DATE OF APPROVAL LETTER: June 18, 2001

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

## NADA 141-099

## CYDECTIN® (moxidectin) 0.5% Pour-On for Beef and Dairy Cattle

This supplemental NADA FOI Summary contains 10 new label indications for adult or $L_4$ stages of gastrointestinal roundworms and for 2 additional persistent activity indications.

Sponsored by

Fort Dodge Animal Health

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## I. GENERAL INFORMATION

| | |
|---|---|
| NADA Number: | 141-099 |
| Sponsor: | Fort Dodge Animal Health<br>800 Fifth St. NW<br>Fort Dodge, Iowa 50501 |
| Established Name: | moxidectin |
| Tradename: | CYDECTIN® (moxidectin) 0.5% Pour-On<br>for Beef and Dairy Cattle |
| Marketing Status: | Over-the-counter (OTC) |
| Effect of Supplement: | New indications for the gastrointestinal roundworms appearing in bold print in Section II and new persistent activity indications of 14 days for *Haemonchus placei* and 28 days for *Oesophagostomum radiatum*. |

**II. INDICATIONS FOR USE:** Effective in the treatment and control of the following internal and external parasites. New indications appear in bold print.

**Gastrointestinal Roundworms**

*Ostertagia ostertagi* - Adult and fourth-stage larvae (including inhibited larvae)
*Haemonchus placei* – Adult and **fourth-stage larvae**
*Trichostrongylus axei* - Adult and fourth-stage larvae
*Trichostrongylus colubriformis* - Adult and **fourth-stage larvae**
*Cooperia oncophora* - Adult and **fourth-stage larvae**
***Cooperia pectinata* - Adult**
*Cooperia punctata* - Adult and **fourth-stage larvae**
***Cooperia spatulata* - Adult**
***Cooperia surnabada* - Adult and fourth-stage larvae**
*Bunostomum phlebotomum* - Adult
*Oesophagostomum radiatum* - Adult and **fourth-stage larvae**
*Nematodirus helvetianus* - Adult and **fourth-stage larvae**

**Lungworms**

*Dictyocaulus viviparus* - Adult and fourth-stage larvae

**Cattle Grubs**

*Hypoderma bovis*
*Hypoderma lineatum*

**Mites**

*Chorioptes bovis*
*Psoroptes ovis* (*Psoroptes communis* var. *bovis*)

**Lice**

*Linognathus vituli*
*Haematopinus eurysternus*
*Solenopotes capillatus*
*Bovicola (Damalinia) bovis*

**Horn Flies**

*Haematobia irritans*

CYDECTIN Pour-On has been proven to effectively control infections and protect from reinfection with ***Haemonchus placei*** for 14 days after treatment, ***Oesophagostomum radiatum*** and *Ostertagia ostertagi* for 28 days after treatment, and *Dictyocaulus viviparus* for 42 days after treatment.

## III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. Form: CYDECTIN (moxidectin) 0.5% Pour-On for Beef and Dairy Cattle is a ready-to-use topical formulation that contains 5 mg moxidectin per mL of solution.

B. Route of Administration: The product should be applied directly to the hair and skin along the top of the back from the withers to the base of the tail. Application should be made to healthy skin avoiding mange scabs, skin lesions or extraneous foreign matter.

C. Recommended Dose Rate: The recommended rate of administration is 1 mL for each 22 lb (10 kg) of body weight which provides 5 mg moxidectin for each 22 lb (10 kg) of body weight.

## IV. EFFECTIVENESS

Effectiveness studies were presented in the original NADA 141-099 FOI Summary dated January 28, 1998 establishing the recommended effective dose of Cydectin Pour-On for the control of a broad spectrum of ecto- and endoparasites as label indications, and periods of persistent effect against *Ostertagia ostertagi* and *Dictyocaulus viviparus*. This summary contains the results of studies conducted to confirm the effectiveness of the recommended dose of 0.5 mg moxidectin/kg body weight against additional species and life stages of nematodes as new therapeutic claims. It also contains the results of studies conducted to determine the period of persistent activity for additional nematode species.

