IVERHART MAX® Chewable Tablets, Medium Size (Reference)†

Parameter	Drug	Product	Geometric Mean*	Ratio+	90% Confidence Interval (Lower, Upper)
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Ivermectin	Test	7.45	1.03	0.93, 1.15
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Ivermectin	Reference	6.80	N/A	N/A
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Praziquantel	Test	404	1.04	0.99, 1.11
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Praziquantel	Reference	389	N/A	N/A
Ln (C_{max}), ng/mL	Ivermectin	Test	0.57	1.10	0.98, 1.23
Ln (C_{max}), ng/mL	Ivermectin	Reference	0.48	N/A	N/A
Ln (C_{max}), ng/mL	Praziquantel	Test	220	2.30	2.09, 2.53
Ln (C_{max}), ng/mL	Praziquantel	Reference	94	N/A	N/A

†Inclusion of the carryover term in the statistical model resulted in an inability to estimate least squares means associated with the pharmacokinetic parameters; thus the means presented are the geometric means of arithmetic log means. The ratio of test/reference and the CI's were estimated based on the statistical model
*Geometric means for the test and reference, values are corrected for dose and body weight
+Ratio = Test/Reference

Table 6. Ivermectin and Praziquantel Comparative Bioavailability Parameters for IVERHART MAX® Soft Chew, Medium Size (Test) versus IVERHART MAX® Chewable Tablets, Medium Size (Reference)†

Parameter	Drug	Product	Geometric Mean*	Ratio+	90% Confidence Interval (Lower, Upper)
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Ivermectin	Test	9.18	1.35	1.21, 1.50
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Ivermectin	Reference	6.80	N/A	N/A
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Praziquantel	Test	491	1.26	1.19, 1.34
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Praziquantel	Reference	389	N/A	N/A
Ln (C_{max}), ng/mL	Ivermectin	Test	0.65	1.33	1.19, 1.49
Ln (C_{max}), ng/mL	Ivermectin	Reference	0.48	N/A	N/A
Ln (C_{max}), ng/mL	Praziquantel	Test	166	1.74	1.58, 1.91
Ln (C_{max}), ng/mL	Praziquantel	Reference	94	N/A	N/A

†Inclusion of the carryover term in the statistical model resulted in an inability to estimate least squares means associated with the pharmacokinetic parameters; thus the means presented are the geometric means of arithmetic log means. The ratio of test/reference and the CI's were estimated based on the statistical model
*Geometric means for the test and reference, values are corrected for dose and body weight
+Ratio = Test/Reference

Table 7. Ivermectin and Praziquantel Comparative Bioavailability Parameters (Dose Corrected Values) for IVERHART MAX® Soft Chew IVERHART MAX® Soft Chew, Toy Size (Test) versus IVERHART MAX® Soft Chew, Medium Size (Reference)†

Parameter	Drug	Product	Geometric Mean*	Ratio+	90% Confidence Interval (Lower, Upper)
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Ivermectin	Test	7.45	0.76	0.69, 0.85
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Ivermectin	Reference	9.18	N/A	N/A
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Praziquantel	Test	404	0.83	0.78, 0.88
Ln($AUC_{0\text{-}Last}$), ng*hour/mL	Praziquantel	Reference	491	N/A	N/A
Ln (C_{max}), ng/mL	Ivermectin	Test	0.57	0.83	0.74, 0.93
Ln (C_{max}), ng/mL	Ivermectin	Reference	0.65	N/A	N/A
Ln (C_{max}), ng/mL	Praziquantel	Test	220	1.32	1.20, 1.45
Ln (C_{max}), ng/mL	Praziquantel	Reference	166	N/A	N/A

†Inclusion of the carryover term in the statistical model resulted in an inability to estimate least squares means associated with the pharmacokinetic parameters; thus the means presented are the geometric means of arithmetic log means. The ratio of test/reference and the CI's were estimated based on the statistical model
*Geometric means for the test and reference, values are corrected for dose and body weight
+Ratio = Test/Reference

Conclusions:

This study demonstrated that the systemic exposure to ivermectin in the IVERHART MAX® Soft Chew ranged from bioequivalent to 35% more bioavailable than ivermectin in the IVERHART MAX® Chewable Tablets. Therefore, this study provides a bridge to the heartworm (*Dirofilaria immitis*) effectiveness study conducted for IVERHART MAX® Chewable Tablets.

The study also demonstrated that the systemic exposure to praziquantel in the IVERHART MAX® Soft Chew ranged from 4% to 26% more bioavailable than praziquantel in the IVERHART MAX® Chewable Tablets. The increased bioavailability and more rapid absorption resulted in peak plasma praziquantel concentrations up to two times higher in dogs administered IVERHART MAX® Soft Chew. Therefore, the study provides a bridge to the tapeworm (*Dipylidium caninum* and *Taenia pisiformis*) effectiveness studies conducted with IVERHART MAX® Chewable Tablets.

3. Comparative Dissolution Profiles

The *in vitro* dissolution profiles of the toy, small, medium, and large size IVERHART MAX® Soft Chew were completed in 1% sodium lauryl sulfate, 900 mL (medium and large chews) or 500 mL (toy and small chews), at 37°C with United States Pharmacopeial Convention (USP) Apparatus 2 at 75 rpm. Samples were analyzed using High Performance Liquid Chromatography (HPLC) methods. The f2 metric was used to compare the profiles for similarity.

