Date of Approval: October 13, 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-257

IVERHART MAX Chewable Tablets

(ivermectin/pyrantel pamoate/praziquantel)

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.
3200 Meacham Blvd.
Fort Worth, TX 76137

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1. 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. Established Name: Ivermectin, pyrantel pamoate, praziquantel

d. Proprietary Name: IVERHART MAX Chewable Tablets

e. Dosage Form: Chewable Tablets

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

g. How Dispensed: Rx

h. Amount of Active Ingredients:

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

i. Route of Administration: Oral

j. Species/Class: Canine

k. Recommended Dosage:

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	

l. Pharmacological Category: Anthelmintic

m. Indications: 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*).

2. EFFECTIVENESS:

a. Dosage Characterization:

The minimum dosage of 6 mcg/kg ivermectin and 5 mg/kg pyrantel (as pamoate) in dogs weighing 6 lbs or greater is supported by data contained in Virbac's ANADA 200-302 for IVERHART PLUS (ivermectin/pyrantel pamoate) Flavored Tablets.

The dosage of 5 mg/kg praziquantel for dogs 15 pounds or greater is supported by information in the veterinary literature.[1,2]

b. Substantial Evidence:

(1) Canine heartworm disease prevention

(a) Purpose:	Demonstrate the non-interference of praziquantel with the ivermectin/pyrantel combination and confirm the Effectiveness of ivermectin/pyrantel pamoate/praziquantel tablets to prevent development of *Dirofilaria immitis* in dogs.
(b) Investigator:	Dr. John W. McCall
(c) Study location:	TRS LABS Inc. Athens, GA
(d) Animals:	12 male and 12 female parasite naïve Beagle dogs aged 4 to 7 months at study initiation
(e) Treatment groups:	Group 1 (n=8): placebo Group 2 (n=8): 5 mg/kg praziquantel

[1] Georgi, JR. Tapeworms. *Veterinary Clinics of North America: Small Animal Practice*. (1987) 17(6): 1285-1305.
[2] Dey-Hazra, A. The Effectiveness of DRONCIT (Praziquantel) against tapeworm infections in dog and cat. *Vet. Med. Rev.* (1976) 2: 131-141.

Group 3 (n=8): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel

(f) Statistical methods: Log worm counts for the treatment group were compared to log worm counts for the control group by means of a Wilcoxon rank sum test. Percent Effectiveness was computed as 100 times:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}}$$

where GM = geometric mean worm count

(g) Study design: Inoculation with *D. immitis* larvae on Day 30
Day 0: treatment per os
Day 119: necropsy

(h) Study results: Group 1: 8 dogs with heartworms GM=37.60 (range: 32-42)
Group 2: 8 dogs with heartworms GM=37.70 (range: 28-45)
Group 3: 0 dogs with heartworms GM=0.00
Group 3 vs. Group 1: 100% effectiveness
Group 3 vs. Group 2: 100% effectiveness

(i) Conclusion: Non-interference of praziquantel at 5 mg/kg with the ivermectin/pyrantel combination. The three-way combination is 100% effective against the prevention of heartworm development.

(j) Adverse reactions: None reported.

(2) Treatment and control of roundworms *(Toxocara canis, Toxascaris leonina)* and hookworms *(Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense)*

Because Virbac's IVERHART PLUS (ivermectin/pyrantel pamoate) is already approved (ANADA 200-302) for treatment and control of the roundworms and hookworms described above, only one additional study was required to show non-interference of the ingredients with each other, and that pyrantel pamoate is required for treatment and control of the dose-limiting ascarid. However, the first study (Study 1) fell short of the 90% Effectiveness required. A second dose-limiting ascarid study (Study 2) was conducted and met the 90% effectiveness requirement. The average effectiveness of the two studies (90%) is acceptable.

Dose-Limiting Roundworm Study 1:

(a) Purpose:	1) Demonstrate the non-interference of praziquantel with the ivermectin/pyrantel combination to treat and control *T. canis* (dose-limiting parasite) 2) Confirm the effectiveness of the three-way combination for the treatment of roundworm (*T. canis*) infection in dogs
(b) Investigator:	Dr. John W. McCall
(c) Study location:	TRS LABS Inc. Athens, GA
(d) Animals:	12 male and 12 female parasite naïve Beagle dogs, 8-9 weeks old at the time of inoculation
(e) Treatment groups:	Group 1 (n=8): placebo Group 2 (n=8): praziquantel 5 mg/kg Group 3 (n=8): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel
(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 100 times: $\frac{\text{(control GM - treated GM)}}{\text{control GM}}$ where GM = geometric mean worm count
(g) Study design:	Day -49: inoculation with 300 embryonated *T. canis* eggs per os Day 0: allocation to a treatment group and treatment Day 7: necropsy (worm counts in digestive tract)
(h) Study results:	Group 1: 8 dogs with roundworms GM=18.33 (range: 6-56) Group 2: 8 dogs with roundworms GM=40.99 (range: 19-66) Group 3: 6 dogs with roundworms GM=3.03 (range: 0-29) Group 3 vs. Group 1 - Effectiveness: 83.5%

