Approval Date: September 16, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-095

B. Sponsor

Pfizer, Inc.
235 East 42nd Street
New York, New York 10017

C. Proprietary Name

Dectomax® Pour-On solution

D. Established Name

doramectin 0.5% pour-on solution

E. Dosage Form

DECTOMAX® Pour-On Solution contains 5 mg doramectin/mL

F. ROUTE OF ADMINISTRATION

A single topical dose of 500 mcg/kg BW. Each mL contains 5 mg of doramectin, sufficient to treat 22 lb (10 kg) of body weight.

G. Dispensing Status

OTC

H. Indication

Gastrointestinal roundworms

Ostertagia ostertagi (adults and L4, including inhibited larvae)

Ostertagia lyrata (adults)

Haemonchus placei (adults and L4)

Trichostrongylus axei (adults)

Trichostrongylus colubriformis (adults and L4)

Cooperia oncophora (adults1 and L4)

Cooperia pectinata (adults)

Cooperia punctata (adults and L4)

Cooperia surnabada (adults)

Bunostomum phlebotomum (adults)

Oesophagostomum radiatum (adults and L4)

Trichuris spp. (adults) [1]Efficacy below 90% was observed against *adult Cooperia oncophora* in some clinical studies

Lungworms

Dictyocaulus viviparus (adults and L4)

Eyeworms

Thelazia gulosa (adults)

Thelazia skrjabini (adults)

Grubs

Hypoderma bovis

Hypoderma lineatum

Lice

Biting Lice

Damalinia bovis

Sucking Lice

Haematopinus eurysternus

Linognathus vituli

Solenopotes capillatus

Mange Mites

Chorioptes bovis

Sarcoptes scabiei

DECTOMAX® pour-on solution has been proved to effectively control infections and to protect cattle from re-infection with *Cooperia oncophora* and *Dictyocaulus viviparus* for 21 days, and *Ostertagia ostertagi, Cooperia punctata* and *Oesophagostomum radiatum* for 28 days after treatment.

II. EFFECTIVENESS

A. Preclinical Investigation:

Results from preclinical evaluation of doramectin pour-on in experimental formulations indicated that a dose of 500 mcg/kg bodyweight was required for

efficacy against the provisionally identified dose-limiting species, *Cooperia oncophora* and *Trichostrongylus colubriformis*. This dose was selected for clinical evaluation in a prototype commercial formulation and a program of clinical studies was initiated to evaluate efficacy against a broader range of nematode and arthropod species. Based on this information, *C. oncophora* and *T. colubriformis* were confirmed as the key dose-limiting species for dose determination studies.

B. Dose Determination:

Summary

Three dose determination studies were conducted against *C. oncophora* and *T. colubriformis* (other nematodes were present in each study), each using three dosages of doramectin pour-on (i.e., 250, 500, and 750 ug/kg of bodyweight). In addition, a study was carried out against the potentially dose limiting arthropod, *Damalinia bovis*, using the same dosages.

STUDY DESIGN - NEMATODES

One natural and two artificial-infection studies were conducted to good clinical practice standards. Forty (40) to forty-eight (48) cattle were used per study. In the artificial-infection studies, calves were inoculated per os on day 0 with L3 *C. oncophora* plus L3 *T. colubriformis* or a mixed L3 nematode inoculum, including L3 of *C. oncophora* and *T. colubriformis*. Study animals were treated with either saline or doramectin pour-on at a dosage of 250, 500, or 750 mcg/kg. All treatments were applied topically in a single passage along the midline of the back from the withers to the tailhead.

STUDY DESIGN - DAMALINIA BOVIS

One artificial infection study was conducted to good clinical practice standards. Forty (40) calves previously infested with lice were treated on day 0 with either saline or doramectin pour-on solution. All treatments were applied topically in a single passage along the midline of the back from the withers to the tailhead. Lice counts were performed weekly for five weeks after treatment.

DATA ANALYSIS

Nematode percentage efficacies were calculated at each dose level using the following formula:

$$\frac{[(\text{Arithmetic mean number of nematodes in non-medicated cattle}) - (\text{Arithmetic mean number of nematodes in doramectin-treated cattle})]}{[\text{Arithmetic mean number of nematodes in non-medicated cattle}]} \times 100 = \text{Percentage Efficacy}$$

Lice (*D. bovis*) percentage efficacies were calculated at each dosage level by determining the percentage reductions in lice counts on study Day 35 for the treated groups compared with the non-medicated group, using the following formula:

$$\frac{[(\text{Arithmetic mean number of lice in non-medicated cattle}) - (\text{Arithmetic mean number of lice in doramectin-treated cattle})]}{[\text{Arithmetic mean number of lice in non-medicated cattle}]} X\ 100 = \text{Percentage Efficacy}$$

RESULTS:

Results are presented on an individual study basis in the section following (see Tables 1 to 4). Only the parasite species and life stage for which there was an adequate number of infected controls (minimum of six) are included in these tables.

OVERALL CONCLUSIONS:

A dosage of 250 mg/kg was not sufficiently effective in some instances for the dose-limiting species. In contrast, doramectin at 500 mg/kg was effective against the dose-limiting species, as well as all other claimed species present in these studies, including the louse *D. bovis*. These data indicate that 500 mcg/kg of doramectin administered as a pour-on solution is an appropriate dosage for the treatment and control of cattle arthropod and nematode parasites.

INDIVIDUAL DOSE DETERMINATION STUDIES

1. Dose determination study #1231C-60-94-019, Dr. L.R. Ballweber, College of Veterinary Medicine, Mississippi State University, Mississippi State, Mississippi

   Forty (40) artificially infected calves were randomly allocated to four groups each of 10 animals (a negative control and three doramectin groups). Animals were treated topically with either doramectin pour-on or saline and slaughtered 14 to 16 days later for determination of worm burdens. The results are summarized in Table 1.

   Table 1 Therapeutic Efficacy of Doramectin Against Adult Nematodes - Percentage Reduction Relative to Controls

Treatment/Dosage (mcg/kg)		**Arithmetic Mean**	**Percentage Efficacy**
***Cooperia oncophora* - Adults**	Non-medicated	442.5	--
	Doramectin (250)	302.5	36
	Doramectin (500)	75.5	83
	Doramectin (750)	20.0	96
***Trichostrongylus colubriformis* - Adults**	Non-medicated	400.0	--
	Doramectin (250)	70.0	67
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100

2. Dose determination study #1232C-60-94-153, Dr. T.A. Yazwinski, Farm of Homer Featherston, Fayetteville, Arkansas

   Forty-eight (48) naturally infected calves were randomly allocated to four groups each of 12 animals (a negative control and three doramectin groups). Animals were treated topically with either doramectin pour-on or saline and slaughtered 14 to 17 days later for determination of worm burdens. The results are summarized in Table 2

Table 2 Therapeutic Efficacy of Doramectin Against Nematodes - Percentage Reduction Relative to Controls

