Date of Approval: June 30, 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-095

DECTOMAX (doramectin) Pour-On

To extend the period of persistent effect for *Cooperia oncophora* and *Dictyocaulus viviparus* from 21 to 28 days and for *Cooperia punctata* from 28 to 35 days.

Sponsored by:
Pfizer Inc

1. GENERAL INFORMATION

a.	File Number:	NADA 141-095
b.	Sponsor:	Pfizer, Inc. 235 East 42nd St. New York, NY 10017 Drug Labeler Code: 000069
c.	Established Name:	Doramectin
d.	Proprietary Name:	DECTOMAX (doramectin) Pour-On
e.	Dosage Form:	Solution
f.	How Supplied:	250 mL, 1 liter, 2.5 liter, and 5 liter containers
g.	How Dispensed:	Over-the-Counter (OTC)
h.	Amount of Active Ingredients:	5 mg doramectin/mL
i.	Route of Administration:	Topical
j.	Species/Class:	Cattle
k.	Recommended Dosage:	500 mcg/kg (5 mL/110 lb body weight)
l.	Pharmacological Category:	Antiparasitic

m. Indications: 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
Haemonchus placei	Adults and fourth-stage larvae
Trichostrongylus axei	Adults and fourth-stage larvae
Trichostrongylus colubriformis	Adults and fourth-stage larvae
Cooperia oncophora[1]	Adults and fourth-stage larvae
Cooperia punctata	Adults and fourth-stage larvae
Cooperia pectinata	Adults
Cooperia surnabada	Adults
Bunostomum phlebotomum	Adults
Oesophagostomum radiatum	Adults and fourth-stage larvae
Trichuris spp.	Adults

[1]Efficacy below 90% was observed against adult *Cooperia oncophora* in some clinical studies

Lungworms

Dictyocaulus viviparus	Adults and fourth-stage larvae

Eyeworms

Thelazia gulosa	Adults
Thelazia skrjabini	Adults

Grubs
Hypoderma bovis
Hypoderma lineatum

Sucking Lice
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Biting Lice
Damalinia bovis

Mange Mites
Chorioptes bovis
Sarcoptes scabiei

Horn Flies
Haematobia irritans

DECTOMAX Pour-On solution has been proved to effectively control infections and to protect cattle from reinfection with: *Cooperia oncophora* and *Dictyocaulus viviparus* for 21 days after treatment, *Ostertagia ostertagi, Cooperia punctata,* and *Oesophagostomum radiatum* for 28 days after treatment and *Haemonchus placei* for 35 days after treatment.

n. Effect of Supplement: To extend the persistent effect periods for *Cooperia punctata* from 28 to 35 days after treatment and *Dictyocaulus viviparus* and *Cooperia oncophora* from 21 to 28 days after treatment. At this time, the labeling is being revised to reflect updated environmental information.

2. EFFECTIVENESS

a. Dose Characterization

Effectiveness studies were presented in the original NADA 141-095 FOI Summary approval dated September 16, 1997, establishing the recommended effective dose of DECTOMAX Pour-On for the treatment and control of internal and external parasites.

b. Substantial Evidence for Persistent Effectiveness against Endoparasites

The original approval for the persistent effect of DECTOMAX Pour-On was demonstrated by two studies (1231C-60-95-199 and 1231C-60-95-204) that appear in the original FOI Summary dated September 16, 1997. Additionally, there were four studies (5231E-03-92-070, 5232C-03-94-090, 5232C-03-94-092, and 5232C-03-94-097) conducted in the European Union (EU) that were submitted with the original approval that were considered supportive, but not reported in the FOI. An additional indication for the persistent effect against *Haemonchus placei* for up to 35 days after treatment is discussed in a supplemental FOI Summary dated August 10, 1999. These studies were evaluated using arithmetic means. Subsequent to the original review, the VICH guidance #90 "Effectiveness of Anthelmintics: General Recommendations VICH GL7" was finalized March 26, 2001. It allowed for the evaluation of parasite effectiveness studies using geometric means and the consideration of studies conducted in the member countries. This supplemental application allows for these six studies to be reevaluated using geometric means and the persistent effect period adjusted accordingly. All six of these studies were reevaluated using geometric means. Two additional studies (2239B-60-97-065 and 2239B-60-97-094) conducted subsequent to the original approval were submitted with this supplement and evaluated using geometric means.

For each study, percent efficacy was determined by comparing the geometric mean worm counts of the treated groups with those of an untreated control group for each parasite species present in at least six adequately infected control animals. The differences in geometric mean numbers of parasite counts between the treated groups and the controls were tested using a one-way analysis of variance. The period of persistent activity was defined as the time during which the effectiveness against a genus species was ≥ 90%.

