

HFA-305

JUN 18 2013

Date of Approval: _____

FREEDOM OF INFORMATION SUMMARY

Original Abbreviated New Animal Drug Application

ANADA 200-297

Ivermectin Chewable Tablets
(ivermectin)

Antilarval

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.

Sponsor:

Phoenix Scientific, Inc.

FOIS |

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-297
- b. Sponsor: Phoenix Scientific, Inc.
3915 South 48th St. Terrace
St. Joseph, MO 64503

Drug Labeler Code: 059130
- c. Established Name: Ivermectin
- d. Proprietary Name: Ivermectin
- e. Dosage Form: Chewable tablet
- f. How Supplied: Each of 3 dosage strengths for dogs of different weights comes in packs of 12 chewable tablets with color coding on foil backing and carton.
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Small tablets contain 68 mcg ivermectin;
medium tablets contain 136 mcg ivermectin;
large tablets contain 272 mcg ivermectin.
- i. Route of Administration: Oral
- j. Species/Class: Dogs
- k. Recommended Dosage: Administered orally at monthly intervals at the recommended minimum dose level of 6.0 mcg of ivermectin per kilogram (2.72 mcg/lb) of body weight. The recommended dosage schedule for prevention of canine heartworm disease is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Color Coding on Foil Backing and Carton
Up to 25 lb	1	68 mcg	Blue
26 to 50 lb	1	136 mcg	Green
51 to 100 lb	1	272 mcg	Brown

Give dogs over 100 lb the appropriate combination of these chewables. Recommended for use in dogs 6 weeks of age and older.

l. Pharmacological Category:

Antilarval

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.

n. Pioneer Product:

HEARTGARD Chewables; ivermectin; NADA 140-886; Merial, Ltd.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

A Suitability Petition (98P-0159/CP1), requested by Phoenix Scientific, Inc., was granted to allow a generic copy of the pioneer's extruded chewable tablet with this compressed chewable tablet. The different oral dosage forms are similar and can be used interchangeably.

The sponsor has demonstrated *in vivo* bioequivalence via a blood-level bioequivalence study of the generic product to the pioneer product to support the safety and efficacy of the generic product against *Dirofilaria immitis* (see Section 2.A.). Palatability was also evaluated in dogs and the study is reported below in Section 2.B.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and pioneer formulations of ivermectin chewables. The dose was increased to three times (3 X) the recommended dose to achieve adequate blood levels for a determination of bioavailability. This is still far below the range where adverse reactions to the drug would be expected and is too low to affect the normal mechanisms associated with the metabolism and excretion of ivermectin in dogs.

Testing Facility: Liberty Research, Inc. (LRI)
Route 17C Box 107
Waverly, NY 14892-0107

Objective: The objective of this study was to determine the comparative blood-levels of Ivermectin (ivermectin) Chewable Tablets and HEARTGARD (ivermectin) Chewables in a 2 way crossover study in dogs.

Summary: Four male and four female Beagle dogs were randomly assigned to groups and used in a 2-way crossover study comparing Ivermectin Chewable Tablets to HEARTGARD Chewables. The dogs ranged in age from 4 to 7 years and weighed 25.6 to 28.6 pounds. The medications were administered one time during each treatment period crushed in food meatballs at a 3X dose to enable appropriate serum levels for a blood-level bioequivalence study. A 28 day washout was observed between treatments. Blood was collected at time 0, 1, 2, 3, 4, 5, 6, 8, 10, 16, and 24 hours, and 2, 3, 5, 7, 14, and 21 days post-treatment. Plasma samples were submitted to PPD Pharmaco, Inc., Middleton, WI for ivermectin analysis at the completion of the study.

Results: The area under the curve (AUC) was computed from time 0 until the last quantifiable concentration using the trapezoidal rule. The natural logarithm of AUC was computed and used as the variable for analysis, denoted by LAUC. The maximum concentration measured for all time periods (C_{max}) was determined and the natural logarithm of C_{max} , denoted by LCMAX, was computed and used as the variable for analysis.

The criteria for determining bioequivalence, as described in CVM's Bioequivalence Guidance, is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of AUC and C_{max} and then take the anti-log of the confidence limits minus 1 multiplied by 100. The resulting bounds should be between -20.00% and +25.00%. As seen in the table below both AUC and C_{max} fall within those bounds.

The variable T_{max} is permitted to be interpreted by clinical judgment. In this case, there is no reason to expect the difference in T_{max} will affect the efficacy of the drug, since both AUC and C_{max} are bioequivalent and the product is administered as a single dose. Therefore, the study objective to determine the bioequivalence of generic and pioneer ivermectin was achieved.