Treatment/Dosage (mcg/kg)		**Arithmetic Mean**	**Percentage Efficacy**
***Cooperia oncophora* - Adults**	Non-medicated	926.6	---
	Doramectin (250)	73.3	92
	Doramectin (500)	0.0	100
	Doramectin (750)	42.7	95
***Haemonchus placei* - Adults**	Non-medicated	437.5	---
	Doramectin (250)	0.0	100
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100
***Ostertagia ostertagi* - Adults**	Non-medicated	1262.5	---
	Doramectin (250)	0.0	100
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100
***Trichostrongylus axei* - Adults**	Non-medicated	683.3	---
	Doramectin (250)	0.0	100
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100
***Cooperia punctata* - Adults**	Non-medicated	806.2	---
	Doramectin (250)	10.8	99
	Doramectin (500)	0.0	100
	Doramectin (750)	3.2	>99
***Cooperia surnabada* - Adults**	Non-medicated	155.0	---
	Doramectin (250)	17.5	89
	Doramectin (500)	0.8	>99
	Doramectin (750)	0.0	100

3. Dose determination study #5032C-03-94-076, Dr. R.N. Titchener, West of Scotland School of Agriculture, Brickrow Farm, Auchincruive, Ayr, Scotland

   Forty (40) artificially infected calves were randomly allocated to four groups each of 10 animals (a negative control and three doramectin groups). Animals were treated topically with doramectin pour-on or did not receive any treatment. Lice counts were conducted at 7, 14, 21 and 35 days after treatment. The results are summarized in Table 3.

   Table 3 Therapeutic Efficacy of Doramectin Against Damalinia bovis - Arithmetic means for each group and Percentage Reduction Relative to Controls

Tx Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 control	420	288	248	261	171	337	136
T2 250 µg/kg	493	272	0 (100%)	1 (99.6%)	2 (98.8%)	4 (98.8%)	2 (98.5%)
T3 500 µg/kg	436	271	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
T4 750 µg/kg	473	228	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)

4. Dose determination study #5232C-03-93-089, Dr. D.J. Burden, Park Farm, St. Briavels, Coleford, Gloucester, England

   Forty-two (42) artificially infected calves were randomly allocated to either a non-medicated group (12 animals) or one of three treated groups (10 animals each). Animals were treated topically with either doramectin pour-on or did not receive any treatment. All animals were slaughtered 14 or 15 days later for determination of worm burdens. The results are summarized in Table 4.

Treatment/Dosage (mcg/kg)		**Arithmetic Mean**	**Percentage Efficacy**
***Cooperia oncophora* - Adults**	Non-medicated	12,656	---
	Doramectin (250)	6,972	45
	Doramectin (500)	1,165	91
	Doramectin (750)	224	98
***Trichostrongylus colubriformis* Adults**	Non-medicated	1,348	---
	Doramectin (250)	1320	76
	Doramectin (500)	5	>99
	Doramectin (750)	0	100
***Dictyocaulus viviparus* - Adults**	Non-medicated	334	---
	Doramectin (250)	0.0	100
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100
***Ostertagia ostertagi* - Adults**	Non-medicated	1,808	---
	Doramectin (250)	4	>99
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100
***Trichostrongylus axei* - Adults**	Non-medicated	616	---
	Doramectin (250)	0.0	100
	Doramectin (500)	0.0	100
	Doramectin (750)	0.0	100

C. Efficacy Confirmation – Nematodes

SUMMARY

A series of controlled efficacy studies, involving cattle with both naturally- and artificially-acquired infections, were conducted. These studies evaluated the efficacy of doramectin pour-on at 500 mcg/kg bodyweight against eyeworms, adult/immature lungworms, and adult/immature gastrointestinal nematodes. Studies were conducted to common protocols in various geographic locations throughout North America in order to obtain broad strain representation of each nematode species.

STUDY DESIGNS

Studies were designed to estimate efficacy against parasites in the adult stage as well as against normally developing and inhibited fourth-stage larvae. Experimental approaches and techniques were standardized sufficiently to allow data from individual studies to be pooled to produce an efficacy estimate for each parasite species/stage tested. Efficacy against adult nematodes was assessed using both naturally- and artificially-acquired infections. Efficacy against fourth-stage larvae was assessed using only artificially-induced infections so that the age of the nematode

species under test was known at the time of treatment. Efficacy against inhibited larvae of *Ostertagia ostertagi* was assessed in naturally-infected cattle.

DATA ANALYSIS

In each study, worm burdens of each species/stage were determined for each animal. Arithmetic mean worm burdens were calculated from the worm counts and used to estimate efficacy as follows:

$$\frac{[(\text{Arithmetic mean number of nematodes in non-medicated cattle}) - (\text{Arithmetic mean number of nematodes in doramectin-treated cattle})]}{[\text{Arithmetic mean number of nematodes in non-medicated cattle}]} X\ 100 = \text{Percentage Efficacy}$$

RESULTS

Results are presented on an individual study basis in the section following (see Tables 5 to 24). All studies had or exceeded the minimum required six adequately infected controls for each species and life stage represented.

OVERALL CONCLUSIONS

A single topical application of doramectin pour-on at a dosage of 500 mcg/kg was highly efficacious against adult nematodes of the following species: O*. ostertagi, O. lyrata, H. placei, T. axei, T. colubriformis, C. oncophora, C. pectinata, C. punctata, C. surnabada, B. phlebotomum, O. radiatum, Trichuris spp., D. viviparus, T. gulosa and T. skrjabini; against L4 of O. ostertagi, H. placei, T. colubriformis, C. oncophora, C. punctata, O. radiatum*; and D. viviparus; and against inhibited L4 of *O. ostertagi*. No significant adverse reaction to treatment was observed in any study.

INDIVIDUAL NEMATODE DOSE CONFIRMATION STUDIES

1. Dose confirmation study #1231C-60-93-016, Dr. T.A. Yazwinski, Farm of Homer Featherston, Fayetteville, Arkansas

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 5.

   Table 5 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Bunostomum phlebotomum (Adults)	332.8	0.1	>99

2. Dose confirmation study #1231C-60-93-017, Dr. L.R. Ballweber, College of Veterinary Medicine, Mississippi State University, Mississippi State, Mississippi

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 6.

Table 6 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Haemonchus placei (L4 stage)	750	0	100
Trichostrongylus colubriformis (L4 stage)	440	0	100
Oesophagostomum radiatum (L4 stage)	451	0	100

3. Dose confirmation study #1231C-60-94-152, Dr. T.A. Yazwinski, Farm of Homer Featherston, Fayetteville, Arkansas

   Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 7.

   Table 7 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	6,014	0	100
Ostertagia lyrata (Adults)	212	0	100
Cooperia oncophora (Adults	3,844	136	97
Cooperia punctata (Adults)	854	2	>99
Cooperia surnabada (Adults)	320	30	91
Bunostomum phlebotomum (Adults)	292	0	100
Trichuris spp. (Adults)	63	1	98

4. Dose confirmation study #1231C-02-94-168, Dr. A. Villeneuve, University of Montreal, St. Hyacinthe, Quebec, Canada

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 8.

   Table 8 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (L4 Stage)	677.2	1.7	94
Cooperia oncophora (L4 Stage)	265.0	8.5	97

5. Dose confirmation study #1231C-60-95-175, Dr. L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 9.

   Table 9 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Trichostrongylus colubriformis (L4 Stage)	5,800	0	100
Cooperia punctata (L4 Stage)	325	0	100
Oesophagostomum radiatum (L4 Stage)	57	0	100
Dictyocaulus viviparus (L4 Stage)	94	0	100

6. Dose confirmation study #1231C-60-95-176, Dr. T.A. Yazwinski, Farm of Homer Featherston, Fayetteville, Arkansas

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 10.