For an indication to be granted, a minimum of two studies is required that have the following: an adequate level of infection in 6 control animals, a statistically significant difference between treated and control animals at $P<0.05$, and 90% efficacy using geometric means for each genus species of parasite and at each persistent effect period. If there are more than 2 studies, then the geometric means of the percent efficacy against a genus species of parasite from each study is added together and divided by the number of studies with that genus species of parasite. If this average is greater than or equal to 90% then the claim may be granted. These eight studies were evaluated using geometric means as described above. The overall percent efficacy from these studies for *Cooperia oncophora* at 28 days is 92.1% (six studies) and *Dictyocaulus viviparus* at 28 days is 95.6% (six studies). There were only two studies for *Cooperia punctata* and both demonstrated percent efficacy ≥ 90% for 35 days after treatment. The extension of the persistent effect periods for *Cooperia oncophora* is from 21 to 28 days after treatment, *Dictyocaulus viviparus* from 21

to 28 days after treatment and *Cooperia punctata* from 28 to 35 days after treatment. The eight trials are individually summarized below.

B.1 Dose Confirmation Study 1231C-60-95-199

1) Investigator: Edward G. Johnson
24007 Highway 20/26
Parma, Idaho

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Ten (10) per group. Cattle were 4 to 6 months old and weighed 127 to 251 kg at the start of the study.

c. Nematode isolate: *Dictyocaulus viviparus* 1994 field isolate from Wisconsin, *Ostertagia ostertagi, Cooperia punctata,* and *C. oncophora* 1995 field isolates from Louisiana and Idaho

d. Controls: Animals in the negative control group (T1) received saline.

e. Procedure: Forty-two (42) animals were weighed and randomly allocated to a saline-treated group (T1, 10 animals) or to one of three doramectin-treated groups (T2 to T4, 10 animals each) on Day 0 or to serve as one of the two larvae viability monitor animals. On Day 0, animals in Groups T1 and T2 were treated topically with saline (1 mL/10 kg BW) or doramectin pour-on (500 µg/kg BW), respectively. Groups T3 and T4 were treated with doramectin pour-on in an identical manner on Days 7 and 14, respectively. Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 14 to 35 with infective nematode larvae (approximately 50, 1,000, and 1,000 of *D. viviparus*, *O. ostertagi,* and *C. punctata*). Other nematode species were present as contaminants of the inocula. Animals from Groups T1 to T4 were euthanized and necropsied on Days 49 and 50 for determination of worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.1.

Table 2.1 1231C-60-95-199 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Cooperia oncophora	224 (100-380)	28 days	99.7
Dictyocaulus viviparus	23 (0-75)	28 days	100.0
Cooperia punctata	243 (120-504)	35 days	94.0

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.2 Dose Confirmation Study 1231C-02-95-204

1) Investigator: R. K. Pritchard, Ph.D.
Institute of Parasitology
McGill University
Ste-Anne de Bellvue
Quebec, Canada

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Ten (10) per group. Cattle were 4 to 6 months old and weighed 90 to 216 kg at the start of the study.

c. Nematode isolate: *Dictyocaulus viviparus* 1995 field isolate from Wisconsin; *Ostertagia ostertagi* and *Cooperia punctata* 1995 field isolates from Louisiana; *C. oncophora* 1995 field isolate from Maryland and Louisiana

d. Controls: Animals in the negative control group (T1) received saline.

e. Procedure: Forty-two (42) animals were weighed and randomly allocated to a saline-treated group (T1, 10 animals) or to one of three doramectin-treated groups (T2 to T4, 10 animals each) on Day 0 or to serve as one of the two larvae viability monitor animals. On Day 0, animals in Groups T1 and T2 were treated topically with saline (1 mL/10 kg BW) or doramectin pour-on (500 µg/kg BW), respectively. Groups T3 and T4 were treated with doramectin pour-on in an identical manner on Days 7 and 14, respectively. Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 14 to 35 with infective nematode larvae (approximately 50, 1,000, and 1,000 of *D. viviparus*, *O. ostertagi,* and *C. punctata*). Other nematode species were present as contaminants of the inocula. Animals from Groups T1 to T4 were euthanized and necropsied on Days 49 and 51 for worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.2.