Variable	Pioneer Mean	Generic Mean	Lower Bound	Upper Bound
Time to Max. Concentration (hours)	6.375	4.125	NA ¹	NA ¹
Log _e (AUC)	5.635	5.649	-11.91%	16.76%
Log _e (C _{MAX})	2.374	2.396	-10.46%	16.86%

¹Not Applicable

B. Palatability Study

Testing Facility: Liberty Research, Inc. (LRI)
Route 17C Box 107
Waverly, NY 14892-0107

Objective: The objective of this study was to evaluate the comparative palatability of Phoenix Scientific, Inc.'s (PSI) Ivermectin (ivermectin) Chewable Tablets to that of Merial, Ltd.'s HEARTGARD (ivermectin) Chewables.

Summary: The study was conducted to compare the palatability, measured as voluntary consumption, of generic (PSI) 136 mcg ivermectin chewable tablets and pioneer (Merial, Ltd.) 136 mcg ivermectin chewables (HEARTGARD Chewables) in the dog. The study involved three treatment groups, Ivermectin Chewable Tablets, HEARTGARD Chewables, and a flavored, unmedicated placebo treatment. Twelve dogs were used where every dog was presented each of the three treatments six times during the eighteen days of the study. Twelve series of treatment offerings were selected such that each animal had a unique series of treatment offerings. The series were selected such that four dogs received each treatment on each day of the study. Voluntary consumption was scored "yes" if the animal consumed and "no" if the animal did not consume the offered tablet during the offering time. The data collected on the placebo (treatment group C) was not used in the analyses.

Results: In this study, the generic product was voluntarily consumed 41 of the 72 offerings (56.9%) and the pioneer product was consumed in 45 of the 72 offerings (62.5%). The Table below (Table 2) provides a summary of the incidence of the results.

Table 2

Overall average percent consumption, based on six tablets presented to each of 12 animals.

Treatment	Average percent consumption
A (generic)	56.9%
B (pioneer)	62.5%

Note: All 12 dogs were offered six tablets of the generic treatment and six tablets of the pioneer treatment, for a total of 72 offerings of each type of tablet.

A paired-t test using an arcsin square root transformation done on the difference in the percent consumption concluded that there was insufficient evidence to show that the generic and pioneer tablets were significantly different ($p=.47$).

3. 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 ANADA.

Human warnings are provided on the package label as follows: “**Keep this and all drugs out of the 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.”

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that Ivermectin Chewable Tablets for Dogs, when used under the proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic animal drug, Ivermectin Chewable Tablets, were established by the demonstration of blood-level bioequivalence to the pioneer product, HEARTGARD Chewables, NADA 140-886, sponsored by Merial, Ltd. Palatability was also tested and found to be equivalent to that of the pioneer product.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as indicated below:

Generic Labeling:

Package Insert

Labels associated with foil packet, carton, and display tray:

12 chewable tablets- Dogs up to 25 lbs (blue).

12 chewable tablets- Dogs 26 to 59 lbs (green).

12 chewable tablets- Dogs 51 to 100 lbs (brown).

Pioneer Labeling:

Package Insert

Labels associated with foil packet and carton:

6 chewable tablets- Dogs up to 25 lbs (blue).

6 chewable tablets- Dogs 26 to 59 lbs (green).

6 chewable tablets- Dogs 51 to 100 lbs (brown).

IVERMECTIN Chewable Tablets

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

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.

DOSAGE: IVERMECTIN Chewable Tablets should be administered orally at monthly intervals at the recommended minimum dose level of 6.0 mcg of ivermectin per kilogram (2.72 mcg/lb) of body weight. (See ADMINISTRATION). The recommended dosage schedule for prevention of canine heartworm disease is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Color Coding on Foil Backing and Carton
Up to 25 lb	1	68 mcg	Blue
26 to 50 lb	1	136 mcg	Green
51 to 100 lb	1	272 mcg	Brown

Give dogs over 100 lb the appropriate combination of these chewables.

IVERMECTIN Chewables are recommended for use in dogs 6 weeks of age and older.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to the box to protect the product from light. Because most dogs find IVERMECTIN Chewable Tablets palatable, the product can be offered to the dog by hand. Alternatively, it may be added to a small amount of dog food. If the dog refuses to eat the tablet, place the tablet well into the back of the dog's mouth. Close the dog's mouth and raise its muzzle at the same time. Gently stroke the dog's throat to encourage swallowing.

Care should be taken to see that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

IVERMECTIN Chewable Tablets should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive in a heartworm disease preventive program, the first dose of IVERMECTIN Chewable Tablets must be given within a month (30 days) after the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. For optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with IVERMECTIN Chewable Tablets and resumption of the recommended dosing regimen minimizes the opportunity for the development of adult heartworms.

EFFICACY: IVERMECTIN Chewable Tablets, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *Dirofilaria immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage.

