Date of Approval Letter:

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-061

DECTOMAX® (doramectin)
1% Injectable Solution for Cattle and Swine

"...effectively controls infections and protects cattle from reinfection with *Cooperia oncophora* for 14 days after treatment and *Oesophagostomum radiatum for 28* days after treatment."

Sponsored by:

Pfizer, Inc.

I. GENERAL INFORMATION

NADA Number:	141-061
Sponsor:	Pfizer, Inc. 235 East 42nd Street New York, New York 10017
Established Name:	doramectin
Trade Name:	DECTOMAX® 1% Injectable Solution for Cattle and Swine
Marketing Status:	over-the-counter (OTC)
Effect of Supplement:	New indications for persistent control of nematodes in cattle adding protection against *Cooperia oncophora* for 14 days and *Oesophagostomum radiatum* for 28 days after treatment.

II. INDICATIONS FOR USE: For the treatment and control of the following in cattle.

Gastrointestinal roundworms	*Ostertagia ostertagi*	Adults and fourth-stage larvae
	Ostertagia ostertagi	Inhibited fourth-stage larvae
	Ostertagia lyrata	Adults and fourth-stage larvae
	Haemonchus placei	Adults and fourth-stage larvae
	Trichostrongylus axei	Adults and fourth-stage larvae
	Trichostrongylus colubriformis	Adults and fourth-stage larvae
	Trichostrongylus longispicularis	Adults
	Cooperia oncophora	Adults and fourth-stage larvae
	Cooperia punctata	Adults and fourth-stage larvae
	Cooperia pectinata	Adults
	Cooperia surnabada (syn. mcmasteri)	Adults and fourth-stage larvae
	Bunostomum phlebotomum	Adults
	Strongyloides papillosus	Adults
	Oesophagostomum radiatum	Adults and fourth-stage larvae
	Trichuris spp.	Adults
Lungworms	*Dictyocaulus viviparus*	Adults and fourth-stage larvae
Eyeworms	*Thelazia* spp.	Adults
Grubs	*Hypoderma bovis* *Hypoderma lineatum*	
Lice	*Haematopinus eurysternus* *Linognathus vituli* *Solenopotes capillatus*	
Mange mites	*Psoroptes bovis* *Sarcoptes scabiei*	

Dectomax injectable solution has been proved to effectively control infections and to protect cattle from reinfection with *Cooperia oncophora* for 14 days; *Ostertagia ostertagi* for 21 days; and *Cooperia punctata, Oesophagostomum radiatum,* and *Dictyocaulus viviparus* for 28 days after treatment.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. Dosage Form: DECTOMAX® 1% Injectable Solution for Cattle and Swine is a sterile solution containing 10 mg doramectin/mL.

B. Route of Administration: DECTOMAX® 1% Injectable Solution for Cattle and Swine may be administered by subcutaneous or intramuscular injection.

C. Approved Dose: 200 mcg doramectin/kg body weight (1 mL/110 lb body weigh)

IV. EFFECTIVENESS

Data demonstrating the effectiveness of DECTOMAX® 1% Injectable Solution for Cattle and Swine of previously approved indications are discussed in the parent NADA 141-061 FOI Summaries (original approval dated July 30, 1996, supplemental approval dated July 18, 1997, and supplemental approval dated September 18, 1997). Data from the following dose confirmation trials demonstrate that DECTOMAX® 1% Injectable Solution administered at the recommended dosage protects cattle against infection or reinfection with *Cooperia oncophora* for 14 days after treatment and *Oesophagostomum radiatum* for 28 days after treatment.

Note: Nematode percentage efficacies were calculated using the following formula:

[Arithmetic mean number of nematodes in control cattle) - (Arithmetic mean number of nematodes in doramectin-treated cattle)] ÷ (Arithmetic mean number of nematodes in control cattle) × 100 = Percent Effectiveness

A. Dose Confirmation: Study No. 1231C-60-95-198

1. Investigator: Dr. Edward G. Johnson, Johnson Research, Parma, Idaho

2. General design:

   a. Purpose: To evaluate the persistent efficacy of doramectin against artificially-induced infections of *Dictyocaulus viviparus* and *Cooperia punctata*.

   b. Animals: Forty-two (42) Holstein calves (10 per group, with 2 larval viability monitors). Animals were approximately 3-6 months old and weighed 75 to 200 kg at the start of the study. All animals were treated with fenbendazole during the acclimation period to eliminate any existing infections as confirmed by negative fecal egg counts done on Day -1.

