Approval Date: September 18, 1997

# FREEDOM OF INFORMATION SUMMARY

## I. GENERAL INFORMATION

### A. File Number

NADA 141-061

### B. Sponsor

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

### C. Proprietary Name

Dectomax® Injectable Solution

### D. Established Name

doramectin 1% injectable solution

### E. Dosage Form

DECTOMAX Injectable

Solution is a sterile 1% solution containing 10 mg doramectin/mL.

### F. Dispensing Status

OTC

### G. Recommended Dosages

Cattle - 200 mcg/kg doramectin/kg bodyweight (1 mL/110 lb)

Swine - 300 mcg/kg doramectin/kg bodyweight (1 mL/75 lb)

### H. Route of Administration

DECTOMAX Injectable Solution may be administered by subcutaneous or intramuscular injection in cattle and by intramuscular injection only in swine.

### I. Indication

For the treatment and control of the following nematode and arthropod parasites in cattle.

**Gastrointestinal Roundworms**

*Ostertagia ostertagi* - Adults and fourth-stage larvae
*Ostertagia ostertagi* - Inhibited fourth-stage larvae
*Ostertagia lyrata* - Adults and fourth-stage larvae
*Haemonchus placei* - Adults and fourth-stage larvae
*Trichostrongylus axei* - Adults and fourth-stage larvae

*Trichostrongylus colubriformis* - Adults and fourth-stage larvae
*Trichostrongylus longispicularis* – Adults
*Cooperia oncophora* - Adults and fourth-stage larvae
*Cooperia punctata* - Adults and fourth-stage larvae
*Cooperia pectinata* – Adults
*Cooperia surnabada* (*syn.mcmasteri*) - Adults and fourth-stage larvae
*Bunostomum phlebotomum* – Adults
*Strongyloides papillosus* – Adults
*Oesophagostomum radiatum* - Adults and fourth-stage larvae
*Trichuris spp*. - Adults

**Lungworms**

*Dictyocaulus viviparus* - Adults and fourth-stage larvae

**Eyeworms**

*Thelazia spp.* - Adults

**Grubs**

*Hypoderma bovis*
*Hypoderma lineatum*

**Lice**

*Haematopinus eurysternus*
*Linognathus vituli*
*Solenopotes capillatus*

**Mange Mites**

*Psoroptes bovis*
*Sarcoptes scabiei*

Dectomax injectable solution has been proved to effectively control infections and to protect cattle from reinfection with *Ostertagia ostertagi* for 21 days, and *Cooperia punctata* and *Dictyocaulus viviparus* for 28 days after treatment. For the treatment and control of the following nematode and arthropod parasites in swine.

**Gastrointestinal Roundworms**

*Hyostrongylus rubidus* – Adults
*Ascaris suum* - Adults, and fourth-stage larvae
*Oesophagostomum dentatum* - Adults, and fourth-stage larvae
*Oesophagostomum quadrispinulatum* – Adults
*Strongyloides ransomi* - Adults

**Lungworms**

*Metastrongylus spp*. - Adults

**Kidneyworms**

*Stephanurus dentatus* - Adults

**Sucking Lice**

*Haematopinus suis* - Adults and Immature stages

**Mange Mites**

*Sarcoptes scabiei var. suis* - Adults and Immature stages

**J. Effect of Supplement**

Adds swine to the previously approved NADA.

## II. EFFECTIVENESS

### A. Preclinical Investigation:

The *in vivo* activity of doramectin against nematodes and arthropods was initially established in laboratory animals and further investigated in the target species. In a preliminary study in swine it was demonstrated that a dosage of 300 mcg/kg was required to control *Oesophagostomum dentatum*, a representative of the large-intestine-dwelling nematodes which, as a group, are recognized to be the least responsive of the avermectin-susceptible parasites. This dosage was therefore provisionally selected for further evaluation in a series of studies to investigate efficacy against a range of avermectin-susceptible nematode and arthropod species. These studies indicated that of the label-claimed species against which doramectin was evaluated, *Oesophagostomum quadrispinulatum* was the least susceptible. Based on these findings, this species together with a representative arthropod, *Sarcoptes scabiei*, were selected for definitive dose titration studies to affirm that 300 mcg/kg was the appropriate dose of doramectin for effective broad spectrum activity.

### B. Dose Determination:

Two dose titration studies were conducted assessing efficacy against *S. scabiei* and *O. quadrispinulatum*. In both studies, doramectin injectable was administered by the intramuscular route at dosages of 150 mcg/kg, 300 mcg/kg and 450 mcg/kg.

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

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

Mite percentage efficacies were calculated at each dosage level by determining the percentage of animals in each treatment group with no mites detected on day 28.

Overall Conclusion: Results indicated that doses of 300 and 450 mcg/kg doramectin were effective and equivalent in resolving infestations of *S. scabiei* and infections of *O. quadrispinulatum*. These doses, in turn, were superior to a 150 mcg/kg doramectin dose. Overall, these data indicate that by intramuscular (IM) injection, 300 mcg/kg of doramectin is an appropriate dosage for the treatment and control of swine arthropod and nematode parasites.

1. Individual Dose Determination Studies

   (i) Dose determination study #1022C-60-91-004, Dr. N.E. Wood-Huels, Altamont Veterinary Clinic, Altamont, Illinois

   Twenty-four (24) swine with naturally acquired infestations of *S. scabiei* were assigned to one of four treatment groups (negative control and three doramectin groups). At 7, 14, 21 and 28 days following treatment, scrapings were collected from all animals for mite counts to determine doramectin efficacy. The results are summarized in Table 1.

   **Table 1: Therapeutic Efficacy of Doramectin Against Naturally Acquired Infestations of *S. scabiei***

| Treatment/Dosage(mcg/kg) | Animals/Group | % of Pigs with No Live Mites Detected on day 28 |
|---|---|---|
| Non-medicated | 6 | 20 |
| Doramectin (150) | 6 | 80 |
| Doramectin (300) | 6 | 100 |
| Doramectin (450) | 6 | 100 |

   (ii) Dose determination study #5222E-03-91-036, Dr. C. Hong, Central Veterinary Laboratory, Weybridge, Surrey, UK

   Forty-four (44) pigs with no pre-existing nematode infection were randomly allocated to four groups each of eleven animals (a negative control and three doramectin groups) and artificially infected with L3 larvae of *O. quadrispinulatum*. Following a period of time sufficient to allow for parasite development to the adult stage, animals were treated IM with either doramectin or saline and slaughtered 14 or 15 days later for determination of worm burdens. The results are summarized in Table 2.

   **Table 2: Therapeutic Efficacy of Doramectin Against *O. quadrispinulatum* - Percentage Reduction Relative to Controls**

| Treatment/Dosage(mcg/kg) | Animals/Group | Percentage Efficacy |
|---|---|---|
| Non-medicated | 11 | - |
| Doramectin (150) | 11 | 91.4 |
| Doramectin (300) | 11 | 99.8 |
| Doramectin (450) | 11 | 100 |

## C. Efficacy Confirmation - Gastrointestinal Nematodes and Lungworms:

SUMMARY:

A series of seven studies, involving swine with either naturally or artificially acquired infections was conducted in a wide range of geographical settings. These studies evaluated the efficacy of doramectin injectable solution, administered by the intramuscular route at a dosage of 300 mcg/kg bodyweight against adult and immature roundworms and lungworms. Studies were designed to evaluate doramectin efficacy against both adult stage and normally developing L4 larvae. Efficacy evaluations against adult stage parasites were assessed in studies using either natural or artificially acquired infections, whereas efficacy against fourth stage larvae were assessed in studies using artificially acquired infections in which the

development age of nematode species being evaluated was known at the time of treatment.