Group 3 vs. Group 2 - Effectiveness: 92.6%

(i) Conclusion: Effectiveness of the three-way combination on *T. canis* infection compared to placebo was not demonstrated (<90%). The non-interference of praziquantel in the combination was not demonstrated.

(j) Adverse reactions: None reported

Dose-Limiting Roundworm Study 2:

(a) Purpose: Confirm the effectiveness of the three-way combination for the treatment of roundworm (*T. canis*) infection in dogs.

(b) Investigator: Dawie J. Kok. D.Sc.

(c) Study location: ClinVet International (Pty) Ltd
Bloemfontein
Republic of South Africa

(d) Animals: 9 male and 11 female dogs, from various breeds, 11 to 27 days old at the time of inoculation

(e) Treatment groups: Day -54: inoculation with 300 larvated *T. canis* eggs per os
Day 0: allocation to a treatment group and treatment
Day 7: necropsy (worm counts in digestive tract)

(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 100 times:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}}$$

where GM = geometric mean worm count

(g) Study design: Group 1 (n=10): placebo
Group 2 (n=10): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel

(h) Study results:	Group 1: 10 dogs with roundworms GM= 38.00 (range: 12-95) Group 2: 7 dogs with roundworms GM= 1.58 (range: 0-11) Group 2 vs. Group 1 - Effectiveness: 95.8%
(i) Conclusion:	Effectiveness of the three-way combination against *T. canis* infection was demonstrated.
(j) Adverse reactions:	One dog died (group 2) on Day 6 because of dehydration associated with diarrhea. This puppy, and others in the study, had high worm burdens and had diarrhea before and after treatment with the test article.

(3) Treatment and control of tapeworms (*Dipylidium caninum, Taenia pisiformis*)

***Dipylidium caninum* studies**
Non-Interference Study:

(a) Purpose:	1) Demonstrate the non-interference of ivermectin/pyrantel with praziquantel to treat and control *D. caninum.* 2) Confirm the effectiveness of the three-way combination for the treatment of tapeworm (*D. caninum*) infection in dogs
(b) Investigator:	Dawie J. Kok. D.Sc.
(c) Study location:	ClinVet International (Pty) Ltd Bloemfontein Republic of South Africa
(d) Animals:	8 male and 16 female adult dogs, from various breeds, naturally infected with *D. caninum*
(e) Treatment groups:	Group 1 (n=8): placebo Group 2 (n=8): 6 mcg/kg ivermectin, and 5 mg/kg pyrantel pamoate Group 3 (n=8): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel
(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 100 times:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}}$$

where GM = geometric mean worm count

(g) Study design: Day -1: allocation to a treatment group
Day 0: treatment
Day 14: necropsy (worm counts in digestive tract)

(h) Study results: Group 1: 8 dogs with tapeworms GM= 7.94 (range: 2-51)
Group 2: 8 dogs with tapeworms GM= 25.43 (range: 5-179)
Group 3: 0 dogs with tapeworms GM= 0.00
Group 3 vs. Group 1 - Effectiveness: 100%
Group 3 vs. Group 2 - Effectiveness: 100%

(i) Conclusion: Effectiveness of the three-way combination against *D. caninum* infection and non-interference of ivermectin/pyrantel pamoate was demonstrated.

(j) Adverse reactions: None reported

Dose-Confirmation Study:

(a) Purpose: Confirm the effectiveness of the three-way combination for the treatment of tapeworm (*D. caninum*) infection in dogs

(b) Investigator: Dr. Dwight D. Bowman

(c) Study location: CHK R&D
Stanwood, MI

(d) Animals: 12 male and 4 female dogs of various breeds naturally infected with *D. caninum*

(e) Treatment groups: Group 1 (n=8): placebo
Group 2 (n=8): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel

(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 100 times:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}}$$

where GM = geometric mean worm count

(g) Study design: Day -1: group allocation
Day 0: treatment
Day 14: necropsy

(h) Study results: Group 1: 7 dogs with tapeworms GM=10.42 (range: 0-54)
Group 2: 0 dogs with tapeworms GM=0.00
Group 1 vs. Group 2: 100% effectiveness

(i) Conclusion: Effectiveness of the three-way combination against *D. caninum* infection was demonstrated.

