

## **I. GENERAL INFORMATION**

### **A. File Number**

NADA 136-483

### **B. Sponsor**

Norden Laboratories  
601 West Cornhusker Hwy  
Lincoln, Nebraska 68521

### **C. Proprietary Name**

Filaribits® Plus Chewable Tablets

### **D. Established Name**

diethylcarbamazine citrate and oxibendazole chewable tablets

### **E. Dosage Form, Route of Administration and Dosage Regimen**

FILARIBITS Plus are chewable tablets that are palatable to most dogs. Tablets may be fed free-choice or placed on food. FILARIBITS Plus are scored for convenient adjustment of dosage.

For the Prevention of Heartworm Disease, Hookworm Infection and for the Removal and Control of Whipworms and Mature and Immature Stages of Intestinal Ascarids in Dogs.

FILARIBITS Plus are given orally (once a day) at a dosage rate of 3 mg diethylcarbamazine citrate and 2.27 mg oxibendazole per pound of body weight. Young dogs may be started on the preventive program at two months of age. Administration of FILARIBITS Plus in heartworm or hookworm endemic areas should start prior to hookworm exposure and at least one month before the beginning of the mosquito season. FILARIBITS Plus administration should continue daily throughout the entire period of exposure to hookworms and two months past the mosquito season since there is little residual effect of the drugs. Continuous low level administration effectively prevents maturation of hookworms (*A. caninum*) and recently inoculated heartworm larva (*D. immitis*) into adults and provides for the removal and control of whipworms (*T. vulpis*) and mature and immature stages of intestinal ascarids (*T. canis*). If FILARIBITS Plus is discontinued because of seasonal heartworm problems, hookworm prevention or therapy and whipworm and ascarid removal and control should be continued.

### **F. Dispensing Status**

Prescription Drug - Accurate laboratory diagnosis for the presence of existing heartworm disease is required in the proper use of the product.

### **G. Species/Class**

Dogs

### **H. Indication**

FILARIBITS Plus are indicated for use in the prevention of infection with *Dirofilaria immitis* (heartworm disease), *Ancylostoma caninum* (hookworm infection), the removal and control of *Trichuris vulpis* (whipworm infection) and the removal and control of mature and immature stages of intestinal *Toxocara canis* (ascarid infection) in dogs. FILARIBITS Plus may be given to dogs of all ages, including bitches, throughout the reproductive period and following whelping.

### **I. Effect of Supplement**

Results in the addition of a label statement to provide for the removal and control of mature and immature stages of intestinal *Toxocara canis* (ascarid infection). Adequate data showing efficacy for the additional use has been submitted in the supplemental application which is the subject of this approval.

## **II. EFFECTIVENESS**

### **A. LABORATORY STUDIES**

The efficacy of FILARIBITS Plus in removing and controlling ascarids is reported in four critical laboratory efficacy studies involving a total of 42 dogs (Table I).

Critical laboratory studies were conducted by the following investigators:

M.L. Sharp, D.V.M.  
Sharp Veterinary Research  
P.O. Box 353  
Vernon, TX 76384

John McCall, Ph.D.  
TRS Labs, Inc.  
295 Research Road  
Athens, GA 30605

S.M. Kruckenberg, D.V.M., Ph.D.  
Kruckenberg Drug Research  
2851 Oregon  
Manhattan, KS 66502

Critical laboratory studies were conducted using each animal as its own control. Efficacy of FILARIBITS Plus was determined using the formula:

$$\%Efficacy = \frac{No. Parasites Removed}{No. Parasites Removed + No. Parasites Remaining} \times 100$$

Treated dogs showed 100% ascarid removal in all four studies, (Tables II, III, IV and V) after a 30 day treatment period.

### **B. CLINICAL (FIELD) STUDIES**

In the clinical (field) trials, 68 dogs from eighteen veterinary practices in twelve states were studied. All dogs were infected with ascarids when entering the study. They received FILARIBITS Plus as the only deworming agent for an average of

73.5 days. Eleven ascarid infected dogs in a control group received a diethylcarbamazine citrate containing product (FILARIBITS) for an average of 71 days. Fecal examinations were conducted in all dogs before and at approximately 4 week intervals during the trials.