*Study Designs:* Three studies were designed to assess efficacy against naturally acquired infections of adult stage parasites. In each study, 20 pigs were selected from herds in which the presence of infection had been confirmed by post mortem examination or positive fecal egg counts. Animals were assigned to either a nonmedicated control group or a medicated group based on liveweight or fecal egg count. Animals were treated appropriately according to group and slaughtered 14 or 15 days after treatment for worm burden determination by standard techniques.

The other four studies (three two-group studies and one three-group study) used induced infections to assess efficacy against adult stage or L4 larval stage parasites. In each study, nine or ten animals with no evident pre-existing nematode infections were selected for each treatment group. All animals were inoculated with infective stages of nematode species. Infections in the two-group studies were phased such that by the day of treatment parasites had matured to the stage against which efficacy was to be evaluated. Infections in the three-group study were similarly phased; however, one group was treated with doramectin to coincide with parasite development to the adult stage. All animals were slaughtered and worm burdens determined by standard techniques between 14 and 47 days after treatment.

*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:

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

*Results:* Results are presented on an individual study basis in the section following (see Tables 3 to 9).

*Conclusions:* A single intramuscular injection of doramectin, administered to swine at a dose of 300 mcg/kg, was efficacious against the adult stages of *Hyostrongylus rubidus, Ascaris suum, Strongyloides ransomi, Oesophagostomum dentatum, O. quadrispinulatum*, and *Metastrongylus* spp. and against L4 larvae of *A. suum* and *O. dentatum*.

1. Individual Dose Confirmation Studies

   (i) Experiment #1221C-60-90-004, Dr. T. Bonner Stewart, School of Veterinary Medicine, Louisiana State University, Baton Rouge, Louisiana

   Twenty (20) artificially infected swine were assigned to two equal groups (negative control and doramectin groups). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy The results are summarized in Table 3.

**Table 3: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Adult and L4 stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Ascaris suum* (L4 stage) | 100 |
| *Strongyloides ransomi* (Adult stage) | 100 |
| *Oesophagostomum dentatum* (L4 stage) | 99 |

(ii) Experiment #1221C-60-90-005, Dr. J. J. Arends, S&J Farms, Willow Springs, North Carolina

Twenty (20) artificially infected swine were assigned to two equal groups (negative control and doramectin groups). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 4.

**Table 4: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Adult Stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Strongyloides ransomi (Adult stage)* | 100 |
| *Oesophagostomum dentatum (Adult stage)* | 100 |
| *Oesophagostomum quadrispinulatum (Adult stage)* | 100 |
| *Metastrongylus spp. (Adult stage)* | 100 |

(iii) Experiment #1221C-02-90-007, Dr. Alain Villeneuve, University of Montreal, Faculty of Veterinary Medicine, Saint Hyacinthe, Quebec, Canada

Thirty (30) artificially infected swine were assigned to three equal groups (negative control and two doramectin groups). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 5.

**Table 5: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Adult and L4 Stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Ascaris suum (Adult stage)* | 100 |
| *Ascaris suum (L4 stage)* | 100 |
| *Oesophagostomum dentatum (Adult stage)* | 100 |
| *Oesophagostomum dentatum (L4 stage)* | 99 |

(iv) Experiment #1221C-60-90-008, Dr. T. Bonner Stewart, School of Veterinary Medicine, Louisiana State University, Baton Rouge, Louisiana

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

**Table 6: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against L4 Stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Ascaris suum* (L4 stage) | 100 |

(v) Experiment #1222C-60-89-001, Dr. T. Bonner Stewart, School of Veterinary Medicine, Louisiana State University, Baton Rouge, Louisiana

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

**Table 7: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Adult Stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Hyostrongylus rubidus* (Adult stage) | 99 |
| *Ascaris suum* (Adult stage) | 100 |
| *Strongyloides ransomi* (Adult stage) | 99 |
| *Oesophagostomum dentatum* (Adult stage) | 100 |
| *Oesophagostomum quadrispinulatum* (Adult stage) | 100 |

(vi) Experiment #1222C-60-89-002, Dr. J. J. Arends, S&J Farms, Willow Springs, North Carolina

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

**Table 8: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Adult Stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Ascaris suum* (Adult stage) | 100 |
| *Strongyloides ransomi* (Adult stage) | 99 |
| *Oesophagostomum dentatum* (Adult stage) | 100 |
| *Oesophagostomum quadrispinulatum* (Adult stage) | 100 |
| *Metastrongylus* spp. (Adult stage) | 100 |

(vii) Experiment #1222C-60-90-006, Dr. T. A. Yazwinski, University of Arkansas, Animal Science Department, Fayetteville, Arkansas

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

**Table 9: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Adult Stage Swine Nematodes**

| **Parasite** | **% Efficacy** |
|---|---|
| *Hyostrongylus rubidus* (Adult stage) | 100 |
| *Ascaris suum* (Adult stage) | 100 |
| *Strongyloides ransomi* (Adult stage) | 100 |
| *Oesophagostomum dentatum* (Adult stage) | 100 |
| *Metastrongylus* spp. (Adult stage) | 100 |

**D. Field Efficacy Against Nematodes:**

SUMMARY:

A series of seven studies was conducted to confirm, under field conditions, the effectiveness of doramectin injectable solution, administered to swine by the intramuscular route at 300 mcg/kg, against naturally acquired gastrointestinal and lung nematode infections. Studies were conducted to a common protocol at different locations throughout the U.S. and Canada, representative of a range of climatic conditions, husbandry and management practices. In each study, animals with confirmed infections of gastrointestinal nematodes were assigned to a doramectin-treated or a non-medicated group and treated accordingly. Efficacy was based on percentage reduction in mean fecal egg count in doramectin-treated animals assessed 20 or 21 days post treatment, the non-medicated controls serving to confirm that no self-cure had occurred. Results of the studies are summarized in Table 10.

**Table 10: Summary of Nematode Field Efficacy Studies**

| **Study** | **Number of Doramectin-Treated Animals** | **Study Location** | **% Reduction in Eggs Per Gram 21 Days Post-Treatment*** |
|---|---|---|---|
| 1233C-60-90-001 | 40 | California | 100 |
| 1233C-60-90-002 | 29 | Kansas | 100 |
| 1233C-60-90-003 | 56 | North Carolina | 100 |
| 1233C-60-90-004 | 56 | Arkansas | 97 |
| 1233C-60-90-005 | 43 | Illinois | 100 |
| 1233C-60-90-006 | 57 | Texas | 100 |
| 1233C-02-91-007 | 23 | Quebec, Canada | 100 |

*- Egg reductions are calculated with geometric means

## E. Efficacy Confirmation - Kidney Worms:

1. Summary

Two studies were conducted to evaluate the efficacy of doramectin injectable administered by the IM route at a dosage of 300 mcg/kg BW, against *Stephanurus dentatus*. Both studies utilized naturally infected sows and were conducted to uniform protocols in two geographic locations within the U.S.

