

# Step into the **NEXT** **GENERATION** of Internal Parasite Protection



**NEW!**

From the maker of  
**HEARTGARD® Plus**  
(ivermectin/pyrantel).

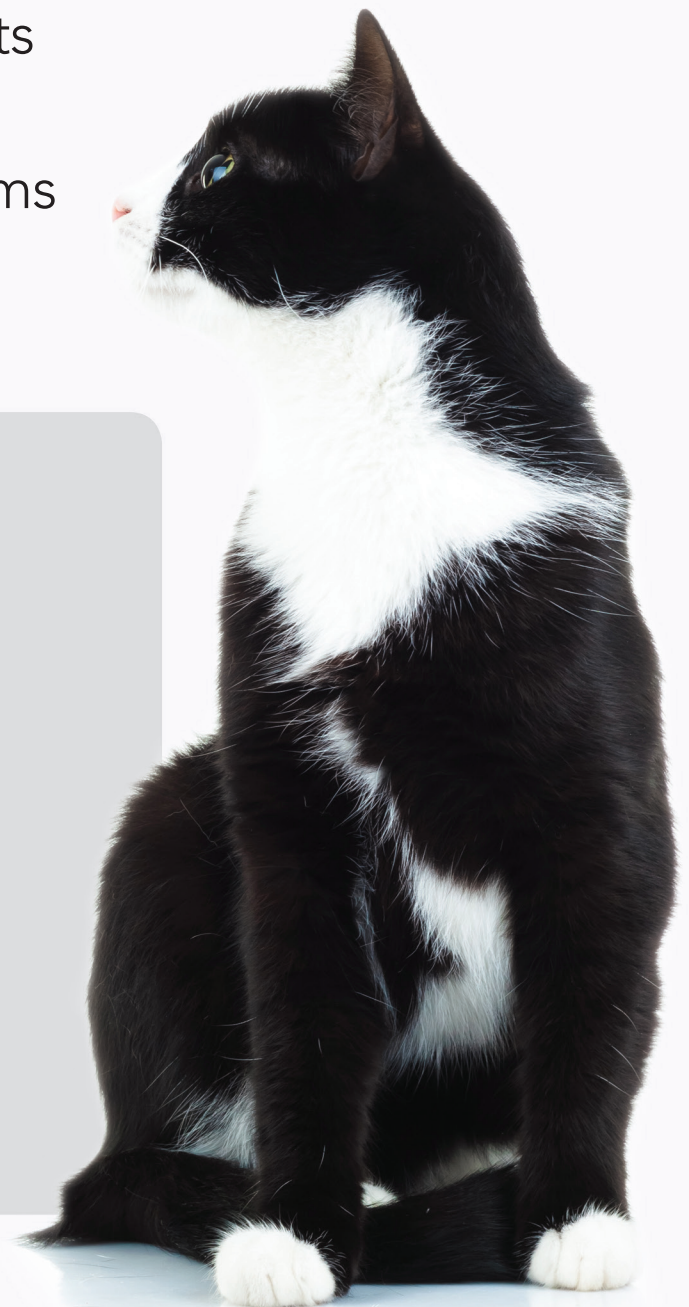


**Centragard™**  
(eprinomectin and praziquantel  
transdermal solution)

# INTRODUCING *AN INNOVATIVE*

transdermal heartworm  
disease preventive that treats  
and controls hookworms,  
roundworms **AND** tapeworms  
in cats and kittens.

- ✓ First feline product to combine  
eprinomectin & praziquantel
- ✓ Broad-spectrum internal parasite protection
- ✓ Approved for cats and kittens as young as 7  
weeks of age and weighing as little as 1.8 lbs
- ✓ Easy-to-use, stress-free applicator
- ✓ Flexible option for your practice. Can be  
used monthly for year-round heartworm  
disease prevention and deworming OR  
as needed for treatment and control of  
hookworms, roundworms, and tapeworms  
for your patients whose owners decline  
year-round heartworm disease protection.