In pivotal studies seven (7) of the eighteen (18) investigators evaluated controls (FILARIBITS) as well as treated cases (FILARIBITS Plus). Using a Mantel-Haenszel test on data from the pivotal studies and evaluated at the first two fecal recheck examinations, the number of dogs cleared of ascarids is significantly greater ( $P < 0.02$ ) for the FILARIBITS Plus groups than the FILARIBITS groups. The results of the field trials are shown in Tables VI and VII.

In corroborative studies eleven (11) of the eighteen (18) investigators evaluated the efficacy of FILARIBITS Plus. The results of these studies are shown in Table VI.

### **III. TARGET ANIMAL SAFETY**

No adverse reactions or unusual observations associated with FILARIBITS Plus were reported by investigators conducting the critical laboratory trials.

Untoward reactions in the clinical trials were minimal in number as well as severity. Investigators in the clinical trials reported one or more of the following side effects in a total of 4 dogs: vomiting, diarrhea, anorexia, tenesmus and depression plus elevated serum alkaline phosphatase and white blood cell count levels. Safety was rated excellent or good in all of the dogs by the investigators.

Labeling contains a boxed warning that addresses the occasional association with hepatic toxicity including several fatalities. It also provides advice for monitoring of animals receiving the drug and the clinical/biochemical criteria which should be considered.

For additional information on target animal safety studies, refer to the Freedom of Information Summary filed for the original approval.

This supplement falls under Category II Supplements in which the safety data is unchanged and re-evaluation was not required. Federal Register, Vol. 42, No. 247, P. 64367-64371.

### **IV. HUMAN FOOD SAFETY**

Data on human food safety, pertaining to consumption of drug residues in food, were not required for the approval of this NADA. The drug is labeled to be used in dogs, which are non-food animals.

Human Safety considerations other than food safety. No identified hazards or characteristics of the drug were observed in a wide range of toxicological studies. No specific precautions over and above those normally used when handling drug substances are indicated.

**V. AGENCY CONCLUSIONS**

The data in support of this supplemental new animal drug application comply with the requirements of Section 512 of the Act and demonstrate that Filaribits-Plus (diethylcarbamazine citrate and oxibendazole) when used as directed is both safe and effective for the removal and control of mature and immature stages of intestinal *Toxocara canis* (ascarid infection) in dogs.

According to the Center's supplemental approval policy (42 FR 64367), this is a Category II change. The approval of this supplemental application had no adverse effect on the safety and effectiveness of this new animal drug because it provides solely for a claim of a new parasite species. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

The product is categorized as Rx because veterinary intervention is needed to diagnose heartworm, hookworm, whipworm and ascarid positive animals. Animals having heartworms and hookworms would have to be converted to a parasite negative status by the veterinarian prior to being placed on prophylactic therapy.

The Clinical Field Trials were conducted by the following investigators:

Dr. Horace Blalock  
Highland Animal Hospital  
2124 Highland  
Augusta, GA 30904

Dr. Mike Groh  
Blue Springs Animal Hospital  
1201 W. 40 Hwy.  
Blue Springs, MO 64015

Dr. W. A. Bryant  
Pulaski Veterinary Clinic  
Rt. 6  
Waynesville, MO 65583

Dr. Gary Heinzle  
610 South Jeffers  
North Platte, NE 69101

Dr. G. W. Buckaloo  
Crysler Animal Hospital  
12440 East New 40 Hwy.  
Independance, MO 64055

Dr. John C. Leite  
Animal Clinic of Westerville  
153 S. Sunbury Road  
Westerville, OH 43081

Dr. G. W. Buckaloo  
Crysler Animal Hospital  
12440 East New 40 Hwy.  
Independance, MO 64055

Dr. Jim Maxted  
2 East Anson  
Marshalltown, IA 50158

Dr. Don Buller  
Bethalto Animal Clinic  
132 Bethalto Blvd.  
Bethalto, IL 62010

Dr. Robert Neunzig  
Forrest Brook Animal Clinic  
3200 Union Road  
Gaston, NC 28052

Dr. Vincent Castellano  
Cobleskill Veterinary Clinic  
Cobleskill, NY 12043

Dr. James Snodgrass  
Baxter County Animal Clinic  
200 Bomber Blvd.  
Mountain Home, AR 72653