*Study Design:* In each study, sows with positive urine egg counts were randomly allocated to a doramectin-medicated group or a non-medicated group and treated accordingly. All animals were slaughtered 56 days after treatment for recovery and counting of kidneyworms.

*Data Analysis:* Efficacy was calculated based on the percentage reduction in worm burdens of doramectin-treated sows compared with the non-medicated group. Percentage efficacy was calculated using the following formula:

$$\frac{[(\textit{Arithmetic mean number of kidneyworms in non-medicated swine}) - (\textit{Arithmetic mean number of kidneyworms in doramectin-treated swine})]}{[\textit{Arithmetic mean number of kidneyworms in non-medicated swine}]} \times 100 = \text{Percentage efficacy}$$

*Results:* Results are presented on an individual study basis in the section following (see Tables 11 and 12).

*Conclusion:* A single IM injection of doramectin administered at a dosage of 300 mcg/kg was 100% efficacious against the adult stage of *S. dentatus*.

2. Individual Kidneyworm Studies

(i) Experiment #1222C-60-90-009, Dr. J. J. Arends, S&J Farms, Willow Springs, North Carolina

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

**Table 11: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Stephanurus dentatus***

| **Parasite** | **% Efficacy** |
|---|---|
| *Stephanurus dentatus* | 100 |

(ii) Experiment #1222C-60-90-010, Dr. T. Bonner Stewart, Louisiana State University, School of Veterinary Medicine, Baton Rouge, Louisiana

Sixteen (16) naturally infected swine were assigned to two equal groups (negative control and doramectin groups). At necropsy, worm counts in the two groups were compared to determine doramectin efficacy. The results are summarized in Table 12.

**Table 12: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against Stephanurus dentatus**

| **Parasite** | **% Efficacy** |
|---|---|
| *Stephanurus dentatus* | 100 |

## F. Efficacy Confirmation - Lice:

1. Summary

Three studies were conducted to evaluate the efficacy of doramectin injectable solution administered by the intramuscular route at a dosage of 300 mcg/kg to swine harboring infestations of *Haematopinus suis*. Two studies were laboratory studies, one against natural infestations and one against artificial infestations, in which adults and immature *H. suis* were counted. The third study was conducted under field conditions against natural infestations, and only adults were counted.

*Study Design:* In each study, between 15 and 100 pigs were selected. In one study (1021C-60-89-004), animals were experimentally infested with *H. suis* prior to treatment, whereas, in the other studies the animals harbored naturally acquired infestations. The animals were randomly allocated between a non-medicated control group and a doramectin-treated group. Prior to the start of each study, a standard procedure for counting lice was designated on the basis of level of infestation and size of the animals. Counts were conducted prior to treatment and at weekly or biweekly intervals thereafter for four weeks.

*Data Analysis:* Efficacy was calculated based on the percentage reduction in lice counts of doramectin-treated pigs compared with the nonmedicated group at each time post-treatment. Percentage efficacy was calculated using the following formula:

$$\frac{[(Arithmetic\ mean\ number\ of\ lice\ in\ non-medicated\ swine) - (Arithmetic\ mean\ number\ of\ lice\ in\ doramectin-treated\ swine)]}{[Arithmetic\ mean\ number\ of\ lice\ in\ non-medicated\ swine]} \times 100 = Percentage\ efficacy$$

*Results:* Results are presented on an individual basis in the section following (see Tables 13 to 15).

*Conclusion:* A single IM injection of doramectin at a dosage of 300 mcg/kg was greater than 99% effective against infestations of *H. suis*.

2. Individual Lice Studies

(iii) Experiment #1021C-60-89-004, Dr. R. Williams, Baker Swine Unit, Baker Research Farm, Purdue University, West Lafayette, Indiana

Fifteen (15) artificially infested swine were assigned to a negative control group (5 pigs) or a doramectin group (10 pigs). Louse counts were conducted on test animals once weekly for five weeks. The results are summarized in Table 13 for Days 7, 14, 21 and 28.

**Table 13: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Haematopinus suis***

| **Parasite** | **% Efficacy** |
|---|---|
| *Haematopinus suis* | 100 |

(iv) Experiment #1022C-60-89-001, Dr. J. J. Arends, S&J Farms, Willow Springs, North Carolina

Fifteen (15) naturally infested swine were assigned to a negative control group (5 pigs) or a doramectin group (10 pigs). Louse counts were conducted on test animals once weekly for five weeks. The results are summarized in Table 14 for Days 7, 14, 21 and 28.

**Table 14: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Haematopinus suis***

| **Parasite** | **% Efficacy** |
|---|---|
| *Haematopinus suis* | 100 |

(v) Experiment #1023C-60-90-001, Dr. N. Wood-Huels, Altamont Veterinary Clinic, Altamont, Illinois

One hundred (100) naturally infested swine were assigned into two equal groups (negative control group and a doramectin group). Louse counts were conducted on test animals bi-weekly for five weeks. The results are summarized in Table 15 for Days 14 and 28.

**Table 15: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Haematopinus suis***

| **Parasite** | **% Efficacy** |
|---|---|
| *Haematopinus suis* | 99 |

## G. Efficacy Confirmation - Mange Mites:

1. Summary

Four studies were conducted to evaluate the efficacy of doramectin injectable solution, at a dosage of 300 mcg/kg given intramuscularly to swine harboring naturally acquired infestations of Sarcoptes scabiei under field conditions. A common protocol was employed at sites throughout North America representative of a range of climatic conditions and husbandry systems.

Study Design: In each study, a minimum of 15 animals with confirmed active mite infestations were selected and randomly assigned to either a doramectin-treated group or a non-medicated control group. Immediately prior to treatment appropriate skin tissue samples were collected for mite counts (adults, nymphs and larvae). Further skin tissue samples were collected for mite counts at either weekly or biweekly intervals for four weeks.

Data Analysis: Efficacy was calculated based on the percentage reduction in live mite counts of doramectin-treated pigs compared with the nonmedicated group at each time post-treatment. Percentage efficacy was calculated using the following formula:

$$\frac{[(Arithmetic\ mean\ number\ of\ mites\ in\ non-medicated\ swine)\ -\ (Arithmetic\ mean\ number\ of\ mites\ in\ doramectin-treated\ swine)]}{[Arithmetic\ mean\ number\ of\ mites\ in\ non-medicated\ swine]} \times 100$$
$$= Percentage\ efficacy$$

Results: Results are presented on an individual study basis in the section following (see Tables 16 to 19).

Conclusion: Doramectin administered intramuscularly at a dosage of 300 mcg/kg was 100% effective in curing *S. scabiei* infestations of swine.

2. Individual Mange Mites Studies

(i) Experiment #1022C-60-89-002, Dr. J. J. Arends, S&J Farms, Willow Springs, North Carolina

Fifteen (15) naturally infested swine were assigned to a control group (5 pigs) or a doramectin group (10 pigs). Mite counts were conducted on test animals once weekly for four weeks after treatment. The results are summarized in Table 16 for Days 14, 21 and 28 post-treatment.