ACCEPTABILITY: In an acceptability trial IVERMECTIN Chewable Tablets were shown to be an acceptable oral dosage form that was consumed at the first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with IVERMECTIN Chewable Tablets which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae prior to initiating a program with IVERMECTIN Chewable Tablets.

While some microfilariae may be killed by the ivermectin in IVERMECTIN Chewable Tablets at the recommended dose level, IVERMECTIN Chewable Tablets are not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin after treatment of some dogs that have circulating microfilariae.

KEEP THIS AND ALL DRUGS OUT OF THE 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.

Store between 15° and 30°C (59° and 86°F). Protect from light.

ADVERSE REACTIONS: The following adverse reactions have been reported following the use of ivermectin tablets: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: Ivermectin has shown a wide margin of safety at the recommended dose level in dogs (See PRECAUTIONS for exceptions) including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines, and steroid preparations have been administered with ivermectin in a heartworm disease preventive program.

Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. Sensitive Collies treated with ivermectin at 10 times the recommended dose (60 mcg/kg) demonstrated no signs of toxicity. Results of these trials support the safety of ivermectin products in dogs, including Collies, when used as recommended.

HOW SUPPLIED: IVERMECTIN Chewable Tablets are available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 12 chewables, packed 12 cartons per tray.

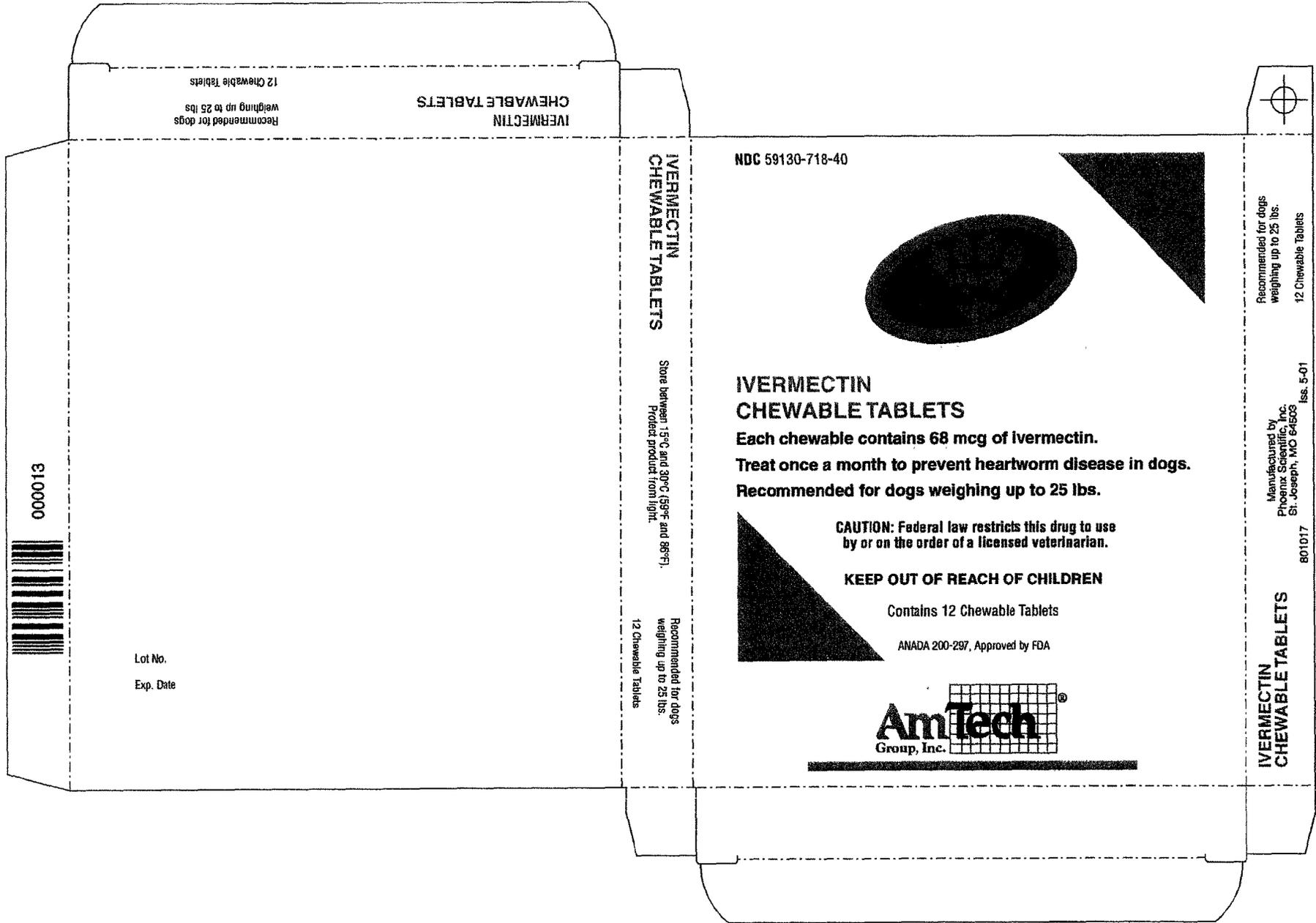
Store between 15°C and 30°C (59°F and 86°F).
Protect product from light.