## **CENTRAGARD™** (epinomectin and praziquantel transdermal solution)



**PREVENTS HEARTWORM DISEASE**



**TREATS & CONTROLS ROUNDWORMS (*Toxocara cati*)**



**TREATS & CONTROLS HOOKWORMS**  
(2 SPECIES: *Ancylostoma tubaeforme* and *Ancylostoma braziliense*)



**TREATS & CONTROLS TAPEWORMS**  
(2 SPECIES: *Dipylidium caninum* and *Echinococcus multilocularis*)



**AVAILABLE IN  
1- & 3-DOSE PACKS**

**IMPORTANT SAFETY INFORMATION:** For topical use only. Side effects may include emesis, anorexia, lethargy, and hair changes and skin reactions at the site of application. If ingested, hypersalivation, vomiting and lethargy may be observed. The safety of CENTRAGARD has not been tested in kittens less than 7 weeks of age or less than 1.8 lbs. For more information, see complete prescribing information.



# BROAD-SPECTRUM PROTECTION

Deadly and dangerous parasites can infect cats, too

## THE FACTS ON FELINE HEARTWORM DISEASE:

According to the American Heartworm Society:

- ♥ Only 5% of cats are on year-round heartworm disease prevention<sup>1</sup>
- ♥ 1 in 4 heartworm-infected cats live indoors<sup>2</sup>

## HEARTWORM DISEASE IN CATS IS VERY DIFFERENT FROM HEARTWORM DISEASE IN DOGS.

- Cats are atypical hosts for heartworms, so many of the heartworm larvae don't survive to adulthood.
- Immature worms can cause serious damage in cats when they first arrive to the blood vessels of the heart and lungs (~3-4 months post-infection) via a condition known as heartworm associated respiratory disease (HARD). The signs associated with this condition often mimic those of other respiratory diseases, such as feline asthma, and thus the diagnosis may be missed.
- The surviving juvenile heartworms mature into adults in about six to eight months and can live up to two or three years in cats. Death of adult heartworms often potentiates HARD signs, and it is also associated with sudden death of infected cats.

## SIGNS OF HEARTWORM DISEASE IN CATS CAN INCLUDE:

- ✓ COUGHING
- ✓ PERIODIC VOMITING
- ✓ LOSS OF APPETITE
- ✓ WEIGHT LOSS
- ✓ DIFFICULTY WALKING
- ✓ FAINTING
- ✓ SEIZURES
- ✓ IN SOME CASES, THE FIRST SIGN IS SUDDEN DEATH

**Centragard**   
(eprinomectin and praziquantel  
transdermal solution)





## HOOKWORMS

- Use their hook-like mouths to attach to the intestinal walls
- Cause blood loss and intestinal inflammation, which can result in diarrhea, weight loss, and anemia
- Large, untreated infestations can cause death, especially in kittens

### How cats get hookworms:

- Ingestion of infective larvae from a contaminated environment (often via grooming)
- Larval penetration of the skin
- Ingesting an infected intermediate host, such as rodents

## ROUNDWORMS

- Live and feed in an infected cat's intestines
- Can cause diarrhea, vomiting and weight loss
- Are the most common feline intestinal parasites in kittens<sup>3</sup>

### How cats get roundworms:

- Kittens can be infected while nursing
- Ingestion of larvated eggs from a contaminated environment (often via grooming)
- Ingesting an infected intermediate host, such as a rodent
- Other animals, such as earthworms, that harbor infective eggs can serve as a source of infection to cats

**CATS THAT HUNT ARE AT AN INCREASED RISK OF ACQUIRING MANY OF THESE INTESTINAL PARASITES.**

## TAPEWORMS

- Attach to the intestines of dogs and cats\*
- Steal nutrients from a cat's intestines\*
- Are often seen by cat owners around the cat's rectum, and in their feces\*

### How cats get tapeworms:

- Ingesting infected fleas while grooming\*
- Ingesting an infected rodent

\* Only applies to *D. caninum*.



# BROAD-SPECTRUM, BREAKTHROUGH SCIENCE

Innovative pairing of proven molecules

**CENTRAGARD** is the first feline product to pair eprinomectin with praziquantel. The result is the first and only transdermal solution that prevents heartworm disease and treats and controls internal parasites that can infect cats and kittens: hookworms, roundworms and tapeworms.