**Table 16: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Sarcoptes scabiei***

| **Parasite** | **% Efficacy** |
|---|---|
| *Sarcoptes scabiei* | 100 |

(ii) Experiment #1022C-60-90-003, Dr. T. A. Yazwinski, University of Arkansas, Physiology/Parasitology Unit, Fayetteville, Arkansas

Twenty-two (22) naturally infested swine were assigned into two equal groups (a control group and a doramectin group). Mite counts were conducted on test animals once weekly for four weeks after treatment. The results are summarized in Table 17 for Days 7, 14, 21 and 28 post-treatment.

**Table 17: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Sarcoptes scabiei***

| **Parasite** | **% Efficacy** |
|---|---|
| *Sarcoptes scabiei* | 100 |

(iii) Experiment #1023C-60-91-003, Dr. L. Smith, Lodi, Wisconsin

Fifty (50) naturally infested swine were assigned to a control group (20 pigs) or a doramectin group (30 pigs). Mite counts were conducted on test animals bi-weekly for four weeks after treatment. The results are summarized in Table 18 for Days 14 and 28 post-treatment.

**Table 18: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Sarcoptes scabiei***

| **Parasite** | **% Efficacy** |
|---|---|
| *Sarcoptes scabiei* | 100 |

(iv) Experiment #1023C-02-91-006, Dr. M. Olson, Thorlakson Feedyard, Airdrie, Alberta, Canada

Seventy-four (74) naturally infested swine were assigned to a control group (29 pigs) or a doramectin group (45 pigs). Mite counts were conducted on test animals bi-weekly for four weeks after treatment. The results are summarized in Table 19 for Days 14 and 28 post-treatment.

**Table 19: Therapeutic Efficacy of Doramectin at 300 mcg/kg Against *Sarcoptes scabiei***

| **Parasite** | **% Efficacy** |
|---|---|
| *Sarcoptes scabiei* | 100 |

## H. Field Efficacy Against Arthropods:

1. Summary:

Confirmation of efficacy against Haematopinus suis and Sarcoptes scabiei under field conditions is provided by the dose confirmation studies presented in Sections F and G. All but one of those studies were conducted with naturally acquired infestations of lice and mites and were conducted in various geographic field locations in North America. The product was demonstrated to be highly effective under these conditions. Table 20 below summarizes these studies which were discussed in more detail in the preceding sections.

**Table 20: Numbers of Doramectin Treated Animals and Geographic Locations of Natural Infection Lice and Mites Studies**

| Study | Parasite | Number of Doramectin-Treated Animals | Study Location |
|---|---|---|---|
| 1022C-60-89-001 | Lice | 20 | North Carolina |
| 1023C-60-90-001 | Lice | 50 | Illinois |
| 1022C-60-89-002 | Mites | 20 | North Carolina |
| 1022C-60-90-003 | Mites | 11 | Arkansas |
| 1023C-02-91-006 | Mites | 45 | Alberta, Canada |
| 1023C-60-91-003 | Mites | 30 | Wisconsin |

## III. ANIMAL SAFETY

The safety of doramectin injectable solution was evaluated in both breeding and non-breeding swine. The objectives of the testing were to demonstrate an adequate margin-of-safety following overdose, to establish safety in breeding animals, to assess local tolerance at the site of injection, and to confirm safety in animals under representative field use conditions.

### A. DRUG TOLERANCE STUDY #1:

1. Experiment number:

   1421N-60-91-008

2. Starting date:

   January 7, 1991

3. Termination date:

   January 21, 1991

4. Study director:

   Dr. J.A. Jackson/Dr. F.E. Phillips

5. Study location:

   Pfizer Animal Health Research Center
   Terre Haute, Indiana

6. Procedure and results:

   Eight pigs (4 females, 4 male castrates) with a mean body weight of approximately 60 kg were placed in one of two groups and treated intramuscularly with either doramectin at a dose of 3 mg/kg body weight (10X the recommended dose) or saline at 0.30 mL/kg body weight. Clinical observations were made during the period immediately following dosing and twice daily for 14 days post-treatment. Blood samples were collected for hematologic and clinical chemistry data prior to treatment and at 4, 7, and 14 days post-treatment. Pigs were weighed on Days 4, 7 and 14.

Transient excess salivation was observed in two doramectin-treated animals. A low serum iron value (54 mcg/dL) was recorded for one doramectin-treated animal on Day 4 of the study. No other abnormal values or trends were identified in any of the routine hematologic or clinical chemistry variables. All animals gained weight over the course of the study, and average daily gains between groups were not significantly different. It was concluded that a single administration of doramectin injectable at 10 times the recommended dose was well tolerated by swine

**B. DRUG TOLERANCE - STUDY #2:**

1. Experiment number:

   1421N-60-91-009

2. Starting date:

   January 7, 1991

3. Termination date:

   January 21, 1991

4. Study director:

   Dr. J.A. Jackson/Dr. F.E. Phillips

5. Study location:

   Pfizer Animal Health Research Center, Terre Haute, Indiana

6. Procedure and results:

   Eight pigs (4 females, 4 male castrates) averaging approximately 60 kg in body weight were placed in one of two groups and treated intramuscularly with either doramectin at a dose of 7.5 mg/kg body weight (25X the recommended dose) or saline at 0.75 mL/kg body weight. Clinical observations were made during the period immediately following dosing and twice daily for 14 days post-treatment. Blood samples were collected for hematologic and clinical chemistry data prior to treatment and at 4, 7, and 14 days post-treatment. Pigs were weighed on Days 4, 7 and 14.

   Throughout the study, none of the saline control animals exhibited any abnormal signs, except for one animal which exhibited abnormal salivation on the evening of Day 0 and the morning of Day 13. One doramectin-treated animal exhibited atypical salivation 31 hours post-treatment. Ataxia and depression were recorded in two of the four pigs dosed with doramectin. One of these pigs was euthanized and had lesions compatible with a viral encephalitis. This pig had a severe serum iron reduction (9 mcg/dL) which could be drug related. No other abnormal values or trends were identified in any of the routine hematologic or clinical chemistry variables of any other animals. All the other animals gained weight over the course of the study, and average daily gains between groups were not significantly different. It was concluded that a single administration of doramectin

injectable at 25 times the recommended dose may be associated with ataxia, depression, and serum iron reduction in some pigs.

## C. SAFETY MARGIN STUDY:

1. Experiment number:

   1423N-60-91-003

2. Starting date:

   June 17, 1991

3. Termination date:

   July 3, 1991

4. Study director:

   Dr. D.J. Fagerberg

5. Study location:

   Colorado Animal Research Enterprises, Inc.
   Fort Collins, Colorado

6. Procedure and results:

   Twenty-four (24) crossbred swine (12 of each sex) weighing from 31.6 to 40 kg were allotted to one of four equal sized groups and treated intramuscularly with either doramectin at doses of 300 (1X), 900 (3X) or 1500 (5X) mcg/kg BW or saline on three consecutive days. Clinical observations were made four times daily on dosing days 0, 1, and 2, twice daily on Days -2, -1, and 3 to 15, and once on Day 16, the last day of the study. Feed intake was measured daily from Days -3 to 16. Body weights were taken on Days -3, 0, and 16. Clinical pathology tests (hematology, clinical chemistry, and urinalysis) were conducted on specimens collected on Days -14, 0, 6 and 16. All test animals were euthanized on Day 16 and evaluated for gross pathology. Histopathologic examination was also conducted on all tissues from placebo and 5X groups, and on tissues from pigs in the 1X and 3X groups in which gross pathological lesions were observed.