Table 2.2 1231C-02-95-204 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Cooperia oncophora	1060 (0-5200)	28 days	91.8
Dictyocaulus viviparus	4 (0-30)	28 days	86.0
Cooperia punctata	512 (50-1900)	35 days	98.4

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.3 Dose Confirmation Study 2239B-60-97-065

1) Investigator: Larry Smith, D.V.M.
Research and Development Inc.
108 Davis Street
Lodi, WI

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Ten (10) per group. Cattle were 2 to 6 months old and weighed 74 to 171 kg at the start of the study.

c. Nematode isolate: *Dictyocaulus viviparus* 1997 field isolate from Mississippi

d. Controls: Animals in the negative control group (T1) received saline.

e. Procedure: Forty-two (42) animals were weighed and randomly allocated to a saline-treated group (T1, 10 animals), the doramectin-treated groups (T2, T3, T4, 10 animals each) on Day 0 or to serve as one of the two larvae viability monitor animals. On Day 0, animals in Group T1 were treated topically with saline (1 mL/10 kg BW). Groups T2, T3, and T4 were treated with doramectin pour-on (500 mcg/kg) on Day 0, 7, or 14, respectively. Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 28 to 42 with infective nematode larvae (approximately 50 of *D. viviparus*). Animals from Groups T1 to T4 were euthanized and necropsied on Days 56 and 57 for determination of worm counts.

3. Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.3.

Table 2.3 2239B-60-97-065 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Dictyocaulus viviparus	39 (3-118)	28 days	87.4

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.4 Dose Confirmation Study 2239B-60-97-094

1) Investigator: Bert E. Stromberg, Ph.D.
205 Veterinary Science
1971 Commonwealth Avenue
University of Minnesota
St. Paul, MN

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Ten (10) per group. Cattle were 2 to 6 months old and weighed 131 to 214 kg at the start of the study.

c. Nematode isolate: *Dictyocaulus viviparus* 1996 field isolate from Wisconsin

d. Controls: Animals in the negative control group (T1) received saline.

e. Procedure: Forty-two (42) animals were weighed and randomly allocated to a saline-treated group (T1), the doramectin-treated groups (T2, T3, T4) on Day 0 or to serve as one of the two larva viability monitor animals. On Day 0, animals in Group T1 were treated topically with saline (1 mL/10 kg BW). Groups T2, T3, and T4 were treated with doramectin pour-on (500 mcg/kg) on Day 0, 7, or 14, respectively. Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 28 to 42 with infective nematode larvae (approximately 50 of *D. viviparus*). Animals from Groups T1 to T4 were euthanized and necropsied on Days 56 and 57 for determination of worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.4.

Table 2.4 2239B-60-97-094 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Dictyocaulus viviparus	10 (3-22)	28 days	100.0

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.5 Dose Confirmation Study 5232E-03-92-070

1) Investigator: C. Hong, Ph.D.
M.A.F.F. Central Veterinary Laboratory
Halls Farm, New Haw
Weybridge
Surry, England

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Ten (10) or seven (7) per group. Cattle were 3 to 6 months old and weighed 94 to 134 kg at the start of the study.

c. Nematode isolate: *Cooperia oncophora* Pfizer in-house culture

d. Controls: Animals in the negative control group (T1) received no treatment.

e. Procedure: Thirty one (31) animals were weighed and randomly allocated to a saline-treated group (T1, 10 animals), the doramectin-treated groups (T2, T3, T4, 7 animals each). No physical contact was permitted between groups. On Day 0, animals in Group T1 were treated topically with saline (1 mL/10 kg BW). Groups T2, T3, and T4 were treated with doramectin pour-on (500 µg/kg) on Day 0, 7, or 14, respectively.

Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 14 to 28 with infective nematode larvae (approximately 1,000 of *C. oncophora*). Animals from Groups T1 to T4 were euthanized and necropsied on Days 42 and 43 for determination of worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.5.

Table 2.5 5232E-03-92-70 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Cooperia oncophora	9200 (2950-13250)	28 days	90.2

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.6 Dose Confirmation Study 5232C-03-94-090

1) Investigator: J. Brebner, Ph.D.
Moredun Animal Health Ltd.
408, Gilmerton Road
Edinburgh
Scotland

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Twelve (12) per group. Cattle weighed 77 to 132 kg at the start of the study.

c. Nematode isolates: *Ostertagia ostertagi*, Ridgeway Science Ltd Culture; *Cooperia oncophora*, Pfizer in-house culture

d. Controls: Animals in the negative control group (T1) received no treatment.

e. Procedure: Forty-eight (48) animals were weighed and randomly allocated to a saline-treated group (T1, 12 animals), or one of the doramectin-treated groups (T2, T3, T4, 12 animals each) on Day 0. No physical contact was permitted between groups. On Day 0, animals in Group T1 were treated topically with saline (1 mL/10 kg BW). Animals in Groups T2, T3, and T4 were treated with doramectin pour-on (500 mcg/kg) on Day 0, 7, or 14, respectively.

Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 14 to 35 with infective nematode larvae (approximately 1,000 of *O. ostertagi* and 1,000 *C. oncophora*). Animals from Groups T1 to T4 were euthanized and necropsied on Days 49 and 50 for determination of worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.6.