   Table 10 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (L4 Stage)	4,878	2	>99
Haemonchus placei (L4 Stage)	792	0	100
Trichostrongylus colubriformis (L4 Stage)	370	0	100
Cooperia punctata (L4 Stage)	688	0	100
Oesophagostomum radiatum (L4 Stage)	1,915	0	100

7. Dose confirmation study #1231C-60-95-193, Dr. T.A. Yazwinski, Farm of Homer Featherston, Fayetteville, Arkansas

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 11.

Table 11 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (L4 Stage)	774	0	100
Haemonchus placei (L4 Stage)	422	0	100
Cooperia oncophora (L4 Stage)	383	8	96
Cooperia punctata (L4 Stage)	224	0	100
Oesophagostomum radiatum (L4 Stage)	1915	0	100

8. Dose confirmation study #1231C-60-95-220, Dr. R. Corwin, Middlebush Veterinary Research Farm, Columbia, Missouri

   Twenty (20) artificially infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 12.

   Table 12 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (L4 Stage)	5,770	5	>99
Dictyocaulus viviparus (L4 Stage)	80	0	100

9. Dose confirmation study #1232C-60-93-015, Dr. H. Ciordia, Southern Piedmont Experiment Station, Watkinsville, Georgia

   Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 13.

Table 13 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	17,310	0	100
Ostertagia ostertagi (Inhibited L4 larvae)	12,055	175	99
Haemonchus placei (Adults)	4,211	0	100
Trichostrongylus axei (Adults)	5,290	0	100
Cooperia oncophora (Adults)	270	0	100
Cooperia pectinata (Adults)	225	0	100
Cooperia punctata (Adults)	1,130	0	100

10. Dose confirmation study #1232C-60-93-016, Dr. L. Smith, Research and Development, Inc., Readstown, Wisconsin

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 14.

    Table 14 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	2,894	10	>99
Cooperia punctata (Adults)	2,733	270	90

11. Dose confirmation study #1232C-02-93-017, Dr. M.J. Kennedy, Alberta Agricultural Animal Health Division, Edmonton, Alberta, Canada

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 15.

    Table 15 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Thelazia gulosa (Adults)	5.1	0	100
Thelazia skrjabini (Adults)	5.7	0.2	96

12. Dose confirmation study #1232C-02-94-018, Dr. M.J. Kennedy, Ronald Johnson Farm, Wetaskiwin, Alberta, Canada

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 16.

    Table 16 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Thelazia gulosa (Adults)	3.2	0	100
Thelazia skrjabini (Adults)	1.3	0	100

13. Dose confirmation study #1232C-02-94-019, Dr. M.J. Kennedy, Ronald Johnson Farm, Wetaskiwin, Alberta, Canada

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 17.

    Table 17 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Thelazia gulosa (Adults)	1.0	0	100
Thelazia skrjabini (Adults)	7.8	0	100

14. Dose confirmation study #1232C-60-94-150, Dr. E.G. Johnson, Johnson Research, Parma, Idaho

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 18.

    Table 18 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	3,260	58	98
Ostertagia ostertagi (Inhibited L4 Stages)	1,944	132	93
Cooperia surnabada (Adults)	335	32	91

15. Dose confirmation study #1232C-60-94-154, Dr. L. Smith, Research and Development Inc., Readstown, Wisconsin

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 19.

    Table 19 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	2,550	10	>99
Cooperia punctata (Adults)	590	56	91
Dictyocaulus viviparus (Adults)	26	0	100

16. Dose confirmation study #1232C-60-94-155, Dr. J.A. Stuedemann, USDA/ARS, Southern Piedmont Conservation Research Center, Watkinsville, Georgia

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 20.

    Table 20 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	2,545	28	99
Ostertagia ostertagi (Inhibited L4 larvae)	1,230	0	100
Haemonchus placei (Adults)	1,510	0	100
Trichostrongylus axei (Adults)	816	4	>99
Cooperia pectinata (Adults)	2,670	90	97
Cooperia punctata (Adults)	4,072	334	92

17. Dose confirmation study #1232C-60-94-163, Dr. T.A. Yazwinski, Farm of Homer Featherston, Fayetteville, Arkansas

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 21.

Table 21 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	2,968	6	>99
Cooperia oncophora (Adults)	1,978	24	99
Cooperia punctata (Adults)	1,476	14	99
Oesophagostomum radiatum (Adults)	298	0	100
Trichuris spp. (Adults)	38	1	>99

18. Dose confirmation study #1232C-60-94-167, Dr. J.E. Miller, School of Veterinary Medicine, Louisiana State University Agriculture & Mechanical College, Baton Rouge, Louisiana

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 22.

    Table 22 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	1,367	0	100
Ostertagia lyrata (Adults)	54	0	100
Haemonchus placei (Adults)	262	2	99
Trichostrongylus colubriformis (Adults)	312	0	100
Cooperia punctata (Adults)	2,598	0	100
Oesophagostomum radiatum (Adults)	367	0	100
Trichuris spp. (Adults)	15	0	100
Dictyocaulus viviparus (Adults)	102	0	100

19. Dose confirmation study #1232C-60-95-183, Dr. J.A. Stuedemann, USDA/ARS Southern Piedmont Conservation Research Center, Watkinsville, Georgia

    Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 23.

Table 23 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Ostertagia ostertagi (Adults)	5,058	0	100
Ostertagia ostertagi (Inhibited L4 Larvae)	1,408	0	100
Haemonchus placei (Adults)	1,378	0	100
Trichostrongylus axei (Adults)	3,048	0	100
Trichostrongylus colubriformis (Adults)	122	0	100
Cooperia oncophora (Adults)	1,571	0	100
Cooperia pectinata (Adults)	1,454	0	100
Cooperia punctata (Adults)	2,900	0	100

20. Dose confirmation study #1232C-60-95-192, Dr. J.A. Stuedemann, USDA/ARS Southern Piedmont Conservation Research Center, Watkinsville, Georgia

Twenty (20) naturally infected calves were assigned to two equal groups (negative control and doramectin). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 24.

Table 24 Arithmetic means and Therapeutic Efficacy of Doramectin at 500 mcg/kg Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**% Efficacy**
Trichostrongylus colubriformis (Adults)	236	0.5	>99
Cooperia oncophora (Adults)	1,135	13	>99
Cooperia pectinata (Adults)	383	0	100
Cooperia punctata (Adults)	1,519	0	100
Bunostomum phlebotomum (Adults)	137	1	99

SUMMARY OF COOPERIA ONCOPHORA PIVOTAL DOSE CONFIRMATION STUDIES

Study Number	**Study Location**	**C. oncophora stage**	**% Efficacy**
1231C-60-94-152	Arkansas	Adult	97
1232C-60-93-015	Georgia	Adult	100
1232C-60-93-016	Wisconsin	Adult	70
1232C-60-94-150	Idaho	Adult	86
1232C-60-94-154	Wisconsin	Adult	75
1232C-60-94-155	Georgia	Adult	82
1232C-60-94-163	Arkansas	Adult	99
1232C-60-95-183	Georgia	Adult	100
1232C-60-95-192	Georgia	Adult	99
1231C-02-94-168	Quebec, Canada	L4s	97
1231C-60-95-176	Arkansas	L4s	>99
1231C-60-95-193	Arkansas	L4s	96

D. Efficacy Confirmation - Grubs:

SUMMARY

A series of studies involving cattle with naturally-acquired infections of *Hypoderma lineatum* and/or *Hypoderma bovis* were conducted to evaluate the efficacy of doramectin pour-on, administered topically at a dosage of 500 mcg/kg bodyweight, against 1st-instar larvae. Studies were carried out under field conditions to common protocols at various locations in North America.