   No significant hematological, clinical chemistry, or pathological abnormalities were observed in swine treated with doramectin, except for one high-dose doramectin-treated animal in which hemoglobin, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration values were decreased on the last sampling day. There were no abnormal clinical observations. Weight gains and feed consumption were not significantly different in doramectin-treated groups compared to the control group.

   The results of this study indicate that doramectin injectable administration at up to five times the recommended dose for three times the recommended duration of treatment was well tolerated by swine.

## D. REPRODUCTIVE SAFETY IN FEMALE SWINE - SEGMENT I STUDY:

1. Experiment number:

   1426N-60-91-001

2. Starting date:

   July 29, 1991

3. Termination date:

   November 13, 1991

4. Study director:

   Dr. G.W. Davis

5. Study location:

   Greenbriar Veterinary Services, Inc.
   6040 Dublin Road
   Delaware, Ohio 43015

6. Procedure and results:

   Ninety-one (91) gilts synchronized for, and confirmed in estrus were assigned at random to eight groups. Gilts in Groups T1 and T2 received saline or doramectin, respectively, 6 days after estrus. Gilts in groups T3 and T4 received saline or doramectin, respectively, 11 days after estrus. Gilts in groups T5 and T6 received saline or doramectin, respectively, 18 days after estrus. All gilts were bred by artificial insemination at the ensuing estrus. Gilts in T7 and T8 received saline or doramectin, respectively, 10 days after insemination. The dose of doramectin injectable solution was 900 mcg/kg BW (3X dose) and the control groups received an equivalent volume of saline. Gilts were observed for at least one hour post-dose and twice daily throughout the remainder of the study for abnormal clinical signs.

   At 42 days after insemination, all gilts were slaughtered for post-mortem examination of the reproductive tract. Gross abnormalities of the reproductive tract were noted and the number of viable and non-viable fetuses was counted.

**Table 21: Summary of Estrus, Insemination, Pregnancy and Fetal Viability in Doramectin and Saline Treated Gilts**

| Treatment | Number of Gilts | | | | Fetuses/Gilt* |
|---|---|---|---|---|---|
| | Total Allotted | Exhibited Estrus | Inseminated | Pregnant | |
| T1 | 10 | 07 | 07 | 07 | 10 |
| T2 | 13 | 11 | 11 | 09 | 09 |
| T3 | 09 | 09 | 09 | 08 | 09 |
| T4 | 10 | 09 | 09 | 08 | 12 |
| T5 | 13 | 13 | 13 | 13 | 10 |
| T6 | 13 | 11 | 11 | 07 | 10 |
| T7 | 11 | 09 | 09 | 09 | 10 |
| T8 | 12 | 11 | 11 | 11 | 10 |

*- Mean number of viable fetuses per pregnant gilt
T1 - Saline 06 days post estrus
T2 - Doramectin 06 days post estrus
T3 - Saline 11 days post estrus
T4 - Doramectin 11 days post estrus
T5 - Saline 18 days post estrus
T6 - Doramectin 18 days post estrus
T7 - Saline 10 days post-insemination
T8 - Doramectin 10 days post-insemination

There were no significant differences between control and doramectin groups in the proportion of gilts returning to estrus, the duration of estrus cycles, or the number of viable fetuses per gilt. There were no significant differences between groups in the number of gilts confirmed pregnant, except for those treated 18 days post-allotment (i.e., during pro-estrus), in which significantly fewer doramectin-treated gilts were pregnant than saline controls.

## E. REPRODUCTIVE SAFETY IN FEMALE SWINE - SEGMENT I STUDY (PROESTRUS):

1. Experiment number:

   1426N-60-92-005

2. Starting date:

   March 23, 1992

3. Termination date:

   July 1, 1992

4. Study director:

   Dr. G.W. Davis

5. Study location:

   Greenbriar Veterinary Services, Inc.
   6040 Dublin Road
   Delaware, Ohio 43015

6. Procedure and results:

   Fifty-five (55) gilts were assigned at random to two treatment groups. At 18 days after a confirmed estrus, gilts received saline or a 3X dose of doramectin (i.e., 900 mcg/kg), and were bred by artificial insemination at the ensuing estrus. Gilts were observed for at least one hour post-dose and twice daily for abnormal clinical signs.

   At 42 days after the day of insemination, all inseminated gilts were slaughtered for post-mortem examination of the reproductive tract. Gross abnormalities of the reproductive tract were noted and the number of viable and non-viable fetuses were counted.

   **Table 22: Summary of Estrus, Insemination, Pregnancy and Fetal Viability in Doramectin and Saline Treated Gilts**

| | Number of Gilts | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Total Allotted** | **Number Treated** | **Exhibited Estrus** | **Inseminated** | **Pregnant** | **Fetuses/ Gilt*** |
| T1 | 28 | 25 | 24 | 24 | 24 | 12 |
| T2 | 27 | 26 | 26 | 26 | 25 | 12 |

*- Mean number of viable fetuses per pregnant gilt
T1 - Saline 18 days post estrus
T2 - Doramectin 18 days post estrus

   There were no significant differences between the control and doramectin-treated groups in the number of gilts returning to estrus, duration of estrus cycle, number of gilts confirmed pregnant or number of viable fetuses per gilt.

   The Segment I female reproductive safety studies, collectively, demonstrated that intramuscular administration of doramectin injectable solution at three times the recommended dose had no adverse effects upon estrus, conception or early gestation (implantation) in swine.

## F. REPRODUCTIVE SAFETY IN FEMALE SWINE - SEGMENT II / III STUDY

1. Experiment number:

   1426N-60-91-002

2. Starting date:

   May 27, 1992

3. Termination date:

   November 13, 1992

4. Study director:

   Dr. G.W. Davis

5. Study location:

   Greenbriar Veterinary Services, Inc.

6040 Dublin Road
Delaware, Ohio 43015

6. Procedure and results:

One hundred and ten (110) gilts were assigned at random to two treatment groups and monitored for signs of estrus. The first 48 gilts in the saline control group and the first 48 gilts in the doramectin-treated group which demonstrated a second, normal estrus were selected as experimental subjects and were artificially inseminated. Animals were subsequently treated with a single dose of saline or a 3X dose of doramectin (i.e., 900 mcg/kg) between 12 and 45 days post-insemination. Gilts were observed for at least one hour post-dose and twice daily for abnormal clinical signs. Gilts returning to estrus prior to treatment were removed from the study (2 gilts from the saline group and 1 gilt from the doramectin group were so removed).

Between 84 and 89 days after insemination, each gilt was pregnancy tested using ultrasound. Each gilt confirmed pregnant then received a second intramuscular injection of the same dose of saline or doramectin.

Gilts were monitored during gestation and over the period of parturition.