Effectiveness of moxidectin pour-on against parasites was calculated as the reduction in the number of a specific stage and species of parasite in treated animals as compared to the number in vehicle or untreated control animals. Percent effectiveness was calculated using geometric means in the following formula.

$$= \left( \frac{\text{mean parasite count in control group - mean parasite count in treated group}}{\text{mean parasite count control group}} \right) \text{x } 100$$

The statistical analysis was performed separately for each species and stage of nematode, as appropriate. Statistical analysis was performed for a nematode species only if at least six animals in the control group were infected with that specific parasite. Counts were transformed by a $Y=\log_{10}(\text{count} + 1)$ transformation before performing a one-way Analysis of Variance (ANOVA) with treatment in the model. The treatment effect was tested against the residual error in the ANOVA for significance at the 5% level. The least square means (LSMEAN) was calculated for each group and the moxidectin-treated group was compared to the control group at the 5% level of significance (one-sided). The Dunnett t-test was used for comparisons when studies contained several moxidectin treatment groups compared to a single control group (e.g., persistent activity studies).

In order for an individual study to be considered an acceptable demonstration of the therapeutic or persistent activity of moxidectin pour-on against a specific parasite, the following criteria were applied.

a) at least six control animals were adequately infected with the specific parasite species/stage;
b) treatment with the recommended dose resulted in at least a 90% reduction in the parasite count as compared to controls; and
c) the reduction was significant at $P<0.05$.

For each claim that was granted there were at least 2 studies with an adequate level of infection that met the 3 criteria above.

**Persistent Effectiveness against Gastrointestinal Roundworms**

The persistent activity of Cydectin Pour-On against gastrointestinal roundworms was evaluated in three studies. Two of these studies also contained a treatment group that was designed to evaluate effectiveness against existing infections of fourth-stage larvae.

**Persistent Effectiveness Studies**

**Study Number 0863-B-US-19-97**

1. Title: Evaluation of the persistent activity of moxidectin 0.5% pour-on against *Haemonchus placei, Trichostrongylus axei* and *Nematodirus helvetianus* (Louisiana).

2. Investigator: James C. Williams, Ph.D.
   Louisiana State University
   Baton Rouge, LA

3. General Design:

   a. Purpose: This study was designed to determine the time period following treatment in which reinfections with certain gastrointestinal roundworms in cattle are prevented.

   b. Animals: Forty Holstein calves weighing between 139 to 244 kg, were assigned to the five treatment groups (8 animals per group) in a completely random fashion. With the exception of one heifer calf, all animals were either bulls or steers. Cattle had been treated with an approved anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

   c. Housing: Calves were maintained in outdoor concrete-floored pens by treatment group and exposed to ambient weather conditions.

   d. Infection: On Day 0, each calf was infected with an inoculating dose of $L_3$ larvae containing approximately 7,996 *Haemonchus placei,* 11,655 *Trichostrongylus axei,* 3,666 *Nematodirus helvetianus,* 2,732 *Cooperia* spp., 3,470 *Ostertagia ostertagi,* and 2,635 *Oesophagostomum radiatum*.

   e. Procedure: To evaluate persistent activity, a different group of cattle were treated with moxidectin pour-on at 35, 28, 21, and 14 days prior to an experimental infection, with the fifth group remaining as untreated

controls. Equal numbers of cattle from each treatment group were necropsied 21 to 23 days postinfection.

f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for parasites present in a minimum of six adequately infected control calves are given in the Table 4.1.

Table 4.1 Geometric mean of control worm counts and percent effectiveness

| | Untreated Control | % Effectiveness of Moxidectin at various Pre-infection Treatment Days[1] | | | |
|---|---|---|---|---|---|
| Nematode | Mean | -35 | -28 | -21 | -14 |
| *H. placei* | 890.7 | 0 | 29.9 | 44.9 | 99.2 |
| *O. ostertagi* | 1140.4 | 0 | 0 | 8.1 | 77.7 |
| *T. axei* | 383.6 | 0 | 0 | 0 | 0 |
| *N. helvetianus* | 867.7 | 0 | 0 | 0 | 0 |
| *Oe. radiatum* | 716.9 | 77.9 | 99.0 | 98.9 | 100 |

[1]Treatment group indicates the day cattle were treated with moxidectin relative to the day they were administered an experimental infection.