STUDY DESIGNS

In each study, 30 to 60 cattle were selected from herds considered likely to harbor natural infections of *Hypoderma spp*. The studies were conducted when the Hypoderma spp. larvae were expected to be in the 1st-instar stage. On day -1 or day 0 (treatment day), animals were randomly allocated in a tiered manner based on bodyweight to a saline-treated (non-medicated in study 1032C-60-93-037) or a doramectin-treated group. All treatments were applied topically in a single passage along the midline of the back from the withers to the tailhead. Subsequently, during the period of *Hypoderma spp*. emergence, the numbers of warbles appearing on the backs of animals were determined at approximately 14-day intervals and larvae were expressed from as many fully developed warbles as possible. Expressed larvae were identified where possible, to stage and species.

DATA ANALYSIS

In each study, warbles were counted for each animal. Percentage efficacy was determined by the percentage of doramectin-treated animals with no warbles on any observation day.

RESULTS

Results are presented on an individual study basis in the section following (see tables 25 to 29).

OVERALL CONCLUSIONS

A single application of doramectin pour-on, administered to cattle at a dosage of 500 mcg/kg, was highly effective in the treatment of 1st-instars of *H. bovis* and *H. lineatum*. No adverse reaction directly attributable to doramectin administration or to larval *Hypoderma spp*. death or disintegration as a result of doramectin treatment was seen in any animal.

INDIVIDUAL GRUB DOSE CONFIRMATION STUDIES

1. Dose confirmation study #1032C-60-93-037, Dr. J.E. Lloyd, Beef Livestock Research Facility, University of Wyoming, Laramie, Wyoming

   Sixty (60) calves with natural Hypoderma spp. infections were divided into two equal groups (doramectin or control). Animals were examined at regular intervals after treatment from Day 40 to Day 180 and warbles were enumerated to determine efficacy. The mean number of warbles in the control group varied from 1.1 on Day 40 to a peak of 18.5 on Day 110. The doramectin-treated animals had no warbles from Day 40 to Day 180. The results are summarized in Table 25.

   Table 25 Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle *Hypoderma* spp.

Parasite	**% Efficacy**
Hypoderma bovis	100
Hypoderma lineatum	100

2. Dose confirmation study #1032C-02-94-039, Dr. D. Colwell, Bovatech Veterinary Services, Shaughnessy, Alberta, Canada

   Thirty (30) calves with natural *Hypoderma spp*. infections were divided into two equal groups (doramectin or control). Animals were examined at regular intervals after treatment from Day 37 to Day 107 and warbles were enumerated to determine efficacy. The mean number of warbles in the control group varied from 1.0 on Day 37 to a peak of 13.6 on Day 79. The doramectin-treated animals had no warbles from Day 37 to Day 107. The results are summarized in Table 26.

   Table 26 Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle *Hypoderma spp*.

Parasite	**% Efficacy**
Hypoderma lineatum	100

3. Dose confirmation study #1032C-60-94-041, Dr. C. Jones, Dixon Springs Agricultural Center, Dixon Springs, Illinois

   Forty (40) calves with natural Hypoderma spp. infections were divided into two equal groups (doramectin or control). Animals were examined at regular intervals after treatment from Day 41 to Day 181 and warbles were enumerated to determine efficacy. The mean number of warbles in the control group varied from 2.9 on Day 41 to a peak of 19.5 on Day 83. The doramectin-treated animals had no warbles from Day 41 to Day 181. The results are summarized in Table 27

Table 27 Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle *Hypoderma spp*.

Parasite	**% Efficacy**
Hypoderma bovis	100
Hypoderma lineatum	100

4. Dose confirmation study #1032C-60-94-162, Dr. L.L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Forty (40) calves with natural *Hypoderma spp*. infections were divided into two equal groups (doramectin or control). Animals were examined at regular intervals after treatment from Day 72 to Day 156 and warbles were enumerated to determine efficacy. The mean number of warbles in the control group varied from 1.7 on Day 72 to a peak of 6.3 on Day 100. The doramectin-treated animals had no warbles from Day 72 to Day 156. The results are summarized in Table 28.

   Table 28 Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle Hypoderma spp.

Parasite	**% Efficacy**
Hypoderma bovis	100
Hypoderma lineatum	100

E. Efficacy Confirmation - Lice:

SUMMARY

A series of studies were conducted under field conditions to evaluate the efficacy of doramectin pour-on administered topically at a dosage of 500 mcg/kg bodyweight to cattle harboring naturally-acquired infestations of one or more species of lice. All studies were conducted following a common protocol at various locations throughout North America in order to obtain broad strain representation for each of the economically important species over a range of climatic conditions and husbandry systems.

STUDY DESIGNS

In each of the studies, 20 cattle harboring infestations of one or more species of lice were selected. The species responsible for the infestation were identified and the animals were randomly allocated in a tiered manner to either a saline-treated/non-medicated group or a doramectin-treated group. All treatments were applied topically in a single passage along the midline of the back from the withers to the tailhead.

Prior to the start of each study, body sites were designated for counts on the basis of louse species present and their distribution on the animals. On day 0, lice counts were carried out on all animals, after which cattle received either saline or doramectin pour-on topically, according to their treatment group, except in study 1033C-60-94-009 where animals in group T1 received no treatment. Further lice counts were carried out at weekly intervals thereafter for five weeks.

DATA ANALYSIS

In each study, lice were counted for each animal. Efficacy was calculated based on the percentage reduction of lice in doramectin-treated cattle compared with the

control group at each time point post-treatment. Percent efficacy was calculated using the following formula:

$$\frac{[(Arithmetic\ mean\ number\ of\ lice\ in\ non-medicated\ cattle) - (Arithmetic\ mean\ number\ of\ lice\ in\ doramectin-treated\ cattle)]}{[Arithmetic\ mean\ number\ of\ lice\ in\ non-medicated\ cattle]} X\ 100 = Percentage\ Efficacy$$

RESULTS

Results are presented on an individual study basis in the section following (see tables 30 to 38).

OVERALL CONCLUSIONS

A single application of doramectin pour-on, administered to cattle at a dosage of 500 mcg/kg, was effective against natural infestations of *Damalinia bovis*, *Haematopinus eurysternus, Linognathus vituli*, and *Solenopotes capillatus*. No adverse reactions to treatment were observed.

1. Dose confirmation study #1032C-60-94-161, Dr. J. Lancaster, 4K Farms, Tontitown, Arkansas

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 30.

   Table 30 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Linognathus vituli*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (saline)	26	33	26	21	19	15	10
T2 (dora)	26	46	0 100%	0 100%	0 100%	0 100%	0 100%

2. Dose confirmation study #1032C-60-95-170, Dr. T.N. TerHune, Health Management Services, Corcoran, California

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 31.