## Eprinomectin

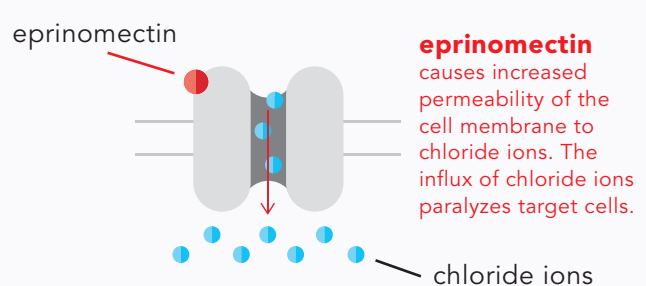
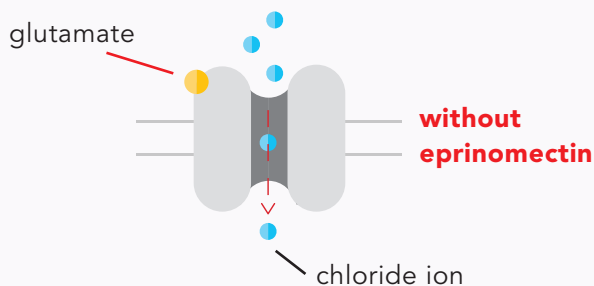
A macrocyclic lactone (ML) anthelmintic, eprinomectin targets specific glutamate-gated chloride ion channels, effectively causing muscle paralysis in the parasite.<sup>4</sup>

## Praziquantel

Praziquantel's mode of action is not precisely known but treated tapeworms undergo muscular paralysis accompanied by a rapid influx of calcium ions and the disruption of the tegument.

## WHAT DOES EPRINOMECTIN DO?

**Eprinomectin** binds to glutamate-gated chloride channels that are present in invertebrate nerve and muscle cells, causing increased permeability of the cell membrane to chloride ions. This triggers hyperpolarization of the nerve or muscle cell resulting in paralysis and death of the parasite.

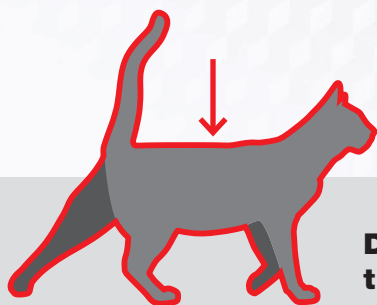


### IN HOOKWORMS & ROUNDWORMS,

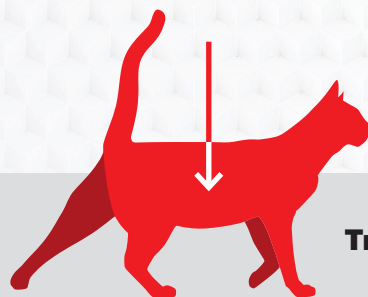
eprinomectin targets the muscles affecting locomotion (movement) and pharyngeal (swallowing) muscles, causing death.<sup>4</sup>

### IN HEARTWORMS,

eprinomectin paralyzes the muscles near the excretory-secretory apparatus, inhibiting the worm's ability to "hide" from the animal's immune system. The animal's immune system kills the microscopic infective larvae and microfilariae.<sup>5</sup>



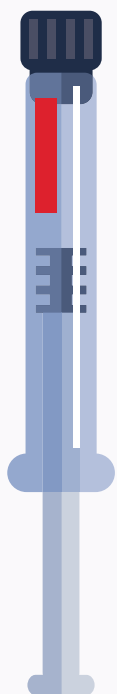
**Distributed  
topically**



**Transdermal**

## WHAT IS TRANSDERMAL ABSORPTION?

- Many topically applied products are designed to deliver the active ingredients to the outer layers of the skin without significant systemic absorption.
- Transdermal products such as CENTRAGARD are absorbed through the skin and taken into the blood stream for distribution throughout the body.



**EASY-TO-USE,  
STRESS-FREE  
APPLICATOR!**

**24**

**HOURS**

Median peak plasma levels of eprinomectin were reached in 24 hours.<sup>6</sup>

**6**

**HOURS**

Median peak plasma levels of praziquantel were reached in 6 hours.<sup>6</sup>

**Centragard™**  
(eprinomectin and praziquantel  
transdermal solution)



**IMPORTANT SAFETY INFORMATION:** For topical use only. Side effects may include emesis, anorexia, lethargy, and hair changes and skin reactions at the site of application. If ingested, hypersalivation, vomiting and lethargy may be observed. The safety of CENTRAGARD has not been tested in kittens less than 7 weeks of age or less than 1.8 lbs. For more information, see complete prescribing information.