(j) Adverse reactions: None reported

***Taenia pisiformis* studies**
Dose-Confirmation Study:

(a) Purpose: Confirm the effectiveness of the three-way combination for the treatment of tapeworm (*T. pisiformis*) infection in dogs

(b) Investigator: Dr. Dwight D. Bowman

(c) Study location: CHK R&D
Stanwood, MI

(d) Animals: 0 male and 10 female dogs of various breeds naturally infected with *T. pisiformis*

(e) Treatment groups: Group 1 (n=10): placebo
Group 2 (n=10): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel

(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 100 times:

$$\frac{\text{(control GM - treated GM)}}{\text{control GM}}$$

where GM = geometric mean worm count

(g) Study design: Day -1: group allocation
Day 0: treatment
Day 14: necropsy

(h) Study results: Group 1: 10 dogs with tapeworms GM=7.18 (range: 2-62)
Group 2: 0 dogs with tapeworms GM=0.00
Group 1 vs. Group 2: 100% effectiveness

(i) Conclusion: Effectiveness of the three-way combination against *T. pisiformis* infection was demonstrated.

(j) Adverse reactions: None reported

Dose-Confirmation Study:

(a) Purpose: Confirm the effectiveness of the three-way combination for the treatment of tapeworm (*T. pisiformis*) infection in dogs

(b) Investigator: Dr. Allan J. Paul

(c) Study location: University of Illinois
Urbana, IL

(d) Animals: 12 male and 6 female dogs of various breeds naturally infected with *T. pisiformis*

(e) Treatment groups: Group 1 (n=9): placebo
Group 2 (n=9): 6 mcg/kg ivermectin, 5 mg/kg pyrantel and 5 mg/kg praziquantel

(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 100 times:

$$\frac{\text{(control GM - treated GM)}}{}$$

control GM

where GM = geometric mean worm count

(g) Study design:	Day -1 or D0: group allocation Day 0: treatment Day 14: necropsy
(h) Study results:	Group 1: 9 dogs with tapeworms GM= 14.96 (range: 7-33) Group 2: 0 dogs with tapeworms GM=0.00 Group 1 vs. Group 2: 100% effectiveness
(i) Conclusion:	Effectiveness of the three-way combination against *T. pisiformis* infection was demonstrated.
(j) Adverse Reactions:	None reported

3. TARGET ANIMAL SAFETY:

a. **A 6-Month Oral Safety Study in Dogs Using 595.12 (Ivermectin/Pyrantel Pamoate/Praziquantel Tablets) Study #963-002**

(1) Type of Study: Target Animal Safety

(2) Investigator: C. Steve Godin, PhD, D.A.B.T.
MPI Research, Inc.
Mattawan, Michigan

(3) Study Design:

(a) Compliance: This study was conducted in accordance with Good Laboratory Practices For Nonclinical Laboratory Studies, U.S. Code of Federal Regulations, Title 21, Part 58.

(b) Purpose: To evaluate the safety of the test article in dogs upon oral dosing at 12.5 mcg ivermectin/kg, 10.47 mg pyrantel pamoate and 10.47 mg praziquantel/kg; 37.5 mcg ivermectin/kg, 31.42 mg pyrantel pamoate and 31.42 mg praziquantel/kg; and 62.5 mcg ivermectin/kg, 52.35 mg pyrantel pamoate and 52.35 mg praziquantel/kg, given every 30 days for 6 consecutive treatments.

(c) Test Animals: Thirty-two (4 dogs per sex per treatment) healthy Beagle dogs (8 weeks of age at the first treatment and weighing 1.48 to 2.46 kg at randomization).

(d) Dosage Form: Tablets

(e) Dosages Used: 0, 1, 3 and 5 times the maximum recommended dose of 12.5 mcg/kg ivermectin, 10.47 mg/kg pyrantel pamoate and 10.47 mg/kg praziquantel was used. The dosages, as described in Table 3.1, were given every 30 days for 6 consecutive treatments (Days 1, 31, 61, 91, 121 and 151). The control dogs received five placebo tablets at each treatment administration.

Table 3.1: Dosage per Treatment Group

Treatment Group	Dosage (0, 1X, 3X, 5X)	Number and Sex of Animals
1	0 mg/kg (0X)	8 (4M, 4F)
2	12.5 mcg ivermectin/kg, 10.47 mg pyrantel pamoate and 10.47 mg praziquantel/kg (1X)	8 (4M, 4F)
3	37.5 mcg ivermectin/kg, 31.42 mg pyrantel pamoate and 31.42 mg praziquantel/kg (3X)	8 (4M, 4F)
4	62.5 mcg ivermectin/kg, 52.35 mg pyrantel pamoate and 52.35 mg praziquantel/kg (5X)	8 (4M, 4F)

(f) Route of Administration: Oral. Dogs were not fasted. If a dog vomited or regurgitated within one hour of dosing, they were redosed.