Table 2.6 5232C-03-94-90 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Cooperia oncophora	12686 (7450-17350)	28 days	99.8

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.7 Dose Confirmation Study 5232C-03-94-092

1) Investigator: D. J. Burden, Ph.D.
Park Farm
St. Braivels
Coleford
Gloucestershire, England

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Fourteen (14) or twelve (12) per group. Cattle were 3 to 6 months old and weighed 85 to 115 kg at the start of the study.

c. Nematode isolates: *Dictyocaulus viviparus*, *Ostertagia ostertagi,* and *Cooperia oncophora* Pfizer in-house cultures

d. Controls: Animals in the negative control group (T1) received no treatment.

e. Procedure: Fifty (50) animals were weighed and randomly allocated to a saline-treated group (T1, 14 animals), or one of the doramectin-treated groups (T2, T3, T4, 12 animals each) on Day 0. On Day 0, animals in Group T1 were treated topically with saline (1 mL/10 kg BW). Groups T2, T3, and T4 were treated with doramectin pour-on (500 mcg/kg) on Day 0, 7, or 14, respectively. Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 21 to 48 with infective nematode larvae (approximately 50 of *D. viviparus*, 1,000 *O. ostertagi,* and 1,000 *C. oncophora*). Animals from Groups T1 to T4 were euthanized and necropsied on Days 56 and 57 for determination of worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.7.

Table 2.7 5232C-03-94-092 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Cooperia oncophora	9194 (4200-16450)	27 days	96.4
Dictyocaulus viviparus	176 (27-396)	27 days	100.0

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

B.8 Dose Confirmation Study 5232C-03-94-097

1) Investigator: D. J. Burden, Ph.D.
Park Farm
St. Braivels
Coleford
Gloucestershire, England

2) General Design:

a. Purpose: To evaluate the persistent efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg body weight against artificially induced nematode infections.

b. Animals: Fourteen (14) or twelve (12) per group. Cattle were 3 to 6 months old and weighed 85 to 115 kg at the start of the study.

c. Nematode isolates: *Dictyocaulus viviparus*, *Ostertagia ostertagi*, *Cooperia oncophora* Pfizer in-house cultures

d. Controls: Animals in the negative control group (T1) received no treatment.

e. Procedure: Fifty (50) animals were weighed and randomly allocated to a saline-treated group (T1, 14 animals), or one of the doramectin-treated groups (T2, T3, T4, 12 animals each) on Day 0. No physical contact was permitted between groups. On Day 0, animals in Group T1 were treated topically with saline (1 mL/10 kg BW). Groups T2, T3, and T4 were treated with doramectin pour-on (500 mcg/kg) on Day 0, 7, or 14, respectively. Each of the animals in Groups T1 to T4 was artificially challenged daily on Days 21 to 48 with infective nematode larvae (approximately 50 of *D. viviparus*, 1,000 *O. ostertagi,* and 1,000 *C. oncophora*). Animals from Groups T1 to T4 were euthanized and necropsied on Days 56 and 57 for determination of worm counts.

3) Results: The percent efficacy based on geometric mean in the doramectin-treated group compared to the non-medicated group is summarized in Table 2.8.

Table 2.8 5232C-03-94-097 – Persistent Effect Periods and Percent Efficacy

Nematode Species	Geometric Mean and range in Controls	Persistent Effect Period	% Efficacy of DECTOMAX Pour-On
Cooperia oncophora	8555 (1500-16800)	27 days	74.8
Dictyocaulus viviparus	133 (41-403)	27 days	99.9

4) Adverse Events: There were no adverse events observed at any time during the study for any of the doramectin-treated cattle.

3. TARGET ANIMAL SAFETY

No further target animal safety data were required from the original approval as discussed in the parent NADA 141-095 FOI Summary approval dated September 16, 1997.

4. HUMAN SAFETY

No further human food safety data were required from the original approval as discussed in the parent NADA 141-095 FOI Summary approval dated September 16, 1997. There is a 45-day withdrawal period for slaughter, a withdrawal period for milk has not been established, and a withdrawal period has not been established for pre-ruminating calves.

5. AGENCY CONCLUSIONS

The data submitted in support of this supplemental 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 DECTOMAX Pour-On for Cattle when administered once at 500 mcg doramectin/kg body weight is safe and effective for the extension of the following persistent effect periods: *Cooperia oncophora from 21 to 28 days, Dictyocaulus viviparus* from 21 to 28 days and for *Cooperia punctata* from 28 to 35 days.

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

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did require a reevaluation of safety or effectiveness data in the parent application. Previously submitted studies were reevaluated using geometric means allowing the persistent effect period for three nematode species to be extended.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the extension of three already approved persistent effect indications listed above.

No patent information was submitted with this application.

6. ATTACHMENTS

Facsimile Labeling is attached as indicated below:

A. 250 mL, 1 liter, 2.5 liter, and 5 liter – bottle label and box carton
B. Package insert for all container sizes