Date of Approval: January 10, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-220

CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle

"for the treatment and control of three additional parasite species and additional life stages for three previously approved parasites of cattle"

Sponsored by:
Fort Dodge Animal Health
Division of Wyeth

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1. GENERAL INFORMATION

A. File Number:	NADA 141-220
B. Sponsor:	Fort Dodge Animal Health Division of Wyeth 800 Fifth St. NW. Fort Dodge, IA 50501 Drug Labeler Code: 000856
C. Established Name:	Moxidectin
D. Proprietary Name:	CYDECTIN Injectable Solution for Beef and Nonlactating Dairy Cattle
E. Dosage Form:	Sterile injectable solution
F. How Supplied:	200 mL and 500 mL polyethylene bottles
G. How Dispensed:	OTC
H. Amount of Active Ingredients:	10 mg moxidectin per mL
I. Route of Administration:	Subcutaneous injection
J. Species/Class:	Beef and Nonlactating Dairy Cattle
K. Recommended Dosage:	1 mL solution for each 110 pound (50 kg) body weight to provide 0.2 mg moxidectin/2.2 pound (1 kg) body weight
L. Pharmacological Category:	Antiparasitic

M. Indications: CYDECTIN Injectable when administered at the recommended dose level of 0.2 mg/2.2 lb (0.2 mg/kg) body weight is effective in the treatment and control of the following internal and external parasites of cattle:

Gastrointestinal Roundworms
Ostertagia ostertagi – Adults and inhibited L_4
Haemonchus placei Adults
Trichostrongylus axei – Adults
Trichostrongylus colubriformis – L_4
Cooperia oncophora – Adults
Cooperia punctata – Adults and L_4
Cooperia surnabada – Adults and L_4
Oesophagostomum radiatum – Adults and L_4
Trichuris spp. – Adults

Lungworms
Dictyocaulus viviparus – Adults and L_4

Cattle Grubs
Hypoderma bovis
Hypoderma lineatum

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

Lice
Linognathus vituli
Solenopotes capillatus

Persistent Activity: CYDECTIN Injectable has been proven to effectively protect cattle from reinfection with *Dictyocaulus viviparus* and *Oesophagostomum radiatum* for 42 days after treatment, *Haemonchus placei* for 35 days after treatment, and *Ostertagia ostertagi* and *Trichostrongylus axei* for 14 days after treatment.

N. Effect of Supplement: Addition of six new therapeutic claims:

Trichostrongylus colubriformis – Adult
Cooperia pectinata – Adult
Cooperia spatulata – Adult
Nematodirus helvetianus – Adult
Ostertagia ostertagi – L_4
Trichostrongylus axei – L_4

2. EFFECTIVENESS

A. Dosage Characterization

Effectiveness studies were presented in the original NADA 141-220 Freedom of Information (FOI) Summary dated May 20, 2005, establishing the recommended effective dose of CYDECTIN Injectable Solution for the control of various ecto- and endoparasites, and periods of persistent effect against a subset of endoparasites.

B. Substantial Evidence for Additional Endoparasite Indications

Six pivotal dose confirmation studies support the effectiveness of moxidectin 1% nonaqueous injectable solution against certain adult and larval stages of the gastrointestinal nematodes that are the subject of this supplemental NADA. All the trials were conducted in accordance with Good Clinical Practices as outlined in the VICH GL 9 Final Guidance (May 9, 2001). These trials utilized experimental infections superimposed on natural nematode burdens or administered to cattle free of nematodes prior to infection. Five of the six studies are summarized in the original FOI Summary (Study Numbers 0693-B-US-9-97, 0693-B-US-30-98, 0693-B-US-31-98, 0963-B-US-8-97, and 0863-B-US-26-98). Only one new study (Study Number 0693-B-US-37-00) was performed to provide supplemental data to complete the requirements for the new claims. Statistical analysis was performed only if six animals in the control group were adequately infected with the specific nematode species and stage. Counts were transformed by a $Y=\log_{10}$ (count +1) transformation before performing a one-way analysis of variance (ANOVA) with treatment as a fixed effect 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 (LS Means) were calculated for each group and the moxidectin group was compared to the control group by the one-sided student's t-test at the 5% level of significance. Percent efficacy was determined by comparing the geometric mean worm counts of the treated group (T) with those of the control group (C) for each parasite present in adequate numbers in at least six control animals using Abbott's formula: % efficacy = [(C-T/C) X 100].