**Table 23: Summary of Pregnancy Rate, Duration of Gestation Period, Litter Size and Piglet Physical Abnormalities**

| Treatment | Gilts Inseminated | Gilts Pregnant | Parturient Gilts | Mean Gestation Period (Days) | Piglets per Parturient Gilt | | |
|---|---|---|---|---|---|---|---|
| | | | | | Live | Dead | Total |
| Saline | 48 (46) | 42 | 42 | 114.9 | 9.4 | 1.2 | 10.6 |
| Doramectin | 48 (47) | 42 | 41 | 115.2 | 9.2 | 1.1 | 10.3 |

There were no significant differences between doramectin-treated and saline-treated groups in duration of gestation period, mean number of piglets (live or dead), or incidence of physical abnormalities in piglets. There were no significant differences between groups in the duration of parturition or the incidence of dsytocia, post-parturient ill-health, or agalactia. There were no differences between groups in neonatal pig viability or in their survival rate to seven days.

Intramuscular administration of doramectin injectable solution to pregnant gilts at three times the intended dose during the period of organogenesis and again during the last third of pregnancy had no adverse effects upon embryo development, maintenance of pregnancy, parturition or neonatal piglet viability and survivability.

## G. BOAR REPRODUCTIVE SAFETY STUDY:

1. Experiment number:

1426N-60-93-008

2. Starting date:

   January 17, 1994

3. Termination date:

   May 4, 1994

4. Study director:

   Dr. D. J. Fagerberg

5. Study location:

   Colorado Animal Research Enterprises Inc.
   Fort Collins, Colorado

6. Procedure and results:

   Twenty (20) healthy, reproductively sound boars were randomly assigned to two groups (10 animals/group). Each animal received single injections of doramectin (900 mcg/kg BW) or saline (9 mL/100 kg BW).

   Boars were subjected to physical and reproductive system examinations and semen collections three times a week for two weeks before treatment, and for seven weeks after treatment. Physical examinations included body weights, rectal temperatures, and evaluation of general physical condition. Reproductive system evaluations included testicular length and width measurements and examinations of the prepuce, penis, scrotum, testes and epididymes. Semen specimens were evaluated for volume of ejaculate, color, spermatozoal mass activity, percent motility, concentration and morphology.

   **Table 24: Semen Volume and Sperm Motility, Concentration, Total Output and Defects Summary**

| **Treatment Group** | **Least Square Means (Adjusted for Pretreatment Differences) and [95% Confidence Bounds]** | | | | | |
|---|---|---|---|---|---|---|
| | **Seminal Fluid Vol. mL)** | **Sperm Motility (%)** | **Sperm Conc./mL Semen** | **Total Sperm Output** | **% Sperm with Defects** | |
| | | | | | **Major** | **Minor** |
| T01 (Placebo) | 84.9 [76.5 - 93.2] | 88.1 [86.4 - 89.8] | 3.15 X $10^8$ [2.82 - 3.49 X $10^8$] | 2.32 X $10^{10}$ [1.96 - 2.68 X $10^{10}$] | 4.72 [2.04 - 7.40] | 3.58 [2.73 - 4.44] |
| T02 (Dora) | 74.5 [66.1 - 83.0] | 88.2 [86.5 - 89.9] | 3.16 X $10^8$ [2.82 - 3.51 X $10^8$] | 2.32 X $10^{10}$[1.95 - 2.69 X $10^{10}$] | 6.90 [4.21 - 9.59] | 4.75 [3.88 - 5.61] |
| p = | 0.0571 | 0.9311 | 0.9667 | 0.9922 | 0.1676 | 0.0585 |

   No significant differences found between treatment groups.

   There were no significant differences between treatment and control groups with respect to reproductive organs/structures or semen quality. Therefore, it was

concluded that doramectin treatment administered to breeding boars at three times the recommended dose had no adverse effects on semen quality or any reproductive organs/structures.

## H. INJECTION SITE TOLERATION:

1. Experiment number:

   1424N-60-92-002

2. Starting date:

   September 1, 1992

3. Termination date:

   October 1, 1992

4. Study director:

   D.E. Mouzin

5. Study location:

   Animal Health Research Center, Pfizer Inc., Terre Haute, Indiana

6. Procedure and results:

   Thirty (30) healthy pigs of uniform weight were randomly assigned to three groups (10 animals/group). Each animal received single injections of doramectin (300 mcg/kg BW) and saline (1.5 mL/50 kg BW) on opposing sides, intramuscularly (IM), in the semimembranosus muscle. An assessment of pain was made at the time of treatment. Injection sites were examined visually and by palpation at regular intervals following treatment. Animals were injected on day 0 (Group T3), day 15 (Group T2) or day 26 (Group T1). All animals were subsequently slaughtered on day 30, to provide for injection site evaluations 4 days (Group T1), 15 days (Group T2) or 30 days (Group T3) post-injection. Injection sites were evaluated for gross abnormalities at necropsy and those exhibiting gross lesions were examined histopathologically.

**Table 25: Summary of Injection Site Pathological Findings**

| Treatment | Days Post-Injection | Incidence of Pathological Findings | |
|---|---|---|---|
| | | Macroscopic | Microscopic |
| Saline | 4 | 0/10 | 0/2 |
| | 15 | 0/10 | 0/3 |
| | 30 | 0/10 | -- |
| Doramectin | 4 | 2/10* | 1/2** |
| | 15 | 3/10* | 3/3** |
| | 30 | 0/10 | -- |

*- Red, tannish-red area of pallor, or area of pallor with firm texture
**- Trace to mild lymphatic dilitation/inflammation or slight fibrosis

The label recommended dose of 1% doramectin injectable solution administered by the intramuscular route is well tolerated by swine.

## I. NEONATAL SAFETY:

1. Experiment number:

   5422N-03-96-150

2. Starting date:

   September 7, 1996

3. Termination date:

   December 5, 1996

4. Study director:

   S. Nolan-Smith, BSc, CBiol, MIBiol

5. Study location:

   Corning Hazelton (Europe)
   Otley Road, Harrogate
   North Yorkshire, HG3 1PY
   England

6. Procedure and results:

   Eighty-five (85) JSR Hybrid piglets (53 males and 32 females), were randomly assigned to two groups and were treated at either 3 or 4 days of age with a single intramuscular injection of either saline (44 animals) or 900 mcg/kg BW (3X the label dose, 41 animals) of doramectin. Clinical observations were conducted twice daily on Day -1 and Days 1 to 6 and once on Day 7. On Day 0, animals were observed prior to dosing and again at 1 to 2 hours, 4 to 6 hours and 8 to 10 hours after treatment. Body weight was recorded on Days 0 and 7, and the animals were euthanized and necropsied on Day 7. There were no clinical observations which were considered to be related to treatment, and there was no treatment-related effect on body weight. There were no findings noted at necropsy which were considered to be related to treatment. It was concluded that doramectin injectable solution, administered intramuscularly at 3X the label dose had no adverse effects on neonatal pigs.

## IV. HUMAN FOOD SAFETY

### A. Toxicology:

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.