5. Conclusion: This study demonstrated that Cydectin Pour-On had persistent activity for 14 days against *H. placei* and for 28 days against *Oe. radiatum*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number 0863-B-US-20-97**

1. Title: Evaluation of the efficacy of moxidectin against fourth-stage larvae and the persistent activity of moxidectin 0.5% pour-on against *Haemonchus placei, Trichostrongylus axei*, and *Nematodirus helvetianus* (Arkansas).

2. Investigator: Thomas A. Yazwinski, Ph.D.
University of Arkansas
Fayetteville, AR

3. General Design:

a. Purpose: This study was designed to determine the time period following treatment in which reinfections with certain gastrointestinal roundworms in cattle are prevented and to determine effectiveness against $L_4$ stage infections present at the time of treatment.

b. Animals: Forty-eight Holstein steer calves weighing between 73 and 175 kg, were assigned to the six treatment groups (8 animals per group)

in a completely random fashion. Cattle had been treated with an approved anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

c. Housing: Calves were maintained in outdoor concrete-floored pens by treatment group and exposed to ambient weather conditions.

d. Infection: On Day 0, each calf was infected with an inoculating dose of $L_3$ larvae containing approximately 4,385 *Haemonchus placei,* 4,827 *Oesophagostomum radiatum*, 673 *Cooperia* spp., 6,442 *Trichostrongylus axei,* and 3,135 *Nematodirus helvetianus*. Additionally, animals received 1,077 *Trichuris* spp. eggs.

e. Procedure: To evaluate persistent activity, a different group of cattle was treated with moxidectin pour-on at 35, 28, 21, and 14 days prior to an experimental infection. One group was treated 6 days postinfection to evaluate effectiveness against an existing infection of $L_4$ larvae. The final treatment group contained untreated control animals. Equal numbers of cattle from each treatment group were necropsied 20 to 24 days postinfection.

f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for parasites present in a minimum of six adequately infected control calves are given in Table 4.2.

Table 4.2 Geometric mean of control worm counts and percent effectiveness

| | Untreated Control | % Efficacy of Moxidectin at various Pre-infection Treatment Days[1] | | | | |
|---|---|---|---|---|---|---|
| Nematode | Geo mean | -35 | -28 | -21 | -14 | Day 6 $L_4$ |
| *H. placei* | 199.5 | 72.7 | 34.9 | 94.3 | 99.6 | 100 |
| *O. ostertagi* | 4724.8 | 25.4 | 23.7 | 84.4 | 98.4 | >99.9 |
| *T. axei* | 542.6 | 12.0 | 26.7 | 38.9 | 89.4 | 100 |
| *N. helvetianus* | 533.7 | 31.2 | 14.2 | 59.3 | 0 | 99.9 |
| *Oe. radiatum* | 1137.0 | 79.6 | 97.9 | 99.3 | 99.7 | >99.9 |

[1]Treatment group indicates the day cattle were treated with moxidectin relative to the day they were administered an experimental infection.

5. Conclusion: This study demonstrated that Cydectin Pour-On had persistent activity for 21 days against *H. placei* and 28 days persistent activity against *Oe. radiatum*. It was also demonstrated to be effective against the $L_4$ stage of *H. placei*, *O. ostertagi, N. helvetianus, T. axei,* and *Oe. radiatum*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number 0863-B-US-25-98**

1. Title: Evaluation of the efficacy of moxidectin 0.5% pour-on against fourth-stage larvae and the persistent activity against *Haemonchus placei, Trichostrongylus axei* and *Nematodirus helvetianus* conducted in New Jersey.

2. Investigator: Siva Ranjan, B.V.Sc., Ph.D.
   Fort Dodge Animal Health
   Princeton, NJ

3. General Design:

   a. Purpose: This study was designed to determine the time period following treatment in which reinfections with certain gastrointestinal roundworms in cattle are prevented and to determine effectiveness against $L_4$ stage infections present at the time of treatment.

   b. Animals: Forty-eight Holstein steer calves weighing between 74 and 133 kg, were assigned to the six treatment groups (8 animals per group) in a completely random fashion. Cattle had been treated with an approved anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

   c. Housing: Calves were maintained in indoor concrete-floored pens by treatment group (4 animals/pen).

   d. Infection: On Day 0, each calf was infected with an inoculating dose of $L_3$ larvae containing approximately 10,000 *Haemonchus placei*, 5,000 *Trichostrongylus axei*, and 3,000 *Nematodirus helvetianus.* Additionally, the inoculum contained *Ostertagia* spp., *Cooperia* spp., and *Oesophagostomum radiatum*.