(g) Study Duration: December 2002 through February 2004

(h) Variables Measured: Clinical observations and mortality checks (performed three times daily); food consumption (daily); bodyweights (on arrival, daily during acclimation and biweekly during the study); physical examinations (Days -1, 2, 30, 32, 60, 62, 90, 92, 120, 122, 150, 152 and 181); post-treatment observations (Days 1, 31, 61, 91, 121 and 151); hematology (Days -10, 2, 62, 122 and 181); clinical chemistry (Days -10, 2, 62, 122 and 181);

urinalysis (Days -10, 2, 62, 122 and 181); organ weights and macroscopic and microscopic anatomical pathology (at necropsy, Days 182 and 183).

(4) Statistical Methods:

For hematology and clinical chemistry parameters, body weight, and other variables observed at several time points during the study, a repeated measures analysis of variance was used to test for possible differences due to treatment effects and its interaction with gender and/or time. For variables assessed only at the end of the study, such as organ weights, the analysis of variance was used to test for differences due to treatment effects and its interaction with gender, if applicable. Pre-treatment values were included as covariates in all models. Follow-up mean comparisons between each treated group and control using linear contrasts were performed as necessary.

(5) Results:

(a) Mortality: All dogs survived to study termination.

(b) Food Consumption: There were no statistically significant differences between treatment groups in food consumption during the study.

(c) Body Weights: There were no statistically significant differences between groups in body weights during the study.

(d) Physical Examinations: Physical examinations conducted prior to treatment revealed minor findings (nasal discharge, ocular discharge, thinness) usual for dogs of this age. All the dogs were considered healthy. On Day 1, clear ocular or nasal discharges were reported in 3 more animals. One animal (3X group) was dehydrated but recovered promptly after adequate treatment. Three animals developed signs of respiratory infection (2 in the 1X group and 1 in the 0X group) and recovered after treatment.

(e) Clinical and Post-Treatment Observations: Vomiting was observed in dogs after treatment. Animals at 5X had the highest incidence of vomiting with 49 separate occurrences in both sexes during the course of the study. There was a dose dependent increase in vomiting episodes. Most of the vomiting episodes in the 3X and 5X groups occurred during the first two hours following dosing (see Tables 3.2 and 3.3).

Table 3.2: Incidence (No. of dogs) and Timing of Vomiting after Treatment.

Group	Day 1	Day 31	Day 61	Day 91	Day 121	Day 151
0X	1 (12 hrs)	1 (4 hrs)	0	0	0	0
1X	0	0	1 (2 hrs)	1 (2 hrs)	1 (6 hrs)	0
3X	3 (0-1 hr)	5 (0-2 hrs)	3 (1-2 hrs)	2 (1-3 hrs)	1 (2 hrs)	2 (1-4 hrs)
5X	6 (0-2 hrs)	8 (0-4 hrs)	5 (1-6 hrs)	5 (1-6 hrs)	4 (1-3 hrs)	3 (2-3 hrs)

There was a dose dependent increase in the number of incidences of soft or watery feces seen post-treatment. The occurrence of soft feces suggests a dose-related effect (37 observations in the control group, 48 observations in the 1X group, 69 observations in the 3X group and 90 observations in the 5X group). See Table 3.3.

Table 3.3: Number of Episodes of Vomiting and Soft Feces after Treatment

Group	Total No. vomiting episodes	Total No. of soft feces episodes
Control	2	37
1X	3	48
3X	21	69
5X	49	90

Other observations during the study were: lacrimation (all groups), swelling in anogenital region (1 animal in 1X group), lethargy (2 episodes: 1 in the 3X group, 1 in the 5X group), tremors (1 dog in the 5X group), head movements (1 episode in the 1X group), shallow breathing (1 episode in the 3X group), audible breathing (2 episodes in the control group, 1 episode in the 1X group) and salivation (1 episode in the control group, 1 episode in the 3X group and 2 episodes in the 5X group). All these signs were transient and no treatment was required.

(f) Clinical Pathology: There were no test article-related adverse effects apparent on hematology, chemistry or urinary parameters at any dose level.

(g) Macroscopic Anatomical Pathology: No test article-related macroscopic changes were noted in dogs of either sex.