1. CALCULATION OF A SAFE CONCENTRATION (S.C.)

   The NOEL used to calculate the S.C. of doramectin is 0.75 mg/kg/day which corresponds to that set for the fetotoxicity study in rabbits. The safety factor applied to this study was 1000 because cleft palate was observed in the 3.0 mg/kg/day group and delayed ossification of the fetal pubic bones occurred in the

1.5 and 3.0 mg/kg/day groups. In addition, a safety factor of 1000 is applied to this study because doramectin is structurally related to ivermectin which has been shown to cause cleft palate in rats, mice, and rabbits. Using the appropriate NOEL and safety factor, an acceptable daily intake (ADI) of up to 0.75 micrograms/kg/day of doramectin residue in food was determined using the formula:

ADI = NOEL / Safety factor

ADI = 0.75 mg/kg/day / 1000 Safety factor = 0.75 µg/kg/day

A safe concentration in muscle tissue of swine is calculated from the acceptable daily intake, assuming the average weight of a man to be 60 kg and the daily human intake of muscle to be 300 g, as follows:

Safe concentration in muscle = (60 kg) (0.75 µg/kg/day) / 300 g/day = 150 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:**

1. TOTAL RESIDUES

The levels of total drug-related residues of doramectin in the tissues of swine treated with [3H]-doramectin were determined in two residue studies. Residues in muscle, liver, kidney, and fat were determined in the first study summarized below. Residues at the sites of injection were determined in the second total residue study. The levels of unchanged doramectin were also determined in both studies.

(i) TITLE: [3H]-doramectin Radiotracer Residue Depletion Study in Edible Tissues of Swine

(ii) PROTOCOL NO.: 1525N-60-90-011

(iii) STUDY DESIGN:

Dose: 300 mcg/kg BW as an intramuscular injection

Radiotracer: doramectin radiolabeled with tritium at the C-5 position

Test animals: 16 adult, crossbred swine (8 male castrate, 8 female)

Withdrawal schedule: 7, 14, 21, and 28 days post-dosing

Following treatment with radiolabeled doramectin, four animals (two of each sex) were sacrificed at each collection time, and tissue samples of liver,

kidney, fat, and muscle were collected and assayed for total drug-derived radiolabeled residues and for unchanged doramectin.

(iv) RESULTS AND CONCLUSIONS:

The results from the study are shown in Tables 26 and 27.

**Table 26: Mean concentrations (±1 SD) of doramectin total residues in tissues of swine (study #1525N-60-90-011)**

| Withdrawal period (days) | Liver Levels (ppb) | Kidney Levels (ppb) | Muscle Levels (ppb) | Fat Levels (ppb) |
|---|---|---|---|---|
| 7 | 186 ± 47 | 79 ± 19 | 35 ± 7 | 412 ± 54 |
| 14 | 111 ± 20 | 46 ± 7 | 19 ± 6 | 255 ± 42 |
| 21 | 46 ± 10 | 17 ± 4 | 6 ± 1 | 90 ± 18 |
| 28 | 37 ± 20 | 8 ± 3 | 4 ± 3 | 58 ± 33 |

**Table 27: Mean concentrations (±1 SD) of unchanaged doramectin in tissues of swine (study #1525N-60-90-011)**

| Withdrawal period (days) | Liver Levels (ppb) | Kidney Levels (ppb) | Muscle Levels (ppb) | Fat Levels (ppb) |
|---|---|---|---|---|
| 7 | 66 ± 15 | 23 ± 7 | 7 ± 1 | 242 ± 22 |
| 14 | 37 ± 11 | 11 ± 3 | <4 | 113 ± 26 |
| 21 | 11 ± 3 | 6 ± 2 | <3 | 42 ± 14 |
| 28 | <7 | 3 ± 1 | <3 | 30 ± 20 |

The levels of total drug-related residues of doramectin in the injection site of swine treated with [3H]-doramectin were determined in a second residue study that was conducted primarily for the environmental data requirements.

(v) TITLE: [3H]-doramectin Radiotracer Residue Depletion Study at the Injection Site and in the Body Fluids and Excreta of Swine

(vi) PROTOCOL NO.: 1525N-60-90-012

(vii) STUDY DESIGN:

Dose: 300 mcg/kg BW as an intramuscular injection

Radiotracer: doramectin radiolabeled with tritium at the C-5 position

Test animals: 16 adult, crossbred swine (8 male castrate, 8 female)

Withdrawal schedule: 7, 14, 21, and 28 days post-dosing

Following treatment with radiolabeled doramectin, four animals (two of each sex) were sacrificed at each collection time. Injection site tissues were collected and assayed for total drug-derived radiolabeled residues and for unchanged doramectin.

(viii) RESULTS AND CONCLUSIONS:

The results from the study are shown in Table 28.

**Table 28: Mean concentrations of doramectin total residues and unchanged doramectin in swine injection sites in study 1525N-60-90-012**

| **Withdrawal Period Days)** | **Injection Site Total Residue Level (ppb)** | **Unchanged Doramectin (ppb)** | **Percent Unchanged Doramectin** |
|---|---|---|---|
| 7 | 5132 ± 4431 | 3660 ± 3037 | 74 ± 21 |
| 14 | 2512 ± 1802 | 2553 ± 1944 | 102 ± 20 |
| 21 | 1078 ± 721 | 1032 ± 850 | 92 ± 31 |
| 28 | 118 ± 38 | 35 ± 6 | 32 ± 10 |

2. METABOLISM IN SWINE

The profiling of doramectin metabolites in swine was conducted with tissues from animals in study 1525N-60-90-011. The swine livers were from animals treated with 300 mcg/kg tritium-labeled doramectin and then sacrificed 7 days later. Samples of the livers were extracted with acetonitrile-methanol, and the extracts were eluted through solid phase extraction columns with methanol. Reverse phase HPLC was used to generate the profiles of extractable metabolites.

The metabolite workup of the liver from animals sacrificed 7 days after dosing revealed that approximately 90% of the radioactivity was extractable, indicating that bound residues constitute, at most, a small fraction of the total residue. Unchanged doramectin was the major metabolite of doramectin in liver, and one other major metabolite was also observed. The compounds identified in liver at 7 days post-dose are listed below (mean ± 1 SD).

| **Liver Metabolites** | **Percent of Extracted Radioactivity** |
|---|---|
| Doramectin | 71 ± 4 |
| 3"-O-desmethyldoramectin | 20 ± 2 |

3. METABOLISM IN RATS AND DOGS

The profiling of doramectin metabolites in rat liver and feces was conducted with samples from Sprague-Dawley rats administered a single 5 mg/kg oral dose of tritium-labeled doramectin. The rats were sacrificed 48 hours after dosing. The dog liver and feces were obtained from a female Beagle dog that was dosed with a single 3.5 mg/kg oral dose of tritium-labeled doramectin. The liver was collected at the time of sacrifice of the dog at 48 hours post-dose. The samples were extracted with acetonitrile-methanol (6:4), and the extracts were subjected to HPLC chromatography through which the metabolites listed in Table 29 were identified.

**Table 29: Doramectin and its metabolites identified in rat liver and feces and dog liver and feces**

| Metabolite | Rat Liver | Rat Feces | Dog Liver | Dog Feces |
|---|---|---|---|---|
| Doramectin | 18% | 22% | 28% | 6% |
| 3"-O-desmethyldoramectin | 12% | 19% | 12% | 8% |
| 3"-O-desmethyldoramectin | 3% | 14% | ND | 5% |
| 24-hydroxymethyl-3"-O-desmethyldoramectin | 2% | 16% | ND | 4% |

ND - Not detected

COMPARATIVE METABOLISM

The correspondence of the exposure of the rat and dog to metabolites of doramectin which arise in swine was established by comparison of the profiles of metabolites observed in the livers and feces of each species. This indicated close agreement between the identities of the metabolites observed and the relative amounts of each metabolite which were present in each species. Liver was selected for examination because this tissue was found to contain the highest amount of total drug-derived radiolabeled material in preliminary studies and corresponds to the target tissue for doramectin in cattle. Feces represent the primary route of elimination of drug-derived material in each species. It was concluded that the toxicology species (rat and dog) are exposed to a qualitatively similar profile of metabolites as are swine following administration of doramectin.