   e. Procedure: To evaluate persistent activity, a different group of cattle were treated with moxidectin pour-on at 35, 28, 21, and 14 days prior to an experimental infection. One group was treated 6 days postinfection to evaluate effectiveness against an existing infection of $L_4$ larvae. The final treatment group contained untreated control animals. Equal numbers of cattle from each treatment group were necropsied 20 to 23 days postinfection.

   f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for parasites present in a minimum of six adequately infected control calves are given in Table 4.3.

Table 4.3 Geometric mean of control worm counts and percent effectiveness

| | Untreated Control | % Effectiveness of Moxidectin at various Pre-infection Treatment Days[1] | | | | |
|---|---|---|---|---|---|---|
| Nematode | Geo mean | -35 | -28 | -21 | -14 | Day 6 $L_4$ |
| *H. placei* | 1087.1 | 14.1 | 99.6 | 97.1 | 98.9 | 100 |
| *O. ostertagi* | 3022.9 | 0 | 98.0 | 96.7 | 98.7 | 100 |
| *T. axei* | 466.0 | 43.1 | 92.8 | 93.9 | 97.9 | 100 |
| *N. helvetianus* | 1798.1 | 0 | 34.1 | 44.9 | 31.3 | 99.7 |
| *Oe. radiatum* | 1190.0 | 72.2 | 100 | 99.9 | 99.9 | 100 |

[1]Treatment group indicates the day cattle were treated with moxidectin relative to the day they were administered an experimental infection.

5. Conclusion: This study demonstrated that Cydectin Pour-On had persistent activity for 28 days against *H. placei* and *Oe. radiatum*. It was also demonstrated to be effective against the $L_4$ stage of *H. placei*, *N. helvetianus, T. axei, O. ostertagi,* and *Oe. radiatum*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

## Dose Confirmation Studies

### Study Number 0863-B-US-21-97

1. Title: Dose confirmation of moxidectin 0.5% pour-on against adult and fourth-stage larvae of various *Cooperia* spp. and *Trichostrongylus colubriformis* (Louisiana).

2. Investigator: James C. Williams, Ph.D.
   Louisiana State University
   Baton Rouge, LA

3. General Design:

   a. Purpose: To confirm effectiveness against a variety of adult and fourth-stage larvae of gastrointestinal nematodes.

   b. Animals: Thirty two Holstein steers weighing between 112 and 241 kg were assigned to the four treatment groups (8 animals per group) in a completely random fashion. Cattle had been treated with an approved

anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

c. Housing: Cattle were maintained in outdoor concrete-floored pens by treatment group and exposed to ambient weather conditions.

d. Infection: On Day 0, each calf was infected with an inoculating dose containing the following approximate numbers of $L_3$ larvae: 34,965 *C. punctata*, *C. pectinata*, *C. spatulata*, and *C. surnabada*; 5,996 *C. oncophora*/*surnabada,* 1,550 *Ostertagia ostertagi,* and 4,996 *T. colubriformis*.

e. Procedure: One group of calves was treated on Day 6 postinfection to evaluate effectiveness against the $L_4$ stage of the nematodes and the other group was treated on Day 23 postinfection to evaluate effectiveness against adult nematodes. There was a corresponding untreated control group for each moxidectin pour-on group. All cattle were experimentally infected on Day 0 of the study. Necropsies were performed on Days 20 and 21 postinfection for one control group and for cattle treated with moxidectin on Day 6. Cattle treated on Day 23 postinfection and their untreated control group were necropsied on Days 37 and 38.

f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for parasites present in a minimum of six adequately infected control calves are given in Table 4.4.