   c. Infection: Infective larvae were given to each animal daily, starting on Day 14 after treatment through Day 28. One thousand *Cooperia punctata* larvae and 50 *Dictyocaulus viviparus* larvae were administered daily. The larval viability monitors were given 30,000 *C. punctata* and 2,000 *D. viviparus* on Day 28.

d. Test article administration: The approved formulation of injectable solution containing 10 mg doramectin per mL was administered by subcutaneous injection. 1 mL/110 lb body weight (200 mcg doramectin/kg body weight) was given once to each animal in three groups. Groups T1 and T2 were treated with saline and doramectin, respectively, on Day 0. Group T3 was treated with doramectin on Day 7, and Group T4 was treated with doramectin on Day 14.

e. Pertinent variables measured: Worm counts were determined at necropsy which was 42 to 43 days after Groups T1 and T2 received treatment, 14 to 15 days after the last *Cooperia punctata* and *Dictyocaulus viviparus* larvae were administered to all groups.

3. Results - *Cooperia oncohora* and *Oesophagostomum radiatum* were contaminants of the inocula that established infections in the experimental animals and were present in adequate numbers for a determination of efficacy.

Table 4.1. Mean worm counts of *C. oncophora* and *O. radiatum* recovered for each group, number of infected animals in parentheses, and percent efficacy

			C. oncophora			*O. radiatum*		
Group	Treatment	Day of Treatment	worm count	infected animals	percent efficacy	worm count	infected animals	percent efficacy
T1	saline	0	442	10	-	276	10	-
T2	doramectin	28	110	8	75%	9	4	97%
T3	doramectin	21	6	1	98%	2	1	99%
T4	doramectin	14	0	0	100%	0	0	100%

4. Conclusion: This study is adequate to establish a level of persistent efficacy for *Cooperia oncophora* for 21 days and *Oesophagostomum radiatum* for 28 days.

5. Adverse reactions: One doramectin-treated animal exhibited salivation at 1 hour post-treatment.

B. Dose Confirmation: Study No. 2239A-60-97-039

1. Investigator: Dr. Edward G. Johnson, Johnson Research, Parma, Idaho

2. General design:

a. Purpose: To evaluate the persistent efficacy of doramectin against artificially-induced infections of *Trichostrongylus colubriformis* and *O. radiatum.*

b. Animals: Forty-two (42) Holstein calves (10 per group, with 2 larval viability monitors). Animals were approximately 2 to 6 months old and weighed 138 to 212 kg at the start of the study. All animals were treated with fenbendazole during the acclimation period to eliminate any existing infections as

confirmed by negative fecal egg counts done on Day -1.

c. Infection: Infective larvae were given to each animal daily, starting on Day 14 after treatment through Day 28. One thousand *T. colubriformis* larvae and 100 *O. radiatum* larvae were administered daily. The larval viability monitors were given 30,000 *T. colubriformis* and 2,500 *O. radiatum* on Day 28.

d. Test article administration: The approved formulation of injectable solution containing 10 mg doramectin per mL was administered by subcutaneous injection. 1 mL/110 lb body weight (200 mcg doramectin/kg body weight) was given once to each animal in three groups. Groups T1 and T2 were treated with saline and doramectin, respectively, on Day 0. Group T3 was treated with doramectin on Day 7 and Group T4 was treated with doramectin on Day 14.

e. Pertinent variables measured: Worm counts were determined at necropsy which was 42 days after Groups T1 and T2 received treatment, and 35 and 28 days respectively after groups T3 and T4 received treatment.

3. Results: **Table 4.2.** Mean worm counts of *O. radiatum* recovered for each group, number of infected animals in parentheses, and percent efficacy

Group	Treatment	Day of Treatment	Worm Count	Infected Animals	Percent Efficacy
T1	saline	0	76	10	-
T2	doramectin	28	0	0	100%
T3	doramectin	21	0	0	100%
T4	doramectin	14	0	0	100%

4. Conclusion: This study is adequate to establish a level of persistent efficacy for *Oesophagostomum radiatum* for 28 days.