# Centragard™

(epinomectin and praziquantel  
transdermal solution)

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

**Description:**

CENTRAGARD is a transdermal solution containing eprinomectin and praziquantel available in 0.3 mL and 0.9 mL unit applicators to treat cats from 1.8 lbs to 33 lbs. Each mL of CENTRAGARD contains 4 mg of eprinomectin and 83 mg of praziquantel, as well as the inactive ingredients (dimethyl isosorbide, glycerol formal, and butylated hydroxytoluene). Eprinomectin belongs to the avermectin class of anthelmintics and is a mixture of homologous components referred to as eprinomectin B1a and B1b. Praziquantel is a pyrazinoisoquinoline anthelmintic.

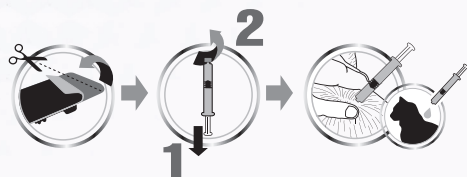
**Indications:**

CENTRAGARD is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*, and for the treatment and control of roundworms (adult and fourth stage larval *Toxocara cati*), hookworms (adult and fourth stage larval *Ancylostoma tubaeforme*, adult *Ancylostoma braziliense*), and tapeworms (adult *Dipylidium caninum* and *Echinococcus multilocularis*) in cats and kittens 7 weeks of age and older and 1.8 lbs or greater.

**Dosage and Administration:**

CENTRAGARD is dosed at a minimum of 0.055 mL/lb (0.12 mL/kg), which delivers a minimum dose of 0.23 mg/lb eprinomectin and 4.55 mg/lb praziquantel. Administer the entire contents of a CENTRAGARD unit applicator topically once a month as specified in the following table:

Cat Weight (lb)	Volume (mL)	Eprinomectin (mg)	Praziquantel (mg)
1.8-5.5	0.3	1.2	24.9
5.6-16.5	0.9	3.6	74.7
16.6-22.0	0.3+0.9	4.8	99.6
22.1-33.0	0.9+0.9	7.2	149.4



To apply CENTRAGARD pull back the plunger of the unit applicator slightly and remove the cap. Part the hair in one spot on the midline of the neck between the base of the skull and the shoulder blades, place the tip of the unit applicator on the skin and apply the contents directly on the skin. If the weight of the cat requires a second application, apply the contents in the same manner as described above in the same location. Discard applicator after use.

**Heartworm Prevention:**

For prevention of heartworm disease, CENTRAGARD should be administered once a month. CENTRAGARD may be administered year round or at a minimum, should start 1 month before the cat's first expected exposure to mosquitoes and continuing at monthly intervals until at least one month after the cat's last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer CENTRAGARD immediately and resume the monthly dosing schedule.

When replacing another monthly heartworm preventive product in a heartworm prevention program, the first treatment with CENTRAGARD should be given within one month of the last dose of the former medication. At the discretion of the veterinarian, cats older than 6 months of age may be tested to determine the presence of existing heartworm infection before treatment with CENTRAGARD.

**Treatment and Control of Roundworms, Hookworms and Tapeworms:**

CENTRAGARD treats and controls roundworms (adult and fourth stage larval *Toxocara cati*), hookworms (adult and fourth stage larval *Ancylostoma tubaeforme*, adult *Ancylostoma braziliense*), and tapeworms (adult *Dipylidium caninum* and *Echinococcus multilocularis*) after a single administration or when given monthly as part of a heartworm prevention program. Cats may be exposed to and can become infected with roundworms, hookworms, and tapeworms throughout the year, regardless of season or climate. Clients should be advised of appropriate measures to prevent reinfection of their cat with intestinal parasites. Because the prepatent period for *E. multilocularis* may be as short as 26 days, cats treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

**Human Warning:**

Not for human use. Keep out of reach of children. Avoid contact with the application site for 5 hours following treatment. Wash hands after administering the product. If the product accidentally gets into the eyes, flush thoroughly with water. In case of accidental ingestion, or if skin or eye irritation occurs, contact a poison control center or physician for treatment advice.