801017
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801019

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

Iss. 8-00

<p>Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.</p> <p>AmTech GROUP, INC 801017 Iss 8-01</p>	<div style="border: 1px solid black; width: 100px; height: 40px; margin-bottom: 5px;"></div> <p>This blister pack is not labeled for sale of individual tablets</p>	<p>KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN</p> <p>Store between 15°-30°C (59°-86°F)</p> <p>Protect from light</p>
<p>IVERMECTIN CHEWABLES 68 mcg Up to 25 lbs</p>	<p>IVERMECTIN CHEWABLES 68 mcg Up to 25 lbs</p>	<p>IVERMECTIN CHEWABLES 68 mcg Up to 25 lbs</p>
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Recommended for dogs weighing up to 25 lbs.
12 Chewable Tablets

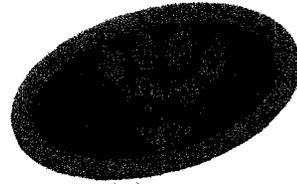
IVERMECTIN CHEWABLE TABLETS

IVERMECTIN CHEWABLE TABLETS

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Protect product from light.

Recommended for dogs weighing up to 25 lbs.
12 Chewable Tablets

NDC 59130-718-40



IVERMECTIN CHEWABLE TABLETS

Each chewable contains 68 mcg of Ivermectin.
Treat once a month to prevent heartworm disease in dogs.
Recommended for dogs weighing up to 25 lbs.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

Contains 12 Chewable Tablets

ANADA 200-297, Approved by FDA



Recommended for dogs weighing up to 25 lbs.
12 Chewable Tablets

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St. Joseph, MO 64508
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IVERMECTIN CHEWABLE TABLETS

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Exp. Date

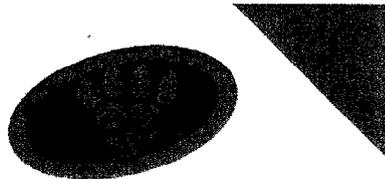
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NDC 59130-718-40



**IVERMECTIN
CHEWABLE TABLETS**

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KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

ANADA 200-297, Approved by FDA



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NDC 59130-718-40

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KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

ANADA 200-297, Approved by FDA



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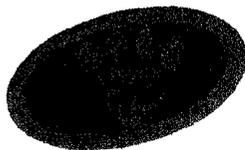


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ANADA 200-297, Approved by FDA



Lot No
Exp. Date

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ANADA 200-297, Approved by FDA