(h) Microscopic Anatomical Pathology: Testicular hypoplasia was seen in two dogs, one each in the 3X and 5X group. The dog in the 3X group was noted to have bilateral hypoplasia graded as moderate (3/4 in the graded scale). The dog in the 5X group was noted to have unilateral hypoplasia, graded as minimal (2/4 in the graded scale).

(i) Organ Weights: There were no statistically significant differences in organ weights when treated groups were compared to the control group.

(6) Conclusions:

The main effects of the test article are vomiting and soft feces following dosing. The incidence rate is low in dogs receiving the 1X dose and increases with dosage. Testicular hypoplasia was seen in the 3X and 5X groups.

Other signs associated with treatment include anogenital swelling, lethargy, tremors, head movements, shallow breathing, and salivation.

b. **90-Day Oral Safety Study in Dogs Using a Tablet Containing Ivermectin/Pyrantel pamoate/Praziquantel Study #813-002**

(1) Type of Study: Target Animal Safety Study

(2) Investigator: Edwin I. Goldenthal, PhD, A.T.S.
MPI Research, Inc.
Mattawan, Michigan

(3) Study Design:

(a) Compliance: This study was conducted in accordance with Good Laboratory Practices For Nonclinical Laboratory Studies, U.S. Code of Federal Regulations, Title 21, Part 58.

(b) Purpose: To evaluate the safety of ivermectin/pyrantel pamoate/praziquantel tablets in dogs upon oral dosing at 1, 3 and 5X the *ad usum* rate given once a week for 3 consecutive months.

(c) Test Animals: Thirty-two (4 dogs per sex per treatment) healthy Beagle dogs (approximately 12 weeks of age at the first treatment and weighing 3.2 to 4.6 kg at randomization).

(d) Dosage Form: Scored tablets containing 68 mcg ivermectin, 57 mg pyrantel, and 57 mg praziquantel.

(e) Dosages: Dogs weighing 2.30 to 4.59 kg received 0, 1, 3 or 5 halves of small tablets at each administration depending on the treatment group. Dogs weighing 4.60 to 11.39 kg received 0, 1, 3 or 5 small tablets at each administration depending on the treatment group (see Table 3.4). The dosing days were: Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and 92. The control dogs were sham-dosed.

Table 3.4: Amount Of Active Ingredient/Tablet

Dog Weights (kg)	Ivermectin (mcg)	Pyrantel pamoate Praziquantel (mg)	# Tablets
2.30 – 4.59	34	28.5	½
4.60 – 11.39	68	57	1

(f) Route of Administration: Oral. Dogs had access to food at all times. They were not fasted.

(g) Test Duration: February 2000 through August 2000

(h) Variables Measured: Cageside observations and mortality checks (twice daily); food consumption (weekly); water consumption (daily and calculated weekly); bodyweights (on arrival, daily during acclimation, weekly during the study, and prior to necropsy); clinical observations (Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 and 91); ophthalmoscopic examinations (pretest and prior to necropsy); physical/neurologic examinations (within 24 hours after the first dose of each month, i.e. on Days 2, 30, 58 and 86); hematology (pretest and Days 2, 30, 58 and 86); clinical chemistry (pretest and Days 2, 30, 58 and 86); urinalysis (pretest and Days 2, 30, 58 and 86); and organ weights and macroscopic and microscopic anatomical pathology (at necropsy).

(4) Statistical Methods:

For hematology and clinical chemistry parameters, body weight, and other variables observed at several time points during the study, a repeated measures analysis of variance was used to test for possible differences due to treatment effects and its interaction with gender and/or time. Pre-treatment values were included as covariates in the model. For variables assessed only at the end of the study, such as organ weights, the analysis of variance was used to test for differences due to treatment effects and its interaction with gender, if applicable. Follow-up mean comparisons between each treated group and control using linear contrasts were performed as necessary. Additionally, a regression analysis of testis/epididymis weight with dose level (0, 1, 3, and 5X) as a continuous covariate was conducted to test for a linear trend in testis/epididymis weight as a function of dose level.

(5) Results:

(a) Mortality: All dogs survived to study termination.

(b) Clinical Findings: No test article-related clinical findings were observed during the study.

(c) Body Weights: There were no statistically significant differences between groups in body weights during the study interval.

(d) Food Consumption: There were no statistically significant differences between treatment groups in the weekly food consumption values during the study.

(e) Ophthalmoscopic Examinations: A few minor findings were seen at the pretest examination, all within the limits of variation commonly encountered in dogs of this age, sex and breed. At the terminal examination, all findings were considered normal. No effect of treatment on ophthalmological findings was observed.