Dr. Charles Conrad  
Fort Plain Animal Hospital  
Fort Plain, NY 13339

Dr. Wm. W. Somerville  
Rt. 2, Box 336  
Hwy 163 W  
Clinton, IN 47842

Dr. Dean Frey  
Frey Animal Clinic  
1823 16th Ave. S.W.  
Cedar Rapids, IA 52404

Dr. John H. Thomas  
P.O. Box 1521  
Martinsville, IN 46151

Dr. Wm. Gengler  
Animal Hospital of Verona  
203 W. Verona Ave.  
Verona, WI 53593

Dr. George Wadley  
Wadley Animal Clinic  
Rt. 4, Box 166  
Searcy, AR 72143

Dr. Brooks K. Glass  
1916 Manchester Exp.  
Columbus, GA 31904

**TABLE I Summary of Filaribits® Plus Efficacy in Removal of Ascarid Infections in Laboratory Studies**

Investigator	Type of Study	Study Number	%Efficacy Dogs cleared at approximately 30 days	
			<i>Toxocara canis</i>	<i>Toxascaris leonina</i>
Sharp	Critical	85-030-0302	(9/9) 100%	
Sharp	Critical	86-001-0102	(16/16) 100%	
Kruckenberg	Critical	86-115-0102	(9/9) 100%	(2/2) 100%
McCall	Critical	86-116-0102	(8/8) 100%	

**TABLE II The Effectiveness of Filaribits® Plus in Removing Ascarids from Dogs (Sharp 85-030-0302)**

Dog Number	Ascarids passed/Ascarids Retained <i>T. canis</i> (Mature)	Ascarids passed/Ascarids Retained <i>T. canis</i> (Immature)
655	6/0	
731	16/0	
688	10/0	
735	23/0	5/0
714	12/0	2/0
627	12/0	5/0
700	37/0	
617		2/0
696	13/0	2/0
Totals		
9 dogs	129/0	16/0

**TABLE III The Effectiveness of Filaribits® Plus in Removing Ascarids from Dogs Weighing Less Than 20 Pounds (Sharp 86-001-0102)**

Dog Number	Ascarids passed/Ascarids Retained <i>T. canis</i> (Mature)	Ascarids passed/Ascarids Retained <i>T. canis</i> (Immature)
729	10/0	10/0
764	7/0	
792		7/0
794		8/0
796		7/0
798		6/0
800		11/0
802		8/0
768	10/0	52/0
770	2/0	21/0
816	15/0	
822	23/0	55/0
824	28/0	85/0
826	9/0	1/0
828	4/0	
830	19/0	
Totals:		
16 dogs	127/0	271/0

**TABLE IV The Effectiveness of Filaribits® Plus in Removing Ascarids from Dogs (Kruckenberg 86-115-0102)**

Dog Number	Mature Ascarids Passed/ Mature Ascarids Retained
1	5/0
5	32/0
6	237/0
7	6/0
8	9/0
11	1/0
12	19/0
13	3/0
15	23/0
16	17/0
17	16/0
Totals:	
11 Dogs	368/0

**TABLE V Effectiveness of Filaribits® Plus in Removing Ascarids from Dogs  
(McCall 86-116-0102)**

Dog Number	Mature Ascarids Passed/ Mature Ascarids Retained
173	28/0
174	30/0
175	22/0
177	33/0
178	10/0
180	4/0
225	20/0
226	21/0
Totals	
8 Dogs	168/0