   Table 31 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Haematopinus eurysternus*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (saline)	18	19	13	16	6	9	1
T2 (dora)	17	17	0.4 97%	0 100%	0 100%	0 100%	0 100%

3. Dose confirmation study #1032C-60-95-173, Dr. J.J. Arends, Bagwell Farm, Garner, North Carolina

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 32.

   Table 32 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Linognathus vituli

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (saline)	73	49	38	30	33	38	35
T2 (dora)	64	41	0 100%	0 100%	0 100%	0 100%	0 100%

4. Dose confirmation study #1032C-60-95-174, Dr. J.J. Arends, Tony Coats Farm, Clayton, North Carolina

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Tables 33 and 34.

   Tables 33 & 34 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle Lice

	Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
Damalinia bovis	T1 (saline)	25	63	69	87	71	76	159
	T2 (dora)	25	98	0 100%	0 100%	0 100%	0 100%	0 100%
Haematopinus eurysternus	T1 (saline)	16	36	39	46	45	40	61
	T2 (dora)	16	27	0 100%	0 100%	0 100%	0 100%	0 100%

5. Dose confirmation study #1032C-60-95-177, Dr. D.G. Meyer, Lucerne Enterprise Research Feedlot, Colon, Nebraska

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Tables 35 and 36.

Tables 35 & 36 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle Lice

	Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
Damalinia bovis	T1 (saline)	21	24	60	48	82	53	133
	T2 (dora)	12	8	0 100%	0 100%	0 100%	0 100%	0 100%
Solenoptes capillatus	T1 (saline)	17	34	74	63	47	57	78
	T2 (dora)	16	31	0 100%	0 100%	0 100%	0 100%	0 100%

6. Dose confirmation study #1032C-60-95-221, Dr. L.L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Tables 37 and 38.

   Tables 37 and 38 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against Cattle Lice

	Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
Damalinia bovis	T1 (saline)	476	693	930	926	1003	511	232
	T2 (dora)	330	571	3 >99%	.4 >99%	.1 >99%	0 100%	0 100%
Solenoptes capillatus	T1 (saline)	1112	925	694	681	594	583	570
	T2 (dora)	1007	841	0 100%	0 100%	0 100%	0 100%	0 100%

7. Dose confirmation study #1033C-60-94-009, Dr. J.E. Lloyd, University of Wyoming, Laramie, Wyoming

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 39.

   Table 39 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Damalinia bovis*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (nonmedicated)	108	153	193	179	151	89	57
T2 (dora)	106	129	0 100%	0 100%	0 100%	0 100%	0 100%

8. Dose confirmation study #1033C-60-94-157, Dr. L.L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 40.

   Table 40 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Linognathus vituli*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (nonmedicated)	540	564	568	439	294	204	103
T2 (dora)	516	576	0 100%	0 100%	0 100%	0 100%	0 100%

9. Dose confirmation study #1033C-60-94-158, Dr. L.L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Twenty (20) cattle with natural lice infestations were divided into two equal groups (doramectin or control). Lice counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 41.

   Table 41 Mean Lice Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Haematopinus eurysternus*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (saline)	446	535	462	348	228	285	222
T2 (dora)	237	399	0 100%	0 100%	0 100%	0 100%	0 100%

F. Efficacy Confirmation - Mange Mites:

SUMMARY

A series of studies was conducted to evaluate the efficacy of doramectin pour-on, administered at a dosage of 500 mcg/kg, in cattle harboring natural or artificial infestations of mange mites under field conditions. The studies were conducted to a common protocol for each mite species at sites in North America and Europe, representative of a range of climatic conditions and husbandry systems.

STUDY DESIGN - CHORIOPTES BOVIS

Artificial-infestation and natural-infestation studies were conducted in North America and Europe to good clinical practice standards. In each study, a minimum of 20 cattle with confirmed, active mite infestations were randomly assigned to a saline-treated/non-medicated group or a doramectin-treated group (each of 10 or 11 animals) in a tiered manner. On day 0, mite counts were carried out on skin scrapings from all animals, after which the animals in each study received doramectin pour-on or saline or no treatment, according to their treatment group. Doramectin and saline treatments were applied topically in a single passage along the midline of the back between the withers and the tailhead. In all studies, mite

counts were also made from skin scrapings obtained from each animal on Days 7, 14/15, 21, 28 and 35.

STUDY DESIGN - SARCOPTES SCABIEI

Natural infestation studies were conducted in Europe to good clinical practice standards. In these studies, a minimum of 14 cattle with confirmed, active mite infestations were randomly assigned to either a doramectin-treated group (11 or 6 animals) or a non-medicated group (12 or 8 animals). On day 0, mite counts were carried out on all non-medicated animals, after which the animals in the treated group in each study received doramectin pour-on (500 mcg/kg) topically in a single passage along the midline of the back between the withers and the tailhead. Animals in the non-medicated groups received no treatment. In both studies, mite counts also were made from skin scrapings taken from each animal on days 7, 14, 21, 28, and 35.

DATA ANALYSIS

In each study, mites were counted for each animal. . Efficacy was calculated based on the percentage reduction in live mites counts of doramectin-treated cattle compared with the control group at each time point post-treatment. Percent efficacy was calculated using the following formula:

$$\frac{[(\text{Arithmetic mean number of mites in non-medicated cattle}) - (\text{Arithmetic mean number of mites in doramectin-treated cattle})]}{[\text{Arithmetic mean number of mites in non-medicated cattle}]} X\ 100 = \text{Percentage Efficacy}$$

RESULTS

Results are presented on an individual study basis in the section following (see Tables 42 to 45).

OVERALL CONCLUSIONS

A single topical application of doramectin pour-on, administered to cattle at a dosage of 500 mcg/kg of body weight, was effective against infestations of Chorioptes bovis or Sarcoptes scabiei. No adverse reactions to treatment were observed.

1. Dose confirmation study #1031C-60-93-009, Dr. L.L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Twenty (20) cattle with artificial mite infestations were divided into two equal groups (doramectin or control). Live mite counts were conducted on Days -8, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 42.

Table 42 Mean Live Mite Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Chorioptes bovis*

Group	**Day -8**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (nonmed)	164	399	376	468	576	594	908
T2 (dora)	154	167	45 88%	29 94%	1 >99%	1 >99%	0.2 >99%

2. Dose confirmation study #1033C-60-94-159, Dr. L.L. Smith, Research and Development, Inc., Readstown, Wisconsin

   Twenty (20) cattle with natural mite infestations were divided into two equal groups (doramectin or control). Live mite counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 43.

   Table 43 Mean Lice Mite Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Chorioptes bovis*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (nonmed)	159	187	150	157	161	217	162
T2 (dora)	150	103	1 >99%	0 100%	0 100%	0 100%	0 100%

3. Dose confirmation study #5032C-81-94-086, Dr. G. Gaina, S.C. Agrozootechnica S.A., Baracia, Romania

   Twenty-three (23) cattle with natural mite infestations were allocated to a non-medicated group (12 animals) or a doramectin-treated group (11 animals). Live mite counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 44.