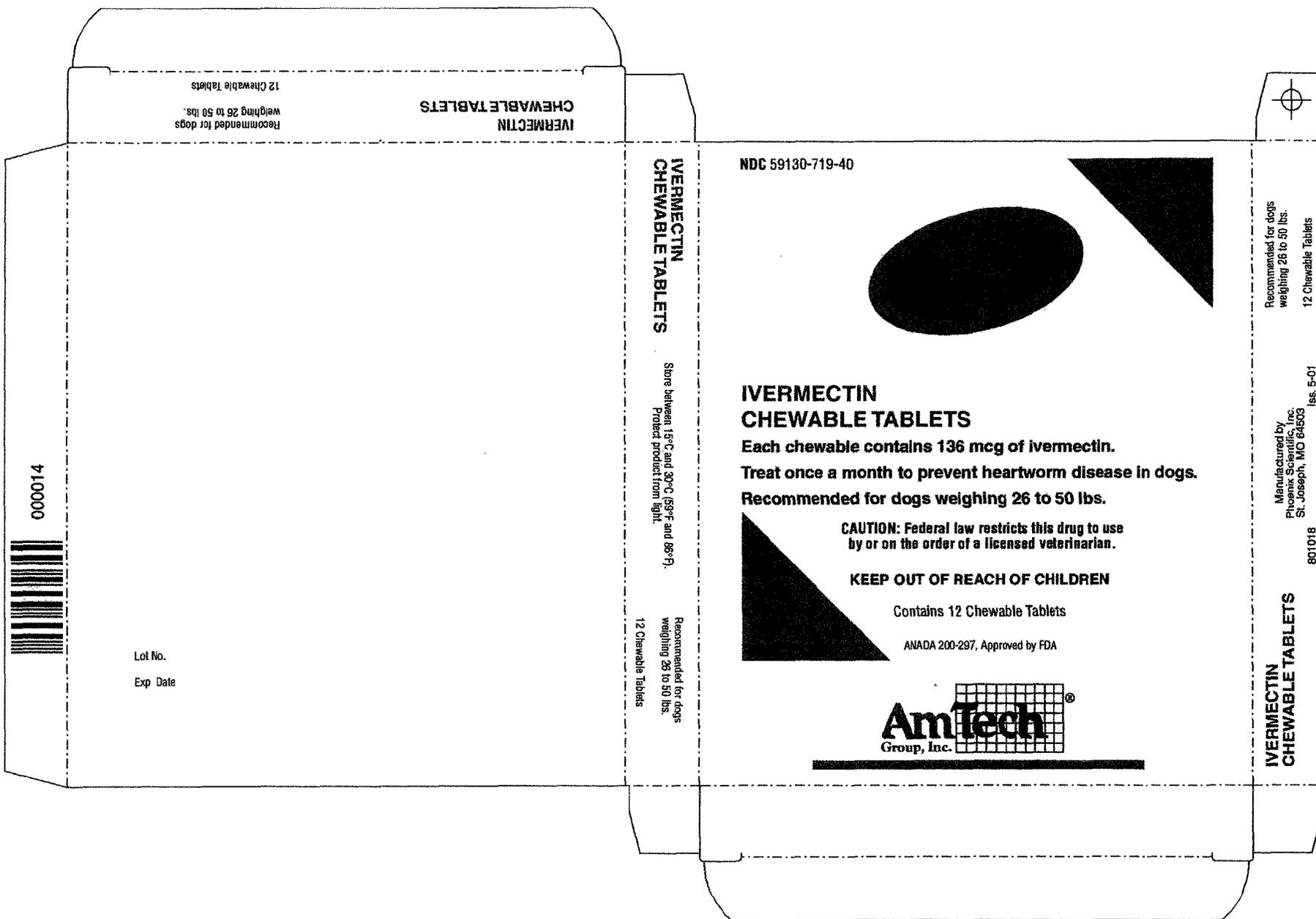
Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

Store between 15°C and 30°C (59°F and 86°F)
Protect product from light.

801017

Iss. 5-01

<p>Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.</p> <p>AmTech GROUP, INC 801018 Iss 8-01</p>	<div data-bbox="646 306 891 391" style="border: 1px solid black; height: 40px; width: 150px; margin-bottom: 5px;"></div> <p>This blister pack is not labeled for sale of individual tablets</p>	<p>KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN</p> <p>Store between 15°-30°C (59°-86°F)</p> <p>Protect from light.</p>
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IVERMECTIN
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Recommended for dogs
weighing 26 to 50 lbs.
12 Chewable Tablets

NDC 59130-719-40



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KEEP OUT OF REACH OF CHILDREN

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ANADA 200-297, Approved by FDA



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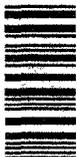
Recommended for dogs
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12 Chewable Tablets

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Iss. 5-01
801018

IVERMECTIN
CHEWABLE TABLETS

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Lot No.
Exp. Date

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KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

ANADA 200-287, Approved by FDA

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Group, Inc.

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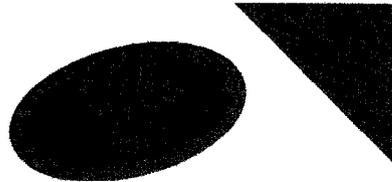


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Manufactured by
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St. Joseph, MO 64503

Store between 15°C and 30°C (59°F and 86°F)
Protect product from light.

801018

Iss. 5-01

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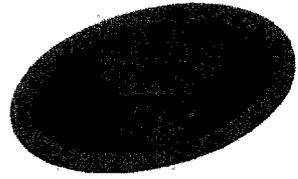


Recommended for dogs weighing 51 to 100 lbs.
12 Chewable Tablets

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503
Iss. 5-01
801019

**IVERMECTIN
CHEWABLE TABLETS**

NDC 59130-720-40



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Treat once a month to prevent heartworm disease in dogs.
Recommended for dogs weighing 51 to 100 lbs.

**CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.**

KEEP OUT OF REACH OF CHILDREN

Contains 12 Chewable Tablets

ANADA 200-297, Approved by FDA



**IVERMECTIN
CHEWABLE TABLETS**

Store between 15°C and 30°C (59°F and 86°F)
Protect product from light.