**TABLE VI Effect Of Filaribits® Plus On The Removal And Control Of Ascarid Infections In Dogs**

Investigator /Location	Treatment	No. Dogs	Number Breeds	Average Days on Test	No. of Dogs Positive for Ascarids Initially	% Ascarid Infection Cleared (Fecal Check)		
						Recheck 1 Av. 30.1 days	Recheck 2 Av. 65.7 days	Recheck 3 Av. 87.2 days
Buller/IL	T1	2	1+mixed	57	2	100% (2/2)	100% (1/1)	100% (1/1)
Conrad/MY	T1	3	2+mixed	71	3	100% (3/3)	100% (3/3)	100% (1/1)
Gengler/WI	T1	4	2	70	4	100% (4/4)	100% (4/4)	
Leite/OH	T1	3	2+Mixed	64	3	100% (3/3)	100% (3/3)	100% (1/1)
Maxted/IA	T1	6	4+Mixed	72	6	100% (6/6)	100% (6/6)	100% (2/2)
Snodgrass/AR	T1	10	2+Mixed	92	10	100% (10/10)	100% (10/10)	100% (10/10)
Sommerville/IN	T1	4	2+Mixed	85	4	100% (3/3)*	100% (4/4)	100% (4/4)
7 Investigators 7 States	TOTALS AND WEIGHTED AVERAGES	32	13 separate breeds and mixed breeds	73	32	100% (31/31)	100% (31/31)	100% (19/19)
Blalock/GA	T2	7	2+mixed	42	7	100% (7/7)	100% (2/2)	
Bryant/MO	T2	2	1+mixed	90	2	100% (2/2)	100% (2/2)	100% (2/2)
Buckaloo/MO	T2	9	2+mixed	74	9	100% (9/9)	100% (9/9)	100% (1/1)
Castellano/NY	T2	1	1	80	1	100% (1/1)	100% (1/1)	100% (1/1)
Frey/IA	T2	2	2	55	2	100% (2/2)	100% (1/1)	100% (1/1)
Glass/GA	T2	3	3	59	3	100% (3/3)	100% (3/3)	
Heinzle/NE	T2	2	2	82	2	100% (2/2)	100% (2/2)	100% (1/1)
Morrow/NM	T2	3	3	79	3	100% (3/3)	100% (3/3)	
Meunzig/NC	T2	3	2+Mixed	90	3	100% (3/3)	100% (3/3)	100% (3/3)
Thomas/IN	T2	1	1	92	1	100% (1/1)	100% (1/1)	100% (1/1)
Wadley/AR	T2	3	Mixed	77	3	67% (2/3)	100% (3/3)	100% (2/2)
11 Investigators 9 States	TOTALS AND WEIGHTED AVERAGES	36	14 separate breeds and mixed breeds	74.5	36	97% (35/36)	100% (30/30)	100% (12/12)

T1 = FILARIBITS Plus (Treatment also included evaluation of control (FILARIBITS) cases. (See Table VII.)

T2 = FILARIBITS Plus

\*No Fecal Sample Available for Dog No.0521 This Fecal Check.

**TABLE VII Effect Of Filaribits® Plus On The Removal And Control Of Ascarid Infections In Dogs**

Investigator /Location	Treatment	No. Dogs	No. Breeds	Average Days on Test	No. of Dogs Positive for Ascarids Initially	% Ascarid Infection Cleared (Fecal Check)		
						Recheck 1 Av. 31.6 days	Recheck 2 Av. 61.7 days	Recheck 3 Av. 87.8 days
Buller/IL	FILARIBITS	1	1	78	1	0% (0/1)	0% (0/1)	0% (0/1)
Conrad/NY	FILARIBITS	1	Mixed	48	1	100% (1/1)		
Gengler/WI	FILARIBITS	2	1+Mixed	55	2	0% (0/2)	50% (1/2)	
Leite/OH	FILARIBITS	1	Mixed	54	1	100% (1/1)	100% (1/1)	
Maxted/IA	FILARIBITS	2	2	65	2	100% (2/2)	50% (1/2)	
Snodgrass/AR	FILARIBITS	3	1+Mixed	92	3	100% (3/3)	100% (3/3)	100% (3/3)
Somerville/IN	FILARIBITS	1	Mixed	85	1	100% (1/1)	100% (1/1)	100% (1/1)
7 Investigators 7 States	TOTALS AND WEIGHTED AVERAGES	11	5 separate breeds and mixed breeds	71	11	72.7% (8/11)	70% (7/10)	80% (4/5)

**VI. LABELING**

1. Package insert Filaribits® Plus
2. Filaribits® Plus 180 mg/136 mg Bottle labels: 50, 100, and 200 tablets
3. Filaribits® Plus 60 mg/45 mg Bottle labels: 100 and 200 tablets

Copies of these labels may be obtained by writing to the:

Food and Drug Administration  
Freedom of Information Staff (HFI-35)  
5600 Fishers Lane  
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.