All IVERHART MAX® Soft Chew sizes had mean ivermectin release greater than 85% in 90 minutes; all sizes had mean praziquantel release greater than 85% in 45 minutes; and all sizes had mean pyrantel release greater than 85% in 60 minutes. The f2 metric values suggested the same two groups of similar profiles for each drug component. The toy and small sizes appeared to compose one group; the medium and large sizes appeared to compose the other group. The toy and medium size IVERHART MAX® Soft Chew were evaluated in the *in vivo* bioequivalence study # 963-008.

The results of the dissolution study allow the results for the sizes evaluated in the *in vivo* bioequivalence study (Study No. 963-008) to be inferred for the other IVERHART MAX® Soft Chew sizes.

III. TARGET ANIMAL SAFETY

A. Overview

Studies demonstrating the safety of IVERHART MAX® Chewable Tablets (ivermectin/pyrantel pamoate/praziquantel) were used to support the approval of IVERHART MAX® Soft Chew. Refer to the FOI summary for IVERHART MAX® Chewable Tablets (NADA 141-257) for summaries of these safety studies. The ivermectin and praziquantel in the IVERHART MAX® Soft Chew is more bioavailable than in IVERHART MAX® Chewable Tablets. The safety of the physical administration and increased bioavailability of ivermectin and praziquantel in the IVERHART MAX® Soft Chew was assessed in the field safety and palatability study (Study No. U-595.710000-3001).

B. Field Safety and Palatability Study

Title: Palatability of 595.71 (Ivermectin, Pyrantel Pamoate, Praziquantel) Soft Chewable Tablets in Client-Owned Dogs. Study No. U-595.710000-3001

Study Dates: June 2011 to April 2013

Study Locations:

Fort Worth, TX
Lewisville, TX
Willow Park, TX
Decatur, TX

Study Design:

Objectives: To evaluate the voluntary consumption of IVERHART MAX® Soft Chew when dosed at a monthly interval for three treatment periods and to establish the safety profile of the formulation and dosage form.

The study was conducted using the principles of Good Clinical Practices (GCP).

Study Animals: The study enrolled 132 client-owned dogs, ranging in age from 10 months to 13 years old, and weighing between 6.3 and 134.8 pounds. All dogs were current on heartworm prophylaxis and negative for heartworm infection at the time of enrollment.

Experimental Design: Three doses, one month apart, were administered orally to 132 client-owned dogs in an open-label, field study conducted at five veterinary clinics. The study did not include a control group. Acceptance and safety of the product were evaluated.

Dosage Form: Soft chew (final market formulation)

Route of Administration: Oral

Dose: The dogs were dosed according to Table 8. For dogs weighing greater than 100 pounds, the appropriate combination of tablets was used. The minimum dose levels were: 6 mcg of ivermectin per kilogram (2.72 mcg/lb), 5 mg of pyrantel (as pamoate salt) per kilogram (2.27 mg/lb), and 5 mg of praziquantel per kilogram (2.27 mg/lb) of body weight.

Table 8. Dosing Chart

Dog Weight (Pounds)	Soft Chew per Month	Soft Chew Size	Ivermectin Content	Pyrantel Pamoate Content	Praziquantel Content
6.0 to 12	1	Toy	34 mcg	28.5 mg	28.5 mg
12.1 to 25	1	Small	68 mcg	57 mg	57 mg
25.1 to 50	1	Medium	136 mcg	114 mg	114 mg
50.1 to 100	1	Large	272 mcg	228 mg	228 mg

Drug Administration: Owners were instructed to offer the soft chew either by hand or in an empty bowl. If not accepted voluntarily within 5 minutes of presentation, the soft chew was offered in a small amount of food or placed onto the back to

the dog's tongue for forced swallowing ("pilling"). In the event that the soft chew was refused, the owner was instructed to contact the investigator.

Results:

A total of 389 dosing events were attempted, the outcomes are summarized in Table 9.

Table 9. Dosing Outcome

Total Dosing Attempts	Voluntarily Accepted	Accepted with Enticement or "Pilled"	Not Accepted/ Administered
389	336 (86.3%)	50 (13.0%)	3 (0.7%)

Adverse Reactions:

Self-limiting adverse reactions included vomiting, diarrhea, lethargy, difficulty swallowing, excessive salivation, increased water consumption, and coughing.

Conclusions:

In this field study, IVERHART MAX® Soft Chew was shown to be a well-accepted and a safe oral dosage form for dogs. This study supports the safety of the increased bioavailability of ivermectin and praziquantel in the IVERHART MAX® Soft Chew when administered at the labeled dose.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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 IVERHART MAX® Soft Chew:

"For use in dogs only. Keep this and all drugs out of reach of children and pets."

"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 (FD&C Act) and 21 CFR part 514. The data demonstrate that IVERHART MAX® Soft Chew, when used according to the label, is safe and effective 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*).

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status) 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

IVERHART MAX® Soft Chew, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of IVERHART MAX® Soft Chew.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.