**Precautions:**

Do not administer orally. Cats may salivate excessively and vomit if CENTRAGARD is accidentally administered orally or is ingested through licking/grooming the application site (see ANIMAL SAFETY).

The safety of CENTRAGARD has not been tested in breeding, pregnant or lactating cats.

The safety of CENTRAGARD has not been tested in kittens less than 7-9 weeks of age or weighing less than 1.8 lbs (0.8 kg).

**Adverse Reactions:**

In a well-controlled field study emesis, anorexia, lethargy, temporary clumping or spiking of the hair, or mild, transient skin reactions (itching, hair loss) were reported. When cats licked the application site after treatment, temporary excessive salivation was observed. Oral ingestion of CENTRAGARD may also result in hypersalivation, vomiting and/or lethargy. In margin of safety studies, transient neurological signs such as ataxia, disorientation, lethargy, and pupil dilation were observed in some cats. Correct application will minimize the occurrence of such events.

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Merial at 1-888-637-4251.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

The Safety Data Sheet (SDS) provides additional occupational safety information. For customer service or to obtain product information, including the SDS, call 1-888-637-4251.

**Information for Owner or Person Treating Animal:**

*Echinococcus multilocularis* is a tapeworm found in wild canids and domestic cats. *E. multilocularis* can infect humans and cause serious disease (alveolar hydatid disease). Owners of cats living in areas where *E. multilocularis* are endemic should be instructed on how to minimize their risk of exposure to this parasite, as well as their cat's risk of exposure. Although ML-635 was 100% effective in laboratory studies in cats against *E. multilocularis*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, cats treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

**Mode of Action:**

Eprinomectin binds to glutamate gated chloride channels that are present in invertebrate nerve and muscle cells and increases the permeability of the cell membrane to chloride ions that triggers hyperpolarization of the nerve or muscle cell resulting in paralysis and death of the parasite.

Praziquantel's mode of action is not precisely known but treated tapeworms undergo muscular paralysis accompanied by a rapid influx of calcium ions and the disruption of the tegument.

**Effectiveness:**

Effectiveness studies were conducted with an early formulation (ML-635), containing 8.3% fipronil, 0.4% eprinomectin, 8.3% praziquantel, and 10% (*S*)-methoprene. The doses of eprinomectin and praziquantel in ML-635 are equivalent to the final formulation of CENTRAGARD (epinomectin and praziquantel transdermal solution).

**Heartworm Disease Prevention:**

In well-controlled laboratory studies, ML-635 provided 100% effectiveness against induced heartworm infections after a single application.

**Treatment and Control of Roundworms, Hookworms, and Tapeworms:**

In well-controlled laboratory studies, ML-635 provided >90% effectiveness against natural and/or induced roundworm (adult and fourth stage larval *Toxocara cati*), hookworm (adult and fourth stage larval *Ancylostoma tubaeforme*, adult *Ancylostoma braziliense*), and adult tapeworm (*Dipylidium caninum*; *Echinococcus multilocularis*) infections.

**Animal Safety:**

**Margin of Safety Study:** A combination of fipronil, eprinomectin, praziquantel, and (*S*)-methoprene was applied topically to 7 to 9 week old healthy kittens at 1, 3, or 5X the maximum dose (8 cats/group) six times at 28 day intervals. One 5X kitten exhibited ataxia, disorientation, and lethargy for 12 hours and exhibited pupil dilation for 24 hours following the 3rd treatment. This 5X kitten exhibited ataxia, disorientation, and lethargy for 6 hours, and moderate pupil dilation for 24 hours following the 4th treatment, and had pupil dilation following the 5th treatment. Hypersalivation was observed for one hour for one 5X kitten following the 1st treatment and one 3X kitten following the 4th treatment. One 5X kitten had slow pupillary light responses for one day after one treatment and one 3X kitten had slow pupillary light responses for 3 hours after one treatment. One control cat had marked pupil dilation and slow pupillary light responses lasting two hours after one treatment. Immediately post-treatment cats in all groups scratched and groomed the application site.