   Table 44 Mean Live Mite Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Sarcoptes scabiei*

Group	**Day -7**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**
T1 (nonmed)	9	16	26	24	25	31	29
T2 (dora)	10	16	1 98%	0 100%	0 100%	0 100%	0 100%

4. Dose confirmation study #5032C-10-94-089, Dr. G. Gräfner, Herr Sommer, Ruting, Germany

   Fourteen (14) cattle with natural mite infestations were allocated to a non-medicated group (8 animals) or a doramectin-treated group (6 animals). Live mite counts were conducted on Days -7, 0, 7, 14, 21, 28, and 35. The results are summarized in Table 45.

Table 45 Mean Live Mite Counts and Therapeutic Efficacy of Doramectin at 500 mcg/kg BW Against *Sarcoptes scabiei*

Group	Day -7	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
T1 (nonmed)	140	131	90	41	26	15	18
T2 (dora)	146	145	1 99%	0 100%	0 100%	0 100%	0 100%

G. Field Efficacy Against Nematodes:

SUMMARY

A series of studies were conducted under field conditions to confirm the effectiveness of doramectin pour-on, administered topically at 500 ug/kg, against naturally-acquired gastrointestinal nematode infections of cattle. Studies were conducted to a common protocol at different locations throughout North America, representative of a range of climatic conditions and management systems. The geographic locations of the studies are presented in Table 43.

EXPERIMENTAL METHOD

Animals were selected from grazing or feedlot herds in which gastrointestinal parasitism had been confirmed by the presence of nematode eggs in the feces. In each study, between 40 and 100 cattle were selected and randomly allocated to a saline- or doramectin-treated group and were treated topically with either doramectin pour-on or saline on day 0. All treatments were applied topically in a single passage along the midline of the back from the withers to the tailhead. Fecal egg counts were carried out using standard methods on samples collected from each animal at the time of treatment and at weekly intervals thereafter for three weeks.

Each animal was observed for abnormal clinical signs at regular intervals throughout the study. Weather conditions were recorded around the time of treatment and daily thereafter for six (one study) or seven days.

DATA ANALYSIS

In each study, fecal egg counts were made for each animal. Arithmetic mean fecal egg counts were calculated and used to estimate efficacy as follows:

$$\frac{[(\text{Arithmetic mean number of eggs in non-medicated cattle}) - (\text{Arithmetic mean number of eggs in doramectin-treated cattle})]}{[\text{Arithmetic mean number of eggs in non-medicated cattle}]} X\ 100 = \text{Percentage Efficacy}$$

RESULTS

A summary of the results are presented in Table 46.

OVERALL CONCLUSIONS

A single topical application of doramectin, administered to cattle at a dosage of 500 mcg/kg, was effective in treatment of mixed infections of gastrointestinal nematodes, including *Haemonchus spp., Ostertagia spp., Trichostrongylus spp.,*

Bunostomum spp., Cooperia spp., and *Oesophagostomum spp*. No adverse reactions to treatment were observed.

Table 46 Summary of Nematode Field Efficacy Studies

Study Number	**Location**	**No. Doramectin Treated Animals**	**% Reduction in EPG 21 Days Post Treatment**
1233C-60-94-156	Watkinsville, Georgia	75	93
1233C-60-94-166	Baton Rouge, Louisiana	36	99
1233C-60-95-181	Amarillo, Texas	30	99
1233C-60-95-184	Clayton, North Carolina	36	96
1233C-60-95-186	Corcoran, California	39	100
1233C-60-95-187	Colon, Nebraska	60	96
1233C-60-95-188	Parma, Idaho	60	60 99

H. Duration of Activity - Nematodes:

SUMMARY

Two studies were conducted to evaluate the persistent efficacy of doramectin, administered at a dosage of 500 mcg/kg (1 mL/10 kg), against artificial infections of nematodes. Each study used larval nematode cultures isolated during 1994 or 1995.

STUDY DESIGN

In each study, calves were selected for use based on the absence of trichostrongyle-type eggs in fecal samples. The animals were randomly assigned to a saline-treated group, to one of three doramectin-treated groups, or as larval viability monitors.

On day 0, each calf in Groups T1 and T2 was treated topically with either saline or doramectin, respectively. Groups T3 and T4 were treated with doramectin in an identical manner on days 7 and 14, respectively. All treatments were applied in a single passage along the midline of the back, from the withers to the tailhead. All animals were observed after each treatment for a sufficient time to permit a reliable assessment of any abnormal clinical condition. Animals were challenged daily on days 14 to 35 by oral gavage with infective nematode larvae. The persistence interval was defined as the period from day of treatment to last day of challenge with infective larvae.

DATA ANALYSIS

In each study, nematodes were counted for each animal. Arithmetic mean nematode counts were calculated and used to estimate efficacy as follows:

$$\frac{[(\text{Arithmetic mean number of nematodes in non-medicated cattle}) - (\text{Arithmetic mean number of nematodes in doramectin-treated cattle})]}{[\text{Arithmetic mean number of nematodes in non-medicated cattle}]} X\ 100 = \text{Percentage Efficacy}$$

RESULTS

The results are presented in Tables 47 to 48.

OVERALL CONCLUSIONS

A single topical application of doramectin, administered at a dosage of 500 mcg/kg, provided persistent efficacy against challenge infections of Dictyocaulus viviparus and Cooperia oncophora for up to 21 days, and against challenge infections of Ostertagia ostertagi, Cooperia punctata and Oesophagostomum radiatum for up to 28 days after treatment. No adverse reaction to treatment was observed during these studies.

1. Dose confirmation study #1231C-60-95-199, Dr. E. Johnson, Johnson Research, Parma, Idaho

   Forty-two (42) calves were allocated to one of four groups of 10 animals each, or as one of two larval viability monitor animals. Each animal was then artificially challenged with nematodes. At necropsy, worm counts between doramectin and saline groups were compared to determine doramectin efficacy. The results are summarized in Table 47.

   Table 47 Arithmetic Means and Persistent Efficacy of Doramectin at 500 mcg/kg BW Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**Duration of Activity**	**% Efficacy**
Dictyocaulus viviparus	40	0	21	100
Ostertagia ostertagi	156	0	28	100
Cooperia punctata	272	6	28	98
Cooperia oncophora	656	57	21	91
Oesophagostomum radiatum	608	0.4	28	>99

2. Dose confirmation study #1231C-02-95-204, Dr. R. Prichard, Institute of Parasitology, McGill University, Ste-Anne de Bellevue, Quebec, Canada

   Forty-two (42) calves were allocated to one of four groups of 10 animals each, or as one of two larval viability monitor animals. Each animal was then artificially challenged with nematodes. At necropsy, worm counts between doramectin and saline groups were compared to determine doramectin efficacy. The results are summarized in Table 48.

Table 48 Arithmetic Means and Persistent Efficacy of Doramectin at 500 mcg/kg BW Against Cattle Nematodes

Parasite	**Control**	**Doramectin**	**Duration of Activity**	**% Efficacy**
Dictyocaulus viviparus	10	0	21	100
Ostertagia ostertagi	1,410	10	28	99
Cooperia punctata	870	75	28	91
Cooperia oncophora	3,200	22	21	99
Oesophagostomum radiatum	1,328	1.2	28	>99

III. TARGET ANIMAL SAFETY

Doramectin target animal safety (cattle) has previously been established in the doramectin injectable solution for cattle file (see: FDA-approved NADA 141-061). Two additional studies were conducted for the doramectin pour-on solution for cattle file. A comparative pharmacokinetics study established lower systemic exposure to doramectin resulting from treatment of cattle with the intended label dose of doramectin pour-on compared with the label dose of doramectin injectable solution. A margin-of-safety study provided direct evaluation of doramectin pour-on solution administered at 1X, 3X and 5X the intended label dose.