5. Adverse reactions: None related to treatment.

C. Dose Confirmation: Study No. 2239A-60-97-231

1. Investigator: Dr. Edward G. Johnson, Johnson Research, Parma, Idaho

2. General design:

a. Purpose: To evaluate the persistent efficacy of doramectin against artificially-induced infections of *Cooperia oncophora.*

b. Animals: Forty-two (42) Holstein calves (10 per group, with 2 larval viability monitors). Animals were approximately 2 to 6 months old and weighed 97 to 208 kg at the start of the study. All animals were treated with fenbendazole during the acclimation period to eliminate any existing infections as confirmed by negative fecal egg counts done on Day -1.

c. Infection: Infective larvae were given to each animal daily, starting on Day 16 after treatment through Day 30. One thousand larvae *C. oncophora* larvae were administered daily. The larval viability monitors were administered 30,000 *C. oncophora* respectively on Day 30.

d. Test article administration: The approved formulation of injectable solution containing 10 mg doramectin per mL was administered by subcutaneous injection. 1 mL/110 lb body weight (200 mcg doramectin/kg body weight) was given once to each animal in three groups. Groups T1 and T2 were treated with saline and doramectin, respectively, on Day 0. Group T3 was treated with doramectin on Day 7, and Group T4 was treated with doramectin on Day 14.

e. Pertinent variables measured: Worm counts were determined at necropsy which was 42 days after Groups T1 and T2 received treatment, and 21 and 28 days respectively after groups T3 and T4 received treatment.

3. Results: **Table 4.3.** Mean worm counts of *C. oncophora* recovered for each group, number of infected animals in parentheses, and percent effectiveness

Group	Treatment	Day of Treatment	Worm Count	Infected Animals	Percent Efficacy
T1	saline	0	1820	10	-
T2	doramectin	30	1150	10	37%
T3	doramectin	23	285	9	84%
T4	doramectin	16	105	6	94%

6. Conclusion: This study is adequate to establish a level of persistent efficacy for *Cooperia oncophora* for 16 days.

7. Adverse reactions: None related to treatment.

V. ANIMAL SAFETY

As discussed in the parent NADA 141-061 FOI Summary (approval date July 30, 1996).

VI. HUMAN SAFETY

A. Toxicology Studies, Acceptable Daily Intake, Safe Concentrations, and Tolerance

The basic toxicology and residue chemistry studies that support the use of doramectin in cattle are summarized in the FOI Summary for the original approval of NADA 141-061. On the basis of those studies, an acceptable daily intake (ADI) for total residues of doramectin of 0.75 mcg/kg body weight/day; safe concentrations for total residues of doramectin in edible tissues of cattle of 150 ppb in muscle, 450 ppb in liver, 900 ppb in kidney and fat; and a tolerance of 100 ppb for residues of unchanged doramectin (marker residue) in liver (target tissue) were established.

B. Assignment of a Muscle Tolerance

Under NADA 141-095 (DECTOMAX® 0.5% Pour-On Solution for Cattle), the Center has codified the existing ADI for doramectin and established and codified a muscle tolerance. A tolerance of 30 ppb parent doramectin is established for cattle muscle and codified in 21 CFR 556.225. Residues of parent doramectin below 30 ppb indicate that muscle residues are below the muscle safe concentration. Muscle residues of drug at or below the muscle tolerance are not indicative of the safety of other edible tissues in cattle for human consumption.

VII. AGENCY CONCLUSION

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and implementing regulations at Part 514 of Title 21, Code of Federal Regulations (21 CFR 514) to demonstrate that DECTOMAX® 1% Injectable Solution for Cattle and Swine, when used under the proposed conditions of use, is safe and effective to control infections and to protect cattle from reinfection with *Cooperia oncophora* for 14 days and *Oesophagostomum radiatum* for 28 days after treatment.

For cattle, a tolerance of 0.1 ppm for parent doramectin (marker residue) in liver (target tissue) is codified at 21 CFR 556.225. The preslaughter withdrawal time is 35 days following one subcutaneous or intramuscular injection of DECTOMAX® 1% Injectable Solution, as specified at 21 CFR 522.770. As described in the FOI Summary for DECTOMAX® 0.5% Pour-On (NADA 141-095), a tolerance of 30 ppb has been established for parent doramectin in cattle muscle.

The agency has concluded that this product shall retain over-the-counter marketing status because adequate directions for use have been written for the layman and the conditions for use prescribed on the label are likely to be followed in practice.

In accordance with 21 CFR 514.106(b)(2), this is a Category II change which did not require a reevaluation of the safety or effectiveness data in the parent application.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals qualifies for THREE (3) years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. The THREE years of marketing exclusivity applies only to the new claims for which the supplemental application is approved.

DECTOMAX® 1% Injectable Solution for Cattle and Swine is under U.S. patent number 5,089,480, which expires on February 18, 2009.

VIII. APPROVED PRODUCT LABELING (attached)

A. Facsimile label - 100-mL, 250-mL, and 500-mL rubber-stoppered, glass vials

B. Facsimile package insert