Table 4.4 Geometric mean of control worm counts and percent effectiveness

| Nematode species | Geometric Mean Control Cattle | % Effectiveness of Moxidectin Pour-On |
|---|---|---|
| *C. oncophora* Adult | 787.2 | 99.9 |
| *C. punctata* Adult | 6545.9 | 99.9 |
| *C. spatulata* Adult | 116.5 | 99.3 |
| *C. surnabada* Adult | 276.9 | 99.7 |
| *T. colubriformis* Adult | 149.3 | 100 |
| *C. punctata* $L_4$ | 1599.6 | 99.7 |

5. Conclusion: This study demonstrated that moxidectin pour-on was effective against the adult stage of *C. oncophora, C. punctata, C. spatulata*, *C. surnabada*, and *T. colubriformis* and against the $L_4$ stage of *C. punctata*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number 0863-B-US-26-98**

1. Title: Dose confirmation study with 0.5% moxidectin pour-on and 1% nonaqueous injectable formulations against adult and $L_4$ stages of various *Cooperia* species, *Trichostrongylus colubriformis,* and $L_4$ stages of *Dictyocaulus viviparus* in cattle conducted in New Jersey.

2. Investigator: Siva Ranjan, B.V.Sc., Ph.D.
   Fort Dodge Animal Health
   Princeton, NJ

3. General Design:

   a. Purpose: To confirm effectiveness against a variety of adult and fourth-stage larvae of gastrointestinal nematodes.

   b. Animals: Forty-eight Holstein steers weighing between 112 and 172 kg were assigned to six treatment groups (8 animals per group) in a completely random fashion. Cattle had been treated with an approved anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

   c. Housing: Calves were maintained in indoor concrete-floored pens by treatment group (4 animals/pen).

   d. Infection: On Day 0, each calf was infected with an inoculating dose containing approximately 30,000 *Cooperia* spp., 10,000 *T. colubriformis,* and 1,500 *Dictyocaulus vivparus* $L_3$ larvae.

   e. Procedure: One group of calves was treated on Day 5 postinfection to evaluate effectiveness against the $L_4$ stage of the nematodes and the other group was treated on Day 26 postinfection to evaluate effectiveness against adult nematodes. There was a corresponding untreated control group for each moxidectin pour-on group. The two remaining groups were not relevant to this NADA and data from these animals are not presented. Necropsies were performed on Days 24 and 25 postinfection for one control group and for cattle treated with moxidectin on Day 5. Cattle treated on Day 26 postinfection and their untreated control group were necropsied on Days 40 and 41.

   f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for the 0.5% pour-on for parasites present in a minimum of six adequately infected control calves are given in Table 4.5.

Table 4.5 Geometric mean of control worm counts and percent effectiveness

| Nematode species | Geometric Mean in Control Cattle | % Efficacy of Moxidectin Pour-On |
|---|---|---|
| **$L_4$ Larvae** | | |
| *Dictyocaulus viviparus* | 47.0 | 100 |
| *Cooperia oncophora* | 1252.7 | 99.8 |
| *Cooperia punctata* | 1772.7 | >99.9 |
| *Cooperia spatulata* | 2247.6 | >99.9 |
| *Cooperia surnabada* | 1266.2 | 99.9 |
| *Trichostrongylus colubriformis* | 618.5 | 100 |
| | | |
| **Adults** | | |
| *Cooperia oncophora* | 501.9 | 98.0 |
| *Cooperia spatulata* | 1608.6 | >99.9 |
| *Cooperia punctata* | 1067.5 | 100 |
| *Cooperia surnabada* | 409.3 | 99.3 |
| *Trichostrongylus colubriformis* | 77.6 | 99.4 |

5. Conclusion: This study demonstrated that moxidectin pour-on was effective against adult and $L_4$ stages of *C. oncophora, C. punctata, C. spatulata, C. surnabada,* and *T. colubriformis*. It was also effective against the $L_4$ stage of *D. viviparus*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number 0693-B-US-30-98**

1. Title: Dose confirmation study of 1% nonaqueous injectable and 0.5% moxidectin pour-on against adult and $L_4$ stages of various *Cooperia* species and *Trichostrongylus colubriformis* (Idaho).