**Study in Heartworm Positive Cats:** Three groups (0X, 1X and 3X) of 12 young, adult cats, 4.7 to 6.6 months of age, were experimentally infected with adult heartworms (*D. immitis*) by venous transplantation. All cats were negative for heartworm antibody, antigen and microfilariae prior to transplantation. Two weeks after transplantation, immunoserology verified positive antigen and the presence of microfilaria in all enrolled cats. A combination of fipronil, eprinomectin, praziquantel, and (*S*)-methoprene was applied topically to cats at 1X or 3X the maximum exposure dose once every 28 days for three consecutive treatments. One cat in the 1X group exhibited cyanotic mucous membranes and tachypnea for 24 hours following the first treatment. The cat recovered and exhibited no abnormal signs following two subsequent treatments. There was no difference between the treatment groups in the number of adult *D. immitis* recovered at the end of the study.

**Oral Administration Study:** Oral tolerance was evaluated to assess the effects of accidental oral ingestion.

Sixteen cats (8 male and 8 female) ranging in age from 9 - 10 months were studied. Eight cats were orally administered a combination of fipronil, eprinomectin, praziquantel, and (*S*)-methoprene at 1X the maximum exposure dose; the 8 control cats were sham dosed. All 8 treated cats immediately exhibited hypersalivation after oral administration, and 2 cats vomited and 3 cats were lethargic during the 1-2 hour post-treatment observations. Treated cats continued to hypersalivate and lick lips/mouth for 1-2 hours after oral administration. Cats were monitored for 14 days thereafter, during which one treated cat vomited on Day 12.

**Storage Information:**

Store at or below 30°C (86°F) with excursions permitted to 40°C (104°F). Protect from light.

**How Supplied:**

CENTRAGARD is packaged as a single dose in 0.3 mL (for cats 1.8 – 5.5 lb) and 0.9 mL (for cats 5.6 – 16.5 lb) applicators.

Each size applicator is available in cartons containing 1, 3 or 6 applications.

NADA 141-492, Approved by FDA

Manufactured for:

Merial, Inc.,

Duluth, GA 30096-4640

USA

Made in France

CENTRAGARD™ is a trademark of Merial.

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# REFERENCES:

<sup>1</sup> Feline Heartworm Facts (infographic). American Heartworm Society website. <https://www.heartwormsociety.org/images/pdf/InfographicTake50nFelineHWD.pdf>. Accessed July 31, 2018.

<sup>2</sup> Heartworm Tall Tales (infographic). American Heartworm Society website. [https://www.heartwormsociety.org/images/pdf/Tall\\_Tales\\_indoor.pdf](https://www.heartwormsociety.org/images/pdf/Tall_Tales_indoor.pdf). Accessed July 31, 2018.

<sup>3</sup> Cornell Feline Health Center. Gastrointestinal Parasites of Cats. Cornell University College of Veterinary Medicine website. <https://www2.vet.cornell.edu/departments-centers-and-institutes/cornell-feline-health-center/health-information/feline-health-topics/gastrointestinal-parasites-cats>. Updated June 2018. Accessed July 31, 2018.

<sup>4</sup> Kvaternick V, Kellerman M, Knaus M, Rehbein S, Rosentel J. Pharmacokinetics and metabolism of eprinomectin in cats when administered in a novel topical combination of fipronil, (S)-methoprene, eprinomectin and praziquantel. *Veterinary Parasitology*. 2014;202(1-2):2-9.

<sup>5</sup> Carithers DS. Examining the role of macrolides and host immunity in combatting filarial parasites. *Parasites & Vectors*. 2017;10(182). DOI 10.1186/s13071-017-2116-6.

<sup>6</sup> Data on file.





**Centragard**<sup>TM</sup> <sup>TM</sup>  
(eprinomectin and praziquantel  
transdermal solution)







# NEW!

From the maker of  
**HEARTGARD® Plus.**  
(ivermectin/pyrantel)

For more information, contact your Boehringer Ingelheim  
Sales Representative or call 1-888-637-4251



CENTRAGARD and HEARTGARD Plus are Merial products.  
Merial is now part of Boehringer Ingelheim.



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