Recommended for dogs weighing 51 to 100 lbs.
12 Chewable Tablets

**IVERMECTIN
CHEWABLE TABLETS**

Recommended for dogs weighing 51 to 100 lbs.
12 Chewable Tablets

000015



Lot No.
Exp. Date

Top Panel

NDC 59130-720-40

**IVERMECTIN
CHEWABLE TABLETS**

Each chewable contains 272 mcg of ivermectin.
Treat once a month to prevent heartworm disease in dogs.
Recommended for dogs weighing 51 to 100 lbs.

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

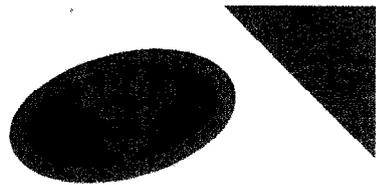
Contains 12 x 12 Chewable Tablets

AMADA 700-297, Approved by FDA

AmTech[®]
Group, Inc.

Left Panel

NDC 59130-720-40



**IVERMECTIN
CHEWABLE TABLETS**

Each chewable contains 272 mcg of Ivermectin.
Treat once a month to prevent heartworm disease in dogs.
Recommended for dogs weighing 51 to 100 lbs.

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

ANADA 200-297, Approved by FDA

AmTech[®]
Group, Inc.

NDC 59130-720-40

**IVERMECTIN
CHEWABLE TABLET**

Each chewable contains 272 mcg of Ivermectin.
Treat once a month to prevent heartworm disease in dogs.
Recommended for dogs weighing 51 to 100 lbs.

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

ANADA 200-297, Approved by FDA

AmTech[®]
Group, Inc.

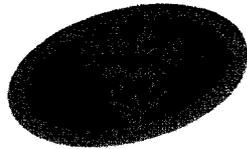


000019



Right Panel

NDC 59130-720-40



**IVERMECTIN
CHEWABLE TABLETS**

Each chewable contains 272 mcg of ivermectin.

Treat once a month to prevent heartworm disease in dogs.

Recommended for dogs weighing 51 to 100 lbs.

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

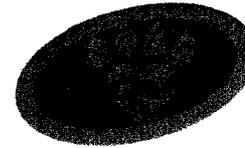
ANADA 200-297, Approved by FDA



Lot No.
Exp. Date

Back Panel

NDC 59130-720-40



**IVERMECTIN
CHEWABLE TABLETS**

Each chewable contains 272 mcg of ivermectin.

Treat once a month to prevent heartworm disease in dogs.

Recommended for dogs weighing 51 to 100 lbs.

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

Contains 12 x 12 Chewable Tablets

ANADA 200-297, Approved by FDA



Manufactured by
Phoenix Scientific, Inc.
St Joseph, MO 64503

Store between 15°C and 30°C (59°F and 86°F)
Protect product from light

801019

Iss. 5-01



08828106

NADA 140-886. Approved by the FDA

8828106

Heartgard®

(ivermectin)

Chewables

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

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.

DOSAGE: HEARTGARD® Chewables should be administered orally at monthly intervals at the recommended minimum dose level of 6.0 mcg of ivermectin per kilogram (2.72 mcg/lb) of body weight. (See ADMINISTRATION). The recommended dosage schedule for prevention of canine heartworm disease is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Color Coding on Foil Backing and Carton
Up to 25 lb	1	68 mcg	Blue
26 to 50 lb	1	136 mcg	Green
51 to 100 lb	1	272 mcg	Brown

Give dogs over 100 lb the appropriate combination of these chewables.

HEARTGARD Chewables are recommended for use in dogs 6 weeks of age and older

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to the box to protect the product from light. Because most dogs find HEARTGARD Chewables palatable, the product can be offered to the dog by hand. Alternatively, it may be added to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken to see that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Chewables should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive in a heartworm disease preventive program, the first dose of HEARTGARD must be given within a month (30 days) after the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. For optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD and resumption of the recommended dosing regimen minimizes the opportunity for the development of adult heartworms.

HEARTGARD is a registered trademark and Dog & Hand logo is a trademark of Merial.

EFFICACY: HEARTGARD® (ivermectin) Chewables, given orally using recommended dose and regimen, are effective against the tissue larval stage *Dirofilaria immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage.

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Chewables were shown to be an acceptable oral dosage form that was consumed at the rate offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD which is not effective against a *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae prior to initiating a program with HEARTGARD.

While some microfilariae may be killed by the ivermectin in HEARTGARD at recommended dose level, HEARTGARD is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin after treatment of some dogs that had circulating microfilariae.

Keep this and all drugs out of the 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 case ingestion by humans.

Store at controlled room temperature of 59°-86°F (15°-30°C). Protect product from light.

ADVERSE REACTIONS: The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomit, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions, hypersalivation.

SAFETY: HEARTGARD has shown a wide margin of safety at the recommended dose level in dogs (See PRECAUTIONS for exceptions) including pregnant breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials many commonly used flea collars, dips, shampoos, anthelmintics, antibiotic vaccines, and steroid preparations have been administered with HEARTGARD Chewables in a heartworm disease preventive program.

Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated dose sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these studies support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HOW SUPPLIED: HEARTGARD Chewables are available in three dose strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 chewables, packed 10 cartons per tray.

For customer assistance, please contact Merial at 1-888-637-4251

Merial Limited
2100 Ronson Road
Iselin, NJ 08830-3077, U.S.A.

(Merial Limited: Registered in England and Wales [Reg. No. 3332751] with registered office at 27 Knightsbridge, London, SW1X 7QT, England and domesticated in Delaware, USA Merial LLC).

U.S. Pat. 4,199,569
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Made in U.S.A.
May 1999



Heartgard[®] [™]
(ivermectin) Chewables

PRODUCT 38174

8826406

MERIAL LIMITED
ISELIN, NJ, USA



EACH CHEWABLE CONTAINS 68 MCG IVERMECTIN
STORE AT CONTROLLED ROOM TEMPERATURE OF
59°-86°F (15°-30°C). PROTECT PRODUCT FROM LIGHT
CAUTION: FEDERAL (U.S.A.) LAW RESTRICTS THIS
DRUG TO USE BY OR ON THE ORDER OF A LICENSED
VETERINARIAN.

KEEP THIS AND ALL DRUGS
OUT OF THE REACH OF CHILDREN.

HEARTGARD[®]
68 MCG IVERMECTIN
CHEWABLES
Merial UP TO 25 LB
JAN/JUL

HEARTGARD[®]
68 MCG IVERMECTIN
CHEWABLES
Merial UP TO 25 LB
APR/OCT

HEARTGARD[®]
68 MCG IVERMECTIN
CHEWABLES
Merial UP TO 25 LB
FEB/AUG

HEARTGARD[®]
68 MCG IVERMECTIN
CHEWABLES
Merial UP TO 25 LB
MAY/NOV

HEARTGARD[®]
68 MCG IVERMECTIN
CHEWABLES
Merial UP TO 25 LB
MAR/SEP

HEARTGARD[®]
68 MCG IVERMECTIN
CHEWABLES
Merial UP TO 25 LB
JUN/DEC

Product 38174
87255

Heartgard[®]
(ivermectin)

6 Chewables

For DOGS
UP TO 25 lbs



000000403926

Lot & Exp

Heartgard[®]
(ivermectin)

6 Chewables
For DOGS
UP TO 25 lbs

Heartgard[®]
(ivermectin)

Treat once a month to prevent
heartworm disease in dogs.

For
DOGS
UP TO 25 lbs

6 Chewables

Each chewable contains 68 mcg of ivermectin.

Keep this and all drugs out
of the reach of children.

Caution: Federal (U.S.A.) law restricts
this drug to use by or on the order of
a licensed veterinarian.



Heartgard[®]
(ivermectin)
For DOGS
UP TO 25 lbs
6 Chewables

Heartgard[®]
(ivermectin)

Heartgard[®]
(ivermectin)



3 50604-40030 1

REXAM

HEARTGARD is a registered trademark and logo is a trademark of Merial.

Merial Limited, Reims, France

U.S. Pat. 4,993,559

Approved by the FDA

NADA 140-886

Protect product from light.

Store at controlled room temperature of 59°-86°F (15°-30°C).

Jan	Feb	Mar	Apr	May	Jun
Jul	Aug	Sep	Oct	Nov	Dec

ENTER DATE ADMINISTERED:

Heartgard[®] 
(ivermectin) Chewables

PRODUCT 38175
8826506

MERIAL LIMITED
ISELIN, NJ, USA



EACH CHEWABLE CONTAINS 136 MCG IVERMECTIN.
STORE AT CONTROLLED ROOM TEMPERATURE OF
59°-86°F (15°-30°C). PROTECT PRODUCT FROM LIGHT
CAUTION: FEDERAL (U.S.A.) LAW RESTRICTS THIS
DRUG TO USE BY OR ON THE ORDER OF A LICENSED
VETERINARIAN.