(f) Physical/Neurological Examinations: An aural hematoma was recorded in one dog during the pretest period. All the other dogs at the pretest period were considered normal. No test article-related physical/neurological examination findings were seen during the study.

(g) Clinical Pathology: The mean increase in cholesterol at 2 and 3 months, calculated as the difference from the pre-treatment evaluation period, was significantly higher for the 1, 3, and 5X

dose groups compared with the mean increase in cholesterol at 2 and 3 months for the 0X dose group.

(h) Macroscopic Anatomical Pathology: No test article-related macroscopic changes were noted in dogs of either sex.

(i) Organ Weights: For the male dogs, the mean absolute testis/epididymis weight was significantly lower in the 3X ($p<0.1$) and 5X ($p<0.01$) dose groups compared to 0X. There was a significant linear dose-response trend ($p=0.0006$) in the negative direction, indicating that animals in the lower dose groups tended to have larger testis/epididymis weight than animals in the higher dose groups.

Testis/epididymis weight relative to body and brain weights were also lower in the 5X ($p<0.01$) dose group compared to 0X.

(j) Microscopic Anatomical Pathology: There were test article-related microscopic findings in the testes. Microscopically, the testes were considered more immature at 3X (1 of 4 dogs) and 5X (4 of 4 dogs) compared to controls. Testes at 1X were comparable to controls. There was a correlation between testis/epididymis weight and immaturity of the testes, where lower weights were associated with more immature testes. The immaturity increased with the increased level of the test article administration. There was no particular correlation between the individual body weight and the testis/epididymis weights. Therefore, there appears to be a test article-related effect on the rate and/or degree of maturation of the testis.

(6) Conclusions:

The oral administration of ivermectin/pyrantel pamoate/praziquantel tablets at 1, 3, 5X the *ad usum* rate once weekly for 90 days in twelve-week old puppies showed an effect on the male reproductive system. Lower testicular weights compared to controls were seen at 3X and 5X. There is a test article-related effect in the rate and/or degree of maturation of the testes. Hypercholesterolemia was significantly higher for all dose groups compared to control at 2 and 3 months.

c. **Male Reproductive Safety Study in Dogs using 595.12 (Ivermectin/Pyrantel Pamoate/Praziquantel Tablets) #U-595.12/40002**

(1) Type of Study: Reproductive Safety Study

(2) Investigator: Anna Bolinder, DVM
International Bio-Institute Corp.
Ontario, Canada

(3) Study Design:

(a) Compliance: This study was conducted in accordance with Good Laboratory Practices For Nonclinical Laboratory Studies, U.S. Code of Federal Regulations, Title 21, Part 58.

(b) Purpose: To assess the reproductive safety of treatment of male dogs with ivermectin/pyrantel pamoate/praziquantel tablets.

(c) Test Animals: Sixteen healthy male Beagle dogs (13 to 40 months old at the start of acclimation).

(d) Dosage Form: Tablets

(e) Dosage: The dose levels were 0 and 3 times the maximum recommended dose of 12.5 mcg/kg ivermectin, 10.47 mg/kg pyrantel pamoate and 10.47 mg/kg praziquantel (0 and 37.5 mcg/kg ivermectin, 0 and 31.4 mg/kg of pyrantel and 0 and 31.4 mg/kg of praziquantel) was administered every 14 days for 9 consecutive treatments (two full spermatogenic cycles) on Days 0, 14, 28, 42, 56, 70, 84, 98 and 112. The control dogs received three placebo tablets at each treatment administration.

(f) Route of Administration: Oral

(g) Test Duration: February 2003 through January 2004

(h) Variables Measured: Clinical observations and mortality checks (twice daily); body weights (Days -8, -1, 13, 27, 41, 55, 69, 83, 97 and 111); physical examinations (Days -8, -1, 0, 14, 28, 42, 56, 70, 84, 98 and 112); post-treatment observations (Days 0, 14, 28, 42, 56, 70, 84, 98 and 112); male genitalia examinations and semen analysis (Days -12, -4, 7, 21, 35, 49, 63, 77, 91, 105 and 119); prostate palpation and testicular size measurements (Days -4 and 119).

(4) Statistical Methods

For body weight, semen analysis parameters and other variables observed at several time points during the study, a repeated measures analysis of variance was used to test for differences due to treatment and its interaction with time. Pre-treatment values were included as covariates. Follow-up mean comparisons between the treated and control groups using linear contrasts were performed as necessary. Testicular volume at the end of the study was compared between groups using the one-way analysis of variance with pre-treatment value as a covariate. The generalized linear mixed model was used to analyze binomial response variables such as percent sperm motility and progression. Alternatively, Fisher's Exact test was used to test for group differences within each observation period.