A. COMPARATIVE BIOAVAILABILITY STUDY

1. *Experiment number:*

   1532N-60-94-160

2. *Type of Study:*

   Comparative bioavailability study comparing blood plasma levels in cattle treated with either doramectin injectable solution at the commercial dose of 200 mcg/kg BW, or doramectin pour-on solution at the proposed dose of 500 mcg/kg BW.

3. *Study director:*

   M.A. Nowakowski, Ph.D., Pfizer Central Research

4. *General Design:*

   a. *Objective:* To compare the plasma kinetic profiles of doramectin administered at recommended doses to cattle by subcutaneous injection and by pour-on application.

   b. Animals: 32 cross-bred beef cattle, 16 males and 16 females, weighing an average of 225 kg at study initiation.

   c. Control: None

   d. Dosage Form: DECTOMAX® injectable solution, 200 mcg/kg

e. Doramectin pour-on solution, 500 mcg/kg

f. Route of Administration: DECTOMAX® injectable solution, subcutaneous injection

g. Doramectin pour-on solution, topical

h. Test Duration: 56 days

i. Pertinent Measurements/Observations: Clinical observations were made daily. Blood was obtained for doramectin assay pre-dose and on days 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 21, 28, 35, 42, 49, and 56 after treatment.

5. *Results:*

Results (±1 SD) are summarized in Table 49.

Table 49: Comparative Pharmacokinetic Parameters - Doramectin Injectable Solution and Doramectin Pour-On Solution

Parameter	**Doramectin Injectable Solution (200 mcg/kg)**	**Doramectin Pour-On Solution (500 mcg/kg)**
$AUC_{0\text{-infinity}}$(ng-day/mL)*	520 ± 30[1]	210 ± 30[2]
C_{max} (ng/mL)*	35 ± 2	9 ± 2
T_{max} (days)	6 ± 2	9 ± 2
Mean half-life*	5.8 days[1]	15 days[2]

*- Significant difference ($P<0.05$)
1- n=16 animals
2- n=12 animals

Because of the nature of drug absorption and elimination demonstrated by the topical route of administration, the elimination constant, k_{el} and, therefore, AUC(0-infinity), could not be estimated for 4 of the 16 topically-treated animals. AUC(0-T_{last}) accounted for 98% of AUC(0-infinity) for the animals dosed with the injectable formulation and for 89% of AUC(0-infinity) for the animals dosed with the topical formulation. The relative bioavailability of the topical formulation was estimated to be 42% of the injectable formulation.

6. *Statistical Analysis:*

AUC, Tmax and Cmax were estimated for each route of administration and analyzed using analysis of variance of a one-period parallel design group. The 5% level of significance was used to determine whether the two routes differed.

7. *Conclusion:*

Systemic exposure of cattle to doramectin was substantially lower when the drug was applied at the recommended dose topically as the pour-on formulation than when administered by subcutaneous injection as the injectable solution.

B. SAFETY MARGIN STUDY

1. *Experiment number:*

   1435N-60-94-002

2. *Type of Study:*

   A 16-day study in which a total of three topical administrations of doramectin pour-on solution at doses of 500, 1,500 or 2,500 mcg/kg BW were administered to beef cattle.

3. *Study director:*

   Dan C. Ronning, M.S.
   Colorado Animal Research Enterprises, Inc.
   Fort Collins, Colorado

4. *General Design:*

   a. *Objective*: To assess the safety of 500, 1,500 or 2,500 mcg/kg BW doramectin when administered topically to cattle on three consecutive days.

   b. *Animals*: Twenty-four (24) beef cattle, 12 males and 12 females, weighing approximately 142 to 194 kg at study initiation

   c. *Control*: Normal physiologic saline

   d. *Dosage Form*: Doramectin pour-on solution, 500 mcg/kg

   e. *Route of Administration*: Topical administration

   f. *Test Duration*: 16 days

   g. *Pertinent Measurements/Observations*: Clinical observations, physical examinations, rectal temperatures, feed consumption, body weights, hematology, serum chemistry, urinalysis, gross pathology, and histopathology.

5. *Results:*

   a. *Clinical Observations: Treatment-related changes were limited to superficial skin flaking at the site of administration in some animals. This observation occurred approximately two weeks post-dose, and was not highly dose-correlated.*

   b. *Rectal temperatures: Rectal temperatures were normal and consistent among all animals throughout the study period.*

   c. *Feed consumption: There was no significant difference in feed consumption among treatment groups.*

   d. *Body weight: There was no significant difference in weight gain among treatment groups.*

e. Hematology/serum chemistry: Hematologic and serum chemistry values were within the normal range in all treatment groups.

f. Urinalysis: Urinalysis results were within the normal range in all treatment groups.

g. *Gross and histopathological observations: Superficial skin flaking at the administration site was correlated with microscopic observations of mild acanthosis and hyperkeratosis of the epidermis.*

6. Statistical Analysis:

For hematologic, serum chemistry, and rectal temperature variables, treatment means and animal within treatment standard deviations were estimated. Average daily weight gain and feed consumption were calculated for each treatment group and analysis of variance procedures was carried out.

7. Conclusions:

Doramectin pour-on produced no significant systemic toxicological effects when administered topically at dosages of 500, 1,500, or 2,500 mcg/kg for three consecutive days. Treatment-related effects were limited to superficial skin flaking at the site of administration in some animals at approximately two weeks post-dose. It was concluded that use of doramectin pour-on as directed provides a wide margin of safety in cattle.

C. BREEDING ANIMAL SAFETY

Safety in male and female breeding animals was determined by comparison with doramectin injectable solution for cattle. Data were previously presented to show that subcutaneous administration of doramectin at 600 mcg/kg (3X the intended SC dose) had no adverse effects on male and female breeding cattle.

To evaluate if topical application of doramectin posed any risk to breeding animals, a comparative bioavailability study was conducted. The results (summarized in study 1532N-60-94-160 above) indicate significantly lower systemic exposure to doramectin administered topically compared to subcutaneous injection. Therefore, doramectin pour-on solution for cattle will be safe in breeding cattle.

IV. HUMAN FOOD SAFETY

A. Toxicology:

1. TOXICITY STUDIES

For a summary of the toxicology tests completed in support of doramectin, please consult the Freedom of Information (FOI) summary for NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle.

2. SAFE CONCENTRATION OF TOTAL RESIDUE

As discussed in the FOI summary for NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle, the safe concentration in muscle has been calculated from the no-observed-effect-level in the most sensitve study in the most sensitive species:

$$\text{Safe concentration in muscle} = \frac{(60\ kg)\ (0.75\ \mu g/kg/day)}{300\ g/day} = 150\ \text{ppb}$$

The safe concentration of residues in liver, kidney and fat are determined from this number using appropriate food consumption values (food factor) for these tissues. Therefore, the safe concentrations are:

Liver: 150 ppb x 3 (food factor) = 450 ppb

Kidney: 150 ppb x 6 (food factor) = 900 ppb

Fat: 150 ppb x 6 (food factor) = 900 ppb

B. Total Residue and Metabolism

For a summary of the total residue and metabolism studies completed in support of doramectin, please consult the Freedom of Information (FOI) summary for NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle.

