DATE OF APPROVAL LETTER:

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-095

DECTOMAX® (doramectin)

0.5% Pour-On Solution for Cattle

"...for treatment and control of horn flies, *Haematobia irritans*"

Sponsored by:

Pfizer, Inc.

I. GENERAL INFORMATION:

NADA Number: 141-095

Sponsor: Pfizer, Inc
235 East 42nd Street
New York, New York 10017

Established Name: doramectin

Trade Name: DECTOMAX® 0.5% Pour-On Solution for Cattle

Marketing Status: over-the-counter (OTC)

Effect of Supplement: Adds to labeling a new indication for treatment and control of horn fly, *Haematobia irritans*.

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
	Haemonchus placei	Adults and fourth-stage larvae
	Trichostrongylus axei	Adults
	Trichostrongylus colubriformis	Adults and fourth-stage larvae
	Cooperia oncophora	Adults and fourth-stage larvae
	Cooperia punctata	Adults and fourth-stage larvae
	Cooperia pectinata	Adults
	Cooperia surnabada (syn. mcmasteri)	Adults
	Bunostomum phlebotomum	Adults
	Oesophagostomum radiatum	Adults and fourth-stage larvae
	Trichuris spp.	Adults
Lungworms	*Dictyocaulus viviparus*	Adults and fourth-stage larvae
Eyeworms	*Thelazia gulosa*	Adults
	Thelazia skrjabini	Adults
Grubs	*Hypoderma bovis* *Hypoderma lineatum*	
Sucking Lice	*Haematopinus eurysternus* *Linognathus vituli* *Solenopotes capillatus*	
Biting Lice	*Damalinia bovis*	
Mange mites	*Psoroptes bovis* *Sarcoptes scabiei*	

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, and *Ostertagia ostertagi*, *Cooperia punctata,* and *Oesophagostomum radiatum* for 28 days after treatment.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE:

A. Dosage Form: Pour-on solution containing 5 mg doramectin/mL.

B. Route of Administration: DECTOMAX® 0.5% Pour-On Solution for Cattle should be applied topically along the mid-line of the back.

C. Approved Dose: 500 mcg doramectin/kg body weight (5 mL/110 lb body weight)

IV. EFFECTIVENESS:

Data demonstrating the effectiveness of DECTOMAX® 0.5% Pour-On Solution for Cattle for previously registered indications are discussed in the parent NADA 141-095 FOI Summary (approval date September 16, 1997). Data from the following dose confirmation trials demonstrate that DECTOMAX® 0.5% Pour-On Solution for Cattle, administered at the recommended dosage reduces infestations of *Haematobia irritans*.

SUMMARY

A laboratory (controlled release) study (1031C-60-93-007), and a field trial (1033C-60-96-255), were conducted to confirm the effectiveness of doramectin pour-on, administered topically at 500 mcg/kg, against horn fly infestations in cattle.

RESULTS

Results are presented on an individual study basis (see Tables 4.1 and 4.2).

OVERALL CONCLUSIONS

A single topical application of doramectin pour-on at a dosage of 500 mcg/kg was efficacious in reducing infestations of *Haematobia irritans*. No significant adverse reaction to treatment was observed in either study.

A. Dose Confirmation Study 1031C-60-93-007

1. Investigator: Dr. R.L. Byford
   New Mexico State Univ. Veterinary Entomology Research Lab.
   Las Cruces, New Mexico

2. General Design:

   a. Purpose: To determine the period over which a single treatment of doramectin pour-on at a dosage of 500 mcg/kg BW will protect cattle against *Haematobia irritans*.

b. Animals: Six (6) per group. Animals were 6 to 8 months old and weighed 222 to 273 kg at the start of the study.

c. Controls: Animals in the negative control group (T1) received no medication.

d. Procedure: Animals in the doramectin group (T2) were treated topically with 500 mcg/kg BW on Day 0, and animals in both groups were challenged with 200 adult horn flies on Days 7, 14, 21, 28, 35, 42, 49 and 56. Six days after each release timepoint, the number of live flies remaining on each animals was counted.

3. Results: The percentage reduction in arithmetic mean live horn flies in the doramectin group at counting, compared to the non-medicated group, is summarized in Table 4.1. There were no abnormal clinical signs observed at any time during the study for any of the doramectin-treated cattle.

Table 4.1. Arithmetic mean live horn fly counts and percent efficacy

Day of Study Flies Released	Non-Medicated (T1)	Doramectin (T2)	% Efficacy
7	172	0	100
14	163	1	99
21	166	5	97
28	157	1	99
35	160	6	97
42	161	7	96
49	154	26	84
56	164	61	63

4. Data analysis: Arithmetic mean live horn fly counts were calculated for each treatment group on each sampling day. These were used to estimate the percentage efficacy in mean live horn fly counts for the treated group compared to the non-medicated group, on each sampling day using the following formula:

   [(Arithmetic mean number of horn flies in non-medicated cattle) - (Arithmetic mean number of horn flies in doramectin-treated cattle)] ÷ [Arithmetic mean number of horn flies in non-medicated cattle] X 100 = Percentage Efficacy

5. Conclusion: A single application of doramectin pour-on administered to cattle at a dose of 500 mcg/kg BW was effective against induced infestations of *Haematobia irritans* in cattle.