(5) Results:

(a) Mortality: All dogs survived to study termination.

(b) Body Weights: There were no statistically significant differences between groups in body weights during the course of the study.

(c) Physical Examinations: No significant clinical findings affecting the animal's health were found during the study.

(d) Clinical and Post-Treatment Observations: Sixty-six post-dose observations (62 in the treated group and 4 in the control group) were reported: 55 episodes of vomiting in the treated group, 9 episodes of soft feces in the treated group, 1 episode of soft feces in the control group and 1 mild front leg lameness (control animal).

Other observations (not made at the post-dose observation times) included 13 observations of loose stool in 9 animals (7 in the treated group, 2 in the control group), and 6 observations of vomiting (3 animals in the treated group and 1 control).

(e) Semen Evaluation: No clinically significant differences were shown between groups for the following variables: total sperm count, percent normal motility, percent progressive motility, spermatozoa progression (speed), percent normal sperm, sperm morphology, semen volume, semen cytology, and pH.

(f) Genitalia Examination: There were no clinically significant findings.

(g) Prostate Palpation: The size, shape and consistency of the prostates were normal in all dogs except in two dogs on Day -4 (soft consistency, increased size) which returned to normal on Day 119.

(h) Testicular size: There were no statistically significant differences in testicular size between groups.

(6) Conclusions:

This study demonstrated that treatment with ivermectin/pyrantel pamoate/praziquantel tablets did not affect adult male reproductive health when given at 3 times the maximum recommended dose every 14 days for 119 days (two full spermatogenic cycles) to healthy adult dogs.

d. **Palatability of 595.12 (Ivermectin/Pyrantel/Praziquantel Tablets) in Client-owned Dogs #U-595.12/60013**

(1) Type of Study: Field study

(2) Study Investigators: Kent Cooper, DVM
Carrier Animal Hospital
Grand Prairie, Texas

Mary King, DVM
Jason Little Road Animal Clinic
Arlington, Texas

(3) Study Design:

(a) Purpose: To determine the palatability and safety of IVERHART MAX (ivermectin/pyrantel pamoate/praziquantel) Chewable Tablets when administered to client-owned dogs under conditions of use.

(b) Test Animals: 44 client-owned dogs (27 females and 17 males) of various breeds, ages (8 weeks to 12 years), and body weights (2.5 to 79.1 lb) were enrolled. All dogs were healthy and free from conditions that would interfere with chewing or tasting (like moderate or advanced periodontal disease).

(c) Control Drug: None. All dogs received the test article.

(d) Dosage Form: Tablets (final market formulation of IVERHART MAX)

(e) Route of Administration: Oral

(f) Dosage: Dogs received the appropriate test article size according to the labeled dosing table based on their body weight at the time of study enrollment. The tablets were offered on approximately Days 0, 30, and 60 (total of three trials per dog).

(h) Duration: February 2005 to September 2005

(i) Variables Measured:

1. Palatability: The tablets were offered to the dog in a bowl and then by hand for a maximum total offering time of 5 minutes. A trial was considered successful if the dog swallowed the tablet(s) entirely from the bowl or from the hand within the allowed time of 5 minutes.

2. Post-dosing observations: Owners observed their dogs for 24 hours after each treatment for any abnormalities.

(4) Data Analysis:

A percent palatability was calculated for as follows:

% palatability = (number of successful trials / total number of trials) X 100.

(5) Results:

(a) Palatability: Data from 10 dogs that received ½ tablets were not evaluated for palatability, because in the field, no dogs will receive ½ tablet doses. Data from trials #2 and 3 for one dog who received a ½ tablet at the first trial, were evaluated. Palatability data were not evaluated for the two dogs removed from the study by their owners. Therefore, palatability was calculated for a total of 32 dogs. Using these data, the calculated percent palatability was (66/95) or 70%.

(b) Safety: Forty-two of the 44 cases were interpretable for complete safety assessments. Adverse drug reactions occurred in five dogs during the study between 20 minutes and 72 hours post treatment. Table 3.5 lists the dogs and the adverse reactions which occurred. Table 3.6 lists the dogs' breeds, ages, and body weights at the time of study enrollment. All adverse reactions resolved without treatment. Although most reactions (diarrhea, vomiting, decreased

appetite, licking lips, belching) were clinically mild, the most significant reactions (lethargy, limpness, and salivation) were seen in the three smallest dogs.