2. Investigator: Edward Johnson, DVM, Johnson Research, Parma, ID; Gary Zimmerman DVM, Ph.D., Zimmerman Research, Livingston, MT

3. General Design:

   a. Purpose: To confirm effectiveness against a variety of adult and fourth-stage larvae of gastrointestinal nematodes.

   b. Animals: Forty-eight Holstein steers weighing between 156 and 245 kg, were assigned to six treatment groups (8 animals per group) in a completely random fashion. Cattle had been treated with an approved

anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

c. Housing: Calves were maintained in dirt-floored pens by treatment group.

d. Infection: On Day 0, each calf was infected with an inoculating dose of $L_3$ larvae containing approximately 5,000 *C. oncophora*/*C. surnabada*, 15,000 *C. punctata/C. pectinata*/*C. spatulata*/*C. surnabada*; and 15,000 *T. colubriformis*.

e. Procedure: One group of calves was treated on Day 6 postinfection to evaluate efficacy against the $L_4$ stage of the nematodes and the other group was treated on Day 23 postinfection to evaluate efficacy against adult nematodes. There was a corresponding untreated control group for each moxidectin pour-on group. The two remaining groups were not relevant to this NADA and data from these animals are not presented. Necropsies were performed on Days 20 postinfection for one control group and for cattle treated with moxidectin on Day 6. Cattle treated on Day 23 postinfection and their untreated control group were necropsied on Days 37.

f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for the 0.5% pour-on for parasites present in a minimum of six adequately infected control calves are given in Table 4.6.

Table 4.6 Geometric mean of control worm counts and percent effectiveness

| Nematode species | Geometric Mean in Control Cattle | % Efficacy of Moxidectin Pour-On |
|---|---|---|
| **$L_4$ Larvae** | | |
| *Cooperia oncophora* | 580.6 | 99.6* |
| *Cooperia pectinata* | 525.0 | 99.8* |
| *Cooperia punctata* | 2645.6 | 99.8* |
| *Cooperia surnabada* | 258.9 | 99.3* |
| *Trichostrongylus colubriformis* | 485.8 | 100.0* |
| **Adults** | | |
| *Cooperia pectinata* | 145.3 | 99.5* |
| *Cooperia surnabada* | 144.4 | 96.7* |

*Nematode counts for moxidectin-treated cattle were less than those from the controls at $P<0.05$ (log transformed counts were analyzed).

5. Conclusion: This study demonstrated that moxidectin pour-on was effective against the $L_4$ stage of *C. oncophora*, *C. pectinata*, *C. punctata*, *C. surnabada*, and *T. colubriformis*. It was also shown to be effective against adult *C. pectinata* and *C. surnabada*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number 0863-B-US-22-97**

1. Title: Dose confirmation study of 1% nonaqueous injectable and 0.5% moxidectin pour-on against experimentally-induced larval and adult *Bunostomum phlebotomum, Oesophagostomum radiatum,* and *Trichuris* spp. infections in cattle (Tennessee).

2. Investigator: Craig R. Reinemeyer, D.V.M., Ph.D.
East Tennessee Clinical Research
Knoxville, TN

3. General Design:

   a. Purpose: To confirm effectiveness against a variety of adult and fourth-stage larvae of gastrointestinal nematodes.

   b. Animals: Forty-eight Holstein and Holstein crossbred steers weighing between 66 and 159 kg, were assigned to six treatment groups (8 animals per group) in a completely random fashion. Cattle had been treated with an approved anthelmintic following purchase and all animals had negative fecal EPG counts at the start of the study.

   c. Housing: Calves were maintained in outdoor concrete-floored pens by treatment group. There was a shelter over approximately 40% of the pen with the remainder being open to ambient weather conditions

   d. Infection: One moxidectin-treated and one untreated control group were used to evaluate efficacy against the $L_4$ stage. These groups were infected with approximately 1,000 larvated *Trichuris* spp. eggs and 640 *Oesophagostomum radiatum* and 430 *Bunostomum phlebotomum* larvae on Day -16. One moxidectin-treated and one untreated control group were used to evaluate efficacy against the adult stage. These groups were infected with approximately 1,000 larvated *Trichuris* spp. eggs on Day -63 and 2500 *Oesophagostomum radiatum* and 500 *Bumostomum phlebotomum* larvae on Day -35.

e. Procedure: One group of calves was infected and treated in a manner such that efficacy against the $L_4$ stage of the nematodes could be evaluated and another group of cattle was infected and treated in a manner to determine activity against the adult stage. There was a corresponding untreated control group for each moxidectin pour-on group. The two remaining groups were not relevant to this NADA and data from these animals are not presented. All cattle were necropsied on Days 14 through 16 posttreatment.

f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for the 0.5% pour-on for parasites present in a minimum of six adequately infected control calves are given in Table 4.7.