KEEP THIS AND ALL DRUGS
OUT OF THE REACH OF CHILDREN

HEARTGARD[®]
136 MCG IVERMECTIN
CHEWABLES
MERIAL 26 TO 50 LB
JAN/JUL

HEARTGARD[®]
136 MCG IVERMECTIN
CHEWABLES
MERIAL 26 TO 50 LB
APR/OCT

HEARTGARD[®]
136 MCG IVERMECTIN
CHEWABLES
MERIAL 26 TO 50 LB
FEB/AUG

HEARTGARD[®]
136 MCG IVERMECTIN
CHEWABLES
MERIAL 26 TO 50 LB
MAY/NOV

HEARTGARD[®]
136 MCG IVERMECTIN
CHEWABLES
MERIAL 26 TO 50 LB
MAR/SEP

HEARTGARD[®]
136 MCG IVERMECTIN
CHEWABLES
MERIAL 26 TO 50 LB
JUN/DEC

Product 38175
84256

HeartgardTM
(ivermectin)

6 Chewables

For **DOGS**
26-50 lbs



090000375055

Lot & Exp

HeartgardTM
(ivermectin)

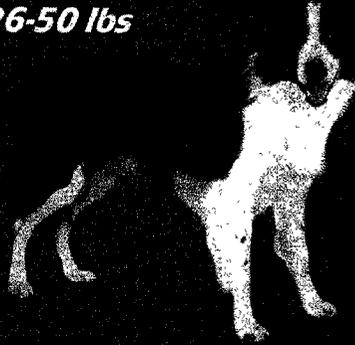
6 Chewables
For **DOGS**
26-50 lbs

HeartgardTM
(ivermectin)

For **DOGS**
26-50 lbs
6 Chewables

Treat once a month to prevent
heartworm disease in dogs.

For
DOGS
26-50 lbs



6 Chewables

Each chewable contains 136 mcg of ivermectin

Keep this and all drugs out
of the reach of children.

Caution: Federal (U.S.A.) law restricts
this drug to use by or on the order of
a licensed veterinarian.



HeartgardTM
(ivermectin)

HeartgardTM
(ivermectin)



3 50604-40040 0

REXAM

HEARTGARD is a registered trademark and Dog & Heart logo is a trademark of Merial.

Merial Limited, Bethel, NJ, USA

U.S. Pat. #1,199,569

Approved by the FDA

NADA 140-886

Store at controlled room temperature of 59°-86°F (15°-30°C).
Protect product from light.

Jul	Aug	Sep	Oct	Nov	Dec
Jan	Feb	Mar	Apr	May	Jun

ENTER DATE ADMINISTERED:

00084256



Heartgard[®]
(ivermectin) Chewables

PRODUCT 38176

8826606

MERIAL LIMITED
ISELIN, NJ, USA



EACH CHEWABLE CONTAINS 272 MCG IVERMECTIN.
STORE AT CONTROLLED ROOM TEMPERATURE OF
59°-86°F (15°-30°C). PROTECT PRODUCT FROM LIGHT.
CAUTION: FEDERAL (U.S.A.) LAW RESTRICTS THIS
DRUG TO USE BY OR ON THE ORDER OF A LICENSED
VETERINARIAN.

KEEP THIS AND ALL DRUGS
OUT OF THE REACH OF CHILDREN

HEARTGARD[®]
272 MCG IVERMECTIN
CHEWABLES
MERIAL 51 TO 100 LB
JAN/JUL

HEARTGARD[®]
272 MCG IVERMECTIN
CHEWABLES
MERIAL 51 TO 100 LB
APR/OCT

HEARTGARD[®]
272 MCG IVERMECTIN
CHEWABLES
MERIAL 51 TO 100 LB
FEB/AUG

HEARTGARD[®]
272 MCG IVERMECTIN
CHEWABLES
MERIAL 51 TO 100 LB
MAY/NOV

HEARTGARD[®]
272 MCG IVERMECTIN
CHEWABLES
MERIAL 51 TO 100 LB
MAR/SEP

HEARTGARD[®]
272 MCG IVERMECTIN
CHEWABLES
MERIAL 51 TO 100 LB
JUN/DEC

Product 38176
84257

Heartgard[®]

(ivermectin)

For DOGS
51-100 lbs

6 Chewables

Lot & Exp

Heartgard[®]

(ivermectin)

For DOGS
51-100 lbs

6 Chewables

Treat once a month to prevent
heartworm disease in dogs.

For
DOGS
51-100 lbs



6 Chewables

Each chewable contains 272 mcg of ivermectin.

Keep this and all drugs out
of the reach of children.

Caution: Federal (U.S.A.) law restricts
this drug to use by or on the order of
a licensed veterinarian.



Heartgard[®]
(ivermectin)

For DOGS
51-100 lbs
6 Chewables

Heartgard[®]
(ivermectin)

Heartgard[®]

(ivermectin)



REXAM

HEARTGARD[®] is a prescription heartworm and flea preventive for dogs. It is a member of Merial.

Merial Limited, Teaneck, NJ, USA

U.S. Pat. 4,155,569

Approved by the FDA

NADA 140-886



Protect product from light.

Store at controlled room temperature of 59°-86°F (15°-30°C).

Jul	Aug	Sep	Oct	Nov	Dec
Jan	Feb	Mar	Apr	May	Jun

ENTER DATE ADMINISTERED:

00084257