Table 3.5: List of Adverse Reactions Occurring During Study

Case Number	Time Post Dose	Adverse Reaction
A10	24 hours	Decreased appetite
B8*	48 hours	Self-limiting diarrhea
	72 hours	Lethargy
B20	1 hour	Licking lips and belching
B22	24 hours	Lethargy
	24 hours	Lethargy and belching
B23*	20 minutes	Salivating, tongue hanging out, limp

*Owners withdrew these dogs from the study.

Table 3.6: Enrollment Information for Dogs with Reactions

Case Number	Breed	Age	Body Weight
A10	Shih Tzu	2 years	13.4 lbs
B8	Chihuahua	3 months	2.5 lbs
B20	English Bulldog	4 months	23.0 lbs
B22	Chihuahua	1 year	9.3 lbs
B23	Yorkshire Terrier	16 months	6.6 lbs

(6) Conclusions:

IVERHART MAX Tablets for Dogs, when administered to client-owned dogs are palatable. Adverse reactions are generally mild and self-limiting (decreased appetite, vomiting, diarrhea, salivation, licking lips, belching, limpness) with the most significant reactions occurring in dogs weighing < 10 lbs.

e. **Laboratory Palatability Study #U-121.04/60001**

(1) Type of Study: Laboratory palatability study

(2) Study Investigator: Lori Carter, BA
Stillmeadow, Inc.
Sugar Land, Texas

(3) Study Design:

(a) Purpose: To determine the palatability of IVERHART MAX (ivermectin/pyrantel pamoate/praziquantel) Tablets when

administered to dogs.

(b) Test Animals: 30 healthy dogs (17 males and 13 females) from various breeds, 7 months to 5 years old, weighing 5.7 to 16.8 kg, and free from conditions that would interfere with chewing or tasting.

(c) Control Drug: None

(d) Dosage Form: Tablets (final market formulation)

(e) Route of Administration: Oral

(f) Dosages: Minimal dose of 6 mcg ivermectin, 5 mg pyrantel (as pamoate), and 5 mg praziquantel per kg body weight daily for three consecutive days.

(g) Test Duration: April 2003 to November 2003.

(h) Study Design: Each dog was treated with the test article a total of three times. The day prior to the sequence of three days, the dog received a treat. Twenty percent of the dogs (the 6 lightest dogs) received the broken form of the test article (1, 2, or 4 halves of a toy tablet, depending on the dog's bodyweight).

(i) Variables Measured:

1. Palatability: The tablets were offered to the dog in a bowl and then by hand for a maximum total offering time of 5 minutes. A trial was considered successful if the dog swallowed the tablet(s) entirely from the bowl or from the hand within the allowed time of 5 minutes.

2. General health: All animals were also observed daily for morbidity, mortality, injury, general health condition and availability of food and water.

3. Body weights: Body weights were measured (in kg) two days before the first administration. Body weights were converted to pounds prior to treatment.

4. Adverse Reactions: All dogs were observed at the time of each treatment and hourly afterwards for 4 hours. All adverse reactions during the study course were recorded.

(j) Data Analysis:

To obtain the overall average percent, a percent voluntary acceptance and an overall average percent voluntary acceptance were calculated for each dog as follows:

- % voluntary acceptance = (number of trials for which the dog ate the entire dose/ total number of trials per dog) X 100.

- Overall average percent voluntary acceptance = sum of all the dogs' voluntary acceptance percentages/the total number of dogs.

(4) Results:

Trials for dogs that received ½ tablets were not evaluated for palatability, because in the field, no dogs will receive ½ tablets. The overall average percent voluntary acceptance for IVERHART MAX Chewable Tablets was calculated to be 68%. Vomiting and diarrhea were seen post dosing. All reactions were considered mild and none required any treatment.

(5) Conclusions:

The overall average percent voluntary acceptance/palatability of IVERHART MAX Chewable Tablets when administered to laboratory dogs was 68%, which is not considered palatable. However, because the field study, which represents conditions of actual use, demonstrated an acceptable level of palatability (70%), the field study results will be used to demonstrate that IVERHART MAX Chewable Tablets are palatable. Adverse reactions seen post dosing included mild vomiting and diarrhea.

4. HUMAN 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, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

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."

5. 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 of the implementing regulations. The data demonstrate that ivermectin, pyrantel pamoate,

praziquantel, when used under the labeled conditions of use 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*).

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine the existence of heartworm infections and to monitor the safe use of the product.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. New studies were conducted to support substantial evidence of effectiveness and target animal safety.

6. *ATTACHMENTS:*

Facsimile labeling is attached as indicated below:

a. Package insert

For each of the Toy, Small, Medium and Large sizes:

b. Blister card labels
c. 6-ct. tablet box
d. 12-ct. tablet box
e. 6-ct. box display
f. 12-ct. box display