Table 4.7 Geometric mean of control worm counts and percent effectiveness

| Nematode species | Geometric Mean in Control Cattle | % Efficacy of Moxidectin Pour-On |
|---|---|---|
| **$L_4$ Larvae** | | |
| *Oesophagostomum radiatum* | 92.7 | 100* |
| *Trichuris* spp. | 135.2 | 99.2* |
| | | |
| **Adults** | | |
| *Oesophagostomum radiatum* | 283.3 | 100* |
| *Trichuris* spp. | 120.9 | 99.8* |

*Nematode counts for moxidectin-treated cattle were less than those from the controls at $P<0.05$ (log transformed counts were analyzed).

5. Conclusion: This study demonstrated that moxidectin pour-on was effective against adult and $L_4$ stages of *Trichuris* spp. and *Oesophagostomum radiatum*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number 0693-B-US-20-98**

1. Title: Dose confirmation study of 1% nonaqueous injectable and 0.5% moxidectin pour-on against both naturally-acquired and experimentally-induced L4 nematode infections in cattle, with emphasis on *Bunostomum phlebotomum* and *Oesophagostomum radiatum* (Kentucky).

2. Investigator: Gil Meyers, Ph.D.
Gil Meyers, Ph.D., Inc.
Magnolia, Kentucky

3. General Design:

   a. Purpose: To confirm effectiveness against a variety of fourth-stage larvae of gastrointestinal nematodes.

   b. Animals: Thirty crossbred beef steers, weighing between 163 and 329 kg, were randomly assigned to three treatment groups (10 animals per group).

   c. Housing: Cattle were maintained together on a common pasture until the treatment day after which they were maintained in separate pastures by treatment group until necropsy.

   d. Infection: Calves had naturally-acquired *Bunostomum phlebotomum* and *Oesophagostomum radiatum* infections. All calves were also administered an experimental infection of 1,000 *Bunostomum* and 1,000 *Oesophagostomum* $L_3$ larvae on Day –15 relative to treatment. The experimental infections were used to evaluate efficacy of moxidectin pour-on against the $L_4$ stage of these nematodes.

   e. Procedure: One group of calves was treated with moxidectin pour-on on Day 0, and one group was untreated control animals. The third group was not relevant to this NADA and data from these animals are not presented. Necropsies were performed on Days 14 to 17 posttreatment.

   f. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for the 0.5% pour-on for parasites present in a minimum of six adequately infected control calves are given in Table 4.8.

   Table 4.8 Geometric mean of control worm counts and percent effectiveness

| Nematode species and stage | Geometric Mean in Control Cattle | % Efficacy of Moxidectin |
|---|---|---|
| *Oesophagostomum radiatum*, $L_4$ | 48.3 | 100* |
| *Oesophagostomum radiatum*, adults | 129.6 | 100* |

   *Nematode counts for moxidectin-treated cattle were less than those from the controls at $P<0.05$ (log transformed counts were analyzed).

5. Conclusion: This study demonstrated that moxidectin pour-on was effective against the adult and $L_4$ stage of *Oesophagostomum radiatum*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

**Study Number B-92-14**

1. Type of Study: Dose confirmation study in cattle with naturally-acquired gastrointestinal roundworm infections and induced infections of hookworm and lungworm.

2. Investigator: J.C. Williams, Ph.D.
   Louisiana State University
   Baton Rouge, LA

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for the control of nematode infections in cattle.

   b. Animals: Twenty mixed beef breed heifers, weighing between 122 and 184 kg, were ranked by pretreatment fecal lungworm larval counts, paired and randomly assigned to either the moxidectin pour-on treated group or the control group.

   c. Housing: Animals were maintained in outdoor pens with concrete floors by treatment group and exposed to ambient weather conditions.

   d. Infection: Cattle were infected with approximately 2,316 hookworm $L_3$ larvae on Day -77. On Day -29, cattle were infected with approximately 1,509 third-stage hookworm larvae and 1,080 third-stage lungworm larvae. These experimentally-induced infections were superimposed over naturally-acquired nematode infections.

   e. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   f. Procedure: Cattle were treated on Day 0. Necropsy was on Day 14 or 15 post-treatment.

   g. Primary Variable: Nematodes collected at necropsy were counted and identified.