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

The total residue values presented in Table 26 establish that liver and fat contain the highest levels of total drug-related doramectin residues, and these are the tissues from which residues deplete most slowly. However, concentration of total residues did not approach the safe concentration in any of the tissues tested at any withdrawal time tested.

Assignment of liver as the target tissue was made, in part, because liver is the assigned target tissue for doramectin in cattle, and use of the same target tissue for both species will facilitate regulatory agency monitoring of carcasses for doramectin residues using a single residue assay method.

Liver was confirmed as the target tissue and parent doramectin was selected as the marker residue following further assay of the tissue samples from the radiolabeled study (1525N-60-90-011) using a determinative HPLC procedure for unchanged doramectin. The results of the assays of the liver samples are shown in Table 30. The ratio of unchanged drug to total residues ranged from 36% on day 7 to <22% on day 28.

**Table 30: Mean concentrations of doramectin total residues and unchanged doramectin in swine liver in study 1525N-60-90-011**

| Withdrawal Period (Days) | Liver Total Residue Level (ppb) | Unchanged Doramectin (ppb) | Percent Unchanged Doramectin |
|---|---|---|---|
| 7 | 186 ± 47 | 66 ± 15 | 36 ± 3 |
| 14 | 111 ± 20 | 37 ± 11 | 34 ± 9 |
| 21 | 46 ± 10 | 11 ± 3 | 24 ± 3 |
| 28 | 37 ± 20 | <7 | <22 |

The data above demonstrated that parent doramectin 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 value of 160 ppb for unchanged doramectin (the marker residue) is assigned as the tolerance for swine liver (the target tissue). That assignment is based on the total residue and marker residue measurements listed in Table 30 for study 1525N-60-90-011.

All total residue measurements in liver tissue in that study were less than the safe concentration of 450 ppb, with a mean level of 186 ppb at the shortest withdrawal time of 7 days. The mean marker residue percentage of 36% in the 7-day liver samples was used to calculate the tolerance, as that percentage declined with longer withdrawal times. The tolerance in liver was obtained by simply taking 36% of the 450 ppb liver safe concentration and rounding the product to 160 ppb.

**E. Study to Establish the Withdrawal Period:**

1. TITLE: Doramectin Residue Depletion Study in Edible Tissues of Swine

2. PROTOCOL NO.: 1521N-60-94-007

3. STUDY DESIGN:

   Dose: 375 mcg/kg BW as an intramuscular injection

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

   Withdrawal schedule: 7, 14, 21, 28, and 35 days post-dosing

   Following treatment with doramectin, six animals (three of each sex) were sacrificed at each collection time, and tissue samples of liver, muscle, kidney, perirenal fat, and injection site were collected and assayed for unchanged doramectin, the marker residue. Two non-medicated animals, one of each sex, were slaughtered 8 days before dosing and tissues were collected to serve as controls.

4. RESULTS:

   The results from the study are shown in Table 31.

**Table 31: Mean doramectin (±1 SD) concentration in swine tissue (study #1521N-60-94-007)**

| Withdrawal period (days) | Liver Levels (ppb) | Injection Site - 500 g (ppb) | Kidney Levels (ppb) | Muscle Levels (ppb) | Fat Levels (ppb) |
|---|---|---|---|---|---|
| 7 | 160 ± 30 | 7000 ± 4000 | 80 ± 20 | 40 ± 9 | 470 ± 120 |
| 14 | 83 ± 8 | 5000 ± 3000 | 43 ± 7 | 24 ± 8 | 290 ± 40 |
| 21 | 40 ± 20 | 900 ± 500 | 18 ± 7 | 11 ± 5 | 130 ± 50 |
| 28 | 23 ± 13 | 700 ± 500 | <13 | <7 | 80 ± 50 |
| 35 | 18 ± 8 | 160 ± 150 | <7 | <6 | 50 ± 20 |

5. WITHDRAWAL TIME

   Using the liver residue values in study 1521N-60-94-007, a withdrawal time of 24 days was calculated for the use of doramectin injectable solution in swine. The withdrawal time was calculated using the agency's statistical tolerance limit method (99% tolerance limit with 95% confidence interval method).

## F. Regulatory Method:

1. DORAMECTIN DETERMINATIVE ASSAY PROCEDURE

   The determinative analytical method is capable of measuring the marker residue, doramectin, in swine liver at concentrations ranging from 20 ppb to 400 ppb. This is the same analytical method that is approved as the regulatory method for doramectin in cattle. The detection and quantitation of doramectin at the ng/g level is based on its extraction from liver homogenate and derivatized using trifluoroacetic anhydride and triethylamine followed by treatment with methanolic ammonia to yield a chemically stable, fluorescent derivative. The range over which the determinative analytical method has been validated in liver tissue (20 ppb to 400 ppb), makes it suitable for monitoring doramectin residues at the tolerance in swine liver.

2. DORAMECTIN CONFIRMATORY ASSAY PROCEDURE

   The doramectin confirmatory assay is an HPLC-MS/MS method capable of confirming the presence of doramectin in swine liver. This is the same analytical method that is approved as the regulatory method for doramectin in cattle. The structural confirmation of doramectin is based on its extraction from liver homogenate and LC/MS/MS analysis.

3. METHOD VALIDATION

   A method trial of the determinative and confirmatory assays was completed by FDA and USDA laboratories, and the methods were accepted as the regulatory method for detection of doramectin residues in cattle liver (see: original NADA 141-061). Since the methods are the same for swine as for cattle, it was unnecessary to conduct a method trial for the swine methods.

## V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Act and demonstrate that DECTOMAX® injectable solution, when used under the proposed conditions of use, is safe and effective for the treatment and control of gastrointestinal roundworms, lungworms, kidneyworms, lice and mites in swine, when administered by intramuscular injection at a dose of 300 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 swine, a tolerance of 160 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 24 days was calculated from the residue depletion study of doramectin residues in swine, following the intramuscular injection of DECTOMAX®. Statistical analysis of the marker residue depletion study using a liver-based tolerance of 160 ppb gave a withdrawal time of 24 days.

The original approval of DECTOMAX® injectable solution was as an over-the-counter drug. The data submitted for DECTOMAX® injectable solution for swine support the marketing of the product as an over-the-counter new animal drug for this additional species. 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 retain over-the-counter marketing status.

Under the Center's supplemental approval policy 21 CFR 514.106(b)(2), this is a Category II change. The approval of this change did not require a reevaluation of the safety or effectiveness data in the parent application.

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)(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 the treatment and control of gastrointestinal roundworms, lungworms, kidneyworms, sucking lice and mange mites in swine, when administered by intramuscular injection at a dose of 300 mcg/kg bodyweight.

DECTOMAX® injectable 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.