B. Field Trial; Study 1033C-60-96-255

1. Investigator: Tony Janes, B.S., Goodwin Farms, Mission, Texas

2. General Design:

   a. Purpose: To determine the efficacy of doramectin pour-on at a dosage of 500 mcg/kg against *Haematobia irritans* infestations of cattle under field conditions.

   b. Animals: Ten (10) per group. Animals were 7 months to 1 year-old and weighed 141 to 370 kg at the start of the study.

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

   d. Procedure: Twenty (20) animals from a herd of cattle with confirmed horn fly infestations were assigned to one of two groups of 10 animals each on non-adjoining pastures, and were treated accordingly with either saline (group T1) or doramectin (group T2). Each group remained on its assigned pasture and fly counts were conducted on each animal on Day 7 post-treatment.

3. Results: The percentage reduction in arithmetic mean live horn flies in the doramectin group at counting, compared to the non-medicated group, is summarized in table 2. There were no abnormal clinical signs observed at any time during the study for any of the doramectin-treated cattle.

   Table 4.2. Arithmetic mean live horn fly counts and percent efficacy

Day of Study	Non-Medicated (T1)	Doramectin (T2)	% Efficacy
-7	87	98	---
0	85	97	---
7	116	6	95

4. Data analysis: Arithmetic mean live horn fly counts were calculated for each treatment group on each sampling day. These were used to estimate the percentage efficacy in mean live horn fly counts for the treated group compared to the non-medicated group, on each sampling day using the following formula:

   [(Arithmetic mean number of horn flies in non-medicated cattle) - (Arithmetic mean number of horn flies in doramectin-treated cattle)] ÷ [Arithmetic mean number of horn flies in non-medicated cattle] X 100 = Percentage Efficacy

5. Conclusion: A single application of doramectin pour-on administered to cattle at a dose of 500 mcg/kg BW was effective against natural infestations of *Haematobia irritans* in cattle.

V. ANIMAL SAFETY:

As discussed in the parent NADA 141-095 FOI Summary (approval date Sept. 16, 1997).

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

Pfizer has conducted four pivotal residue studies which contained values for parent doramectin in cattle muscle (*see* original FOI Summaries for NADA 141-061 and NADA 141-095). For analytical methodology reasons, the data reported in Study No. 1535N-60-93-016 were considered the best for calculating a tolerance in muscle. The data show that unchanged doramectin represents approximately 80% of the residue present in muscle tissue as long as several weeks post dosing. Those results, summarized in Table 6.1, confirm that parent doramectin can serve as the marker residue in muscle.

Table 6.1. Mean concentrations (ppb) of doramectin total residue, unchanged doramectin, and percent marker (doramectin) in muscle of cattle following a 200 mcg/kg bw intramuscular dose of ^{3}H-doramectin

Days Post Dosing	Total Residue in Muscle	Unchanged Doramectin	Percent Doramectin
7	40 ± 5	33 ± 4.2	84%
14	20 ± 6	16 ± 5.1	78%
21	13 ± 3	11 ± 3	80%
28	10 ± 7	8 ± 3.2	75%
35	<3	<2.4	--

A tolerance of 30 ppb was calculated from the values for parent (unchanged) doramectin. The 30 ppb tolerance represents the upper tolerance limit obtained by CVM's standard statistical procedure (99% tolerance limit with 95% confidence) at 22 days of withdrawal. That withdrawal interval was chosen for the tolerance assignment because 22 days is the withdrawal period originally calculated for the doramectin injectable product on the basis of the depletion of residues in liver.

The 22-day withdrawal period was extended to 35 days for the original approval of the injectable product to cover the high residues that occur occasionally at injection sites.

A tolerance of 30 ppb doramectin in cattle muscle makes it possible to identify animals that have been treated with the injectable product and slaughtered shortly thereafter. The 30 ppb muscle tolerance applies to samples collected remotely from the sites of injection. Muscle tissue collected at the site of injection of the doramectin injectable product may contain doramectin residues that significantly exceed 30 ppb, even though the animals were withheld from slaughter for the required period. A higher safe concentration for residues at the injection site is allowed based on acute toxicity considerations and the minimal chance of that type of tissue being consumed in a single serving. See the FOI Summary for the original approval of NADA 141-061 for a discussion of doramectin injection site residues.

VII. 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 implementing regulations at Part 514 of Title 21, Code of Federal Regulations (21 CFR 514) to demonstrate that DECTOMAX® 0.5% Pour-On Solution for Cattle, when used under the proposed conditions of use, is safe and effective for the treatment and control of *Haematobia irritans* infestations in cattle.

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 45 days following one topical application of DECTOMAX® 0.5% Pour-On Solution, as specified in 21 CFR 524.770. As described in Section VI., a tolerance of 30 ppb is 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 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 claim for which the supplemental application is approved.

DECTOMAX® 0.5% Pour-On Solution for Cattle is under U.S. patent number 5,089,480, which expires on February 18, 2009.

VIII. APPROVED PRODUCT LABELING (attached)

A. Facsimile label - 250 mL, 1 liter and 2.5 liter, and 5 liter containers

B. Facsimile package insert.