4. Results: Effectiveness data for the 0.5% pour-on for parasites present in a minimum of six adequately infected control calves are given in Table 4.9.

   Table 4.9 Geometric mean of control worm counts and percent effectiveness

| Nematode species and stage | Geometric Mean in Control Cattle | % Efficacy of Moxidectin Pour-on 0.5 mg/kg |
|---|---|---|
| *Cooperia pectinata,* male adult | 26 | 100 |
| *Cooperia spatulata,* male adult | 62 | 100 |

5. Conclusions: This study demonstrated that moxidectin pour-on was effective against the adult stage of *Cooperia pectinata* and *Cooperia spatulata*.

6. Adverse Reactions: No adverse reactions to treatment were observed.

Persistent effect of CYDECTIN against *Ostertagia ostertagi* was demonstrated to be 28 days in studies conducted for the original approval. Two of three studies conducted for this supplement failed to support persistent activity for 28 days. The following table gives a summary of results for all studies demonstrating the persistent effect of CYDECTIN against *Ostertagia ostertagi*. An advisory statement has been added to the labeling that effectiveness was less than 90% in some field studies.

TABLE 4.10 SUMMARY OF PERSISTENT ACTIVITY AGAINST *OSTERTAGIA OSTERTAGI*

0863 PERSISTENCE TRIALS - OVERSEAS

| Study # | UK-03-92 | AU-04-92 | BE-10-94 | BE-13-95 | FR-13-93 | FR-14-94 | NZ-09-92 |
|---|---|---|---|---|---|---|---|
| Year | 1992 | 1992 | 1994 | 1995 | 1993 | 1994 | 1992 |
| Site | Scotland | Australia | Belgium | Belgium | France | France | N.Z. |
| Geo Mean Control | 13,826 | 3,453 | 26,104 | 15,503 | 18,078 | 28,508 | 1,113 |
| Eff Day 28 | 99.1% | 99.7% | 96.6% | 97.9% | 86.9% | 99.9% | 99.2% |
| Eff Day 21 | >99.9% | >99.9% | | | 99.9% | 99.9% | 99.2% |
| Eff Day 14 | 99.1% | >99.9% | | | 99.9% | >99.9% | |

0863 PERSISTENCE TRIALS – U.S.

| Study # | US-5-95 | US-6-95 | US-8-96 | US-19-97 | US-20-97 | US-25-98 |
|---|---|---|---|---|---|---|
| Year | 1996 | 1996 | 1996 | 1998 | 1998 | 1998 |
| Site | N. Carolina | Idaho | N.J. | Louisiana | Arkansas | N.J. |
| Geo Mean Control | 1,031 | 5,072.3 | 3,480.3 | 835.4 | 2,335.3 | 1,724.5 |
| Eff Day 28 | 98.9% | 100% | 99.8% | 0% | 26.2% | 97.9% |
| Eff Day 21 | 99.7% | 100% | 99.9% | 0% | 84.9% | 96.0% |
| Eff Day 14 | 99.1% | >99.9% | | 93.5% | 98.5% | 98.7% |

## V. TARGET ANIMAL SAFETY

Target animal safety data were presented in the original NADA 141-099 FOI Summary dated January 28, 1998. No additional data were required for approval of this supplement.

## VI. HUMAN SAFETY

All human safety information appear in the original NADA 141-099 FOI Summary dated January 28, 1998 and the supplemental FOI Summary dated November 2, 1999. No additional information was required for this supplemental approval.

## VII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and implementing regulations at Part 514 of Title 21, Code of Federal Regulations (21 CFR 514) to demonstrate that CYDECTIN® (moxidectin) Pour-On Solution for Cattle, is safe and effective for the treatment and control of infections and infestations of certain internal and external parasites in beef and dairy cattle, when administered topically at a dose of 500 mcg/kg bodyweight.

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

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

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

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue

studies) required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new claim for which the supplemental application is approved.

CYDECTIN® (moxidectin) Pour-On Solution for Beef and Dairy Cattle is under U.S. patent number 4,916,154, which expires on April 10, 2007.

## VIII. APPROVED PRODUCT LABELING

Facsimile bottle labeling, insert, and box container for the 500 mL, 1 liter, 2.5 liter, 5 liter and 10 liter size container are attached.

Copies of applicable labeling may be obtained by writing to:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855