C. Selection of Target Tissue and Marker Residue for Doramectin in Cattle:

The data from the total residue metabolism studies referenced above establish that liver contains the highest levels of total drug-related doramectin residues and it is the tissue in cattle from which residues are the last to deplete to the safe concentration. Similarly high concentrations occur in fat; however, these did not exceed the safe concentration at any time point tested. These observations suggested that liver was the most likely target tissue for doramectin in cattle.

The metabolism data confirmed liver as the target tissue and selection of the parent doramectin as the marker residue. Those data demonstrated that the parent was present in sufficiently high concentration and had the proper depletion characteristics in liver to serve as the marker residue in that tissue.

D. Tolerance for the Marker Residue:

A liver tolerance of 100 ppb was assigned for setting the withdrawal time in cattle under NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle. Since both injection and topical administration are considered to be parenteral routes of administration, a liver tolerance of 100 ppb is also applicable to doramectin pour-on solution for cattle.

E. Studies Establishing the Withdrawal Period:

Depletion of the marker residue was determined following topical administration of doramectin.

TITLE: Marker Residue Study of Edible Tissue from Cattle Treated Topically with Doramectin

STUDY NO.: 1531N-60-94-054

STUDY DESIGN:

Dose: 625 mcg/kg BW as a topical administration

Test animals: 32 adult, crossbred beef cattle (16 male, 16 female)

Withdrawal schedule: 14, 21, 28, 42 and 56 days post-dosing

Following treatment with doramectin, six animals were sacrificed at each collection time, and tissue samples of liver, muscle (longissimus dorsi and semimembranosus), kidney, and perirenal fat were collected and assayed for unchanged doramectin, the marker residue.

RESULTS:

The results from the study are shown in Table 50:

Table 50: Mean doramectin (1 SD) concentration in cattle tissue (study #1531N-60-94-054)

Withdrawal period (days)	**Liver Levels (ng/g)**	**Fat Levels (ng/g)**	**Kidney Levels (ng/g)**	**Muscle Levels *semimembranosus*[1] (ng/g)**	**Muscle Levels *longissimus dorsi*[2] (ng/g)**
14	90 ± 40	130 ± 60	20 ± 8	7 ± 3	9 ± 4
21	70 ± 30	90 ± 20	17 ± 5	7 ± 2	6 ± 2
28	60 ± 30	70 ± 30	13 ± 6	<4	<4
42	28 ± 7	38 ± 11	6 ± 2	<3	<3
56	15 ± 8	18 ± 9	<4	<lloq[3]	<lloq[3]

[1]- semimembranosus muscle represents edible muscle
[2]- longissimus dorsi muscle represents tissue deep to the site of topical drug administration
[3]- value below the lower limit of assay quantitation

WITHDRAWAL TIME

Statistical analysis of the marker residue depletion study (1531N-60-94-054) using a liver-based tolerance of 100 ppb results in a withdrawal time of 45 days.

F. Regulatory Method:

DORAMECTIN DETERMINATIVE ASSAY PROCEDURE

For a summary of determinative analytical procedure, please consult the Freedom of Information (FOI) summary for NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle.

DORAMECTIN CONFIRMATORY ASSAY PROCEDURE

For a summary of confirmatory analytical procedure, please consult the Freedom of Information (FOI) summary for NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle.

METHOD VALIDATION

The determinative and confirmatory analytical methods were evaluated and accepted under NADA 141-061, DECTOMAX® (doramectin) 1% injectable solution for cattle.

V. USER SAFETY

Potential for exposure to doramectin solution by end users was assessed under field conditions. Two commercialized dosing guns recommended for use with the product and the custom designed dosing cup to be provided with the smaller volume presentations of the product were employed by users to apply doramectin pour-on solution to cattle. User exposure to drug was then evaluated by quantitating drug exposure to the hands, arms and face during dosing.

USER SAFETY STUDY

TITLE: User Exposure for Doramectin Pour-On Application in Cattle

PROTOCOL NO.: 1530N-60-96-227

STUDY DESIGN: Dose: 500 mcg/kg BW as a topical administration

Test animals: 75 adult, crossbred beef

Five individuals (referred to as "users") each dosed a total of 15 cattle, 5 each with either a dosing cup or one of two commercially available dosing guns. Users wore a tyvek coverall, face mask, and gloves, each with absorbent patches affixed for the purpose of capturing ambient drug product as a measure of potential human exposure during normal drug use.

RESULTS:

Doramectin was detected on the outside gloves of four of the five users handling the dosing cup at quantities per glove of 0.05 mL or less of formulated product. Doramectin was detected on the outside gloves of four of the five users handling either dosing gun at quantities of 0.2 mL of formulated product. Doramectin was not detected on any inside gloves (separated from outside gloves by latex gloves), or on any of the absorbent pads.

Doramectin was detected on the outside of the outer gloves, but was not detected on any inside gloves (separated from the outer pair by latex gloves), nor on any absorbent pads. Latex gloves were judged to be impervious to the product, since doramectin was not detected on the inner gloves. Therefore, users are protected from exposure during product application, provided they comply with label precautions which recommend the use of rubber gloves, boots and a waterproof coat.

CONCLUSION

The label-recommended equipment, procedures and precautions eliminate potential for exposure to doramectin under normal handling of doramectin pour-on solution, thus preventing absorption of any toxicologically significant quantities of the drug. Accidental exposure through spillage is unlikely to result in any significant adverse reactions, since the product is only minimally irritating and recommended washing after contact should minimize the potential for irritation, which is largely due to the solvent.

Doramectin pour-on solution presents no unusual risks to the handler under normal conditions of use in compliance with recommended procedures and precautions.

VI. AGENCY CONCLUSIONS

The data submitted in support of this original 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 solution is safe and effective for the treatment and control of gastrointestinal roundworms, lungworms, kidneyworms, biting and sucking lice, and mange mites in cattle, when administered topically at a dose of 500 mcg/kg bodyweight.

The safe concentrations of doramectin residues assigned in association with the original DECTOMAX® injectable solution for cattle NADA are 150 ppb in muscle, 450 ppb in liver, 900 ppb in kidney, and 900 ppb in fat. Based on metabolism studies in cattle, a tolerance of 100 ppb for marker residue, parent doramectin, has been established in liver. The tolerance (Rm) refers to the residue measured by the regulatory method described herein.

A pre-slaughter withdrawal period of 45 days was calculated from the residue depletion study of doramectin residues in cattle, following topical administration of DECTOMAX® pour-on solution. Statistical analysis of the marker residue depletion study using a liver-based tolerance of 100 ppb gave a withdrawal time of 45 days.

The data submitted for DECTOMAX® pour-on solution for cattle support the marketing of the product as an over-the-counter new animal drug. 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. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall have the over-the-counter marketing status.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding contained in an environmental assessment may be seen in the Dockets Management Branch (HFV-305), Park Building (Room 1-23), 12420 Parklawn Dr., Rockville, Maryland 20855.

Under section 512(c)(2)(F)(ii) 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. DECTOMAX® pour-on solution is under U.S. patent number 5,089,480, which expires on February 18, 2009.

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.