For an indication to be granted, a minimum of two studies was required that had the following: an adequate level of infection in at least 6 control animals, the treatment effect was significant at alpha = 0.05, and 90% or greater efficacy using geometric means for each genus species of parasite. If there were more than 2 studies with an adequate level of infection, then the geometric means of the percent efficacy against a genus species of parasite from each study was added together and divided by the number of studies with that genus species of parasite. If this average was greater than or equal to 90%, then the claim was granted.

The individual studies are summarized below.

B1. Study Number 0693-B-US-37-00

1) Type of Study: Dose confirmation study in cattle with experimentally induced nematode infections

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

3) General Design:

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

b. Animals: Twenty Holstein steers weighing between 87 and 138 kg were randomly assigned to two treatment groups of 10 animals each. One group of animals was treated with moxidectin 1% nonaqueous injectable solution and one group served as the untreated control.

c. Housing: These cattle were maintained in concrete floored pens (5 animals/pen).

d. Infection: On Day 0 all cattle were inoculated with a mixed population of L_3 larvae containing *Nematodirus helvetianus, Cooperia spatulata, Cooperia pectinata*, and *Trichostrongylus colubriformis*. On Day 22 all cattle were inoculated with a mixed population of L_3 larvae containing *Ostertagia ostertagi* and *Trichostrongylus axei*.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Placebo vehicle injectable solution was administered on Day 0 at 0.02 mL/kg body weight to provide 0 mg moxidectin/kg body weight.

i. Test Duration: All cattle were necropsied 14 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against the following parasite species and stages. The percent efficacies are summarized in Table 2.B1:

Table 2.B1 Study Number 0693-B-US-37-00

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg
Treatment during Adult Stage:		
Cooperia pectinata	207.3	99.7
Cooperia spatulata	943.5	94.5
Nematodirus helvetianus	489.6	99.3
Trichostrongylus colubriformis	142.3	100.0
Treatment during L_4 Stage:		
Ostertagia ostertagi	3764.3	100.0
Trichostrongylus axei	131.3	100.0

5) Adverse Reactions: No adverse reactions to treatment were noted.

B2. Study Number 0693-B-US-9-97

1) Type of Study: Dose confirmation study in cattle with a combination of experimentally induced and naturally acquired nematode infections

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

3) General Design:

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

b. Animals: Thirty beef crossbred steers weighing between 73 and 133 kg were blocked by pretreatment fecal egg count and randomly assigned within blocks to three treatment groups of 10 animals each.

c. Housing: These cattle were maintained in indoor pens by treatment group.

d. Infection: All cattle had an experimentally-induced lungworm infection superimposed on naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

f. Route of Administration: Single subcutaneous injection in the neck region

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once on Day 0 at 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Controls: Injectable vehicle containing no moxidectin was administered at

0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: All cattle were necropsied 14 to 16 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The percent efficacies against parasites pertinent to this supplement at the approved dose are summarized in Table 2.B2:

Table 2.B2 Study Number 0693-B-US-9-97

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin 0.2 mg/kg
Treatment during Adult Stage:		
Trichostrongylus colubriformis	55.6	100
Nematodirus helvetianus	2559.4	95.9

5) Adverse Reactions: Fifteen study animals (4 from the control group, 7 from the 0.2 mg/kg treatment group, and 4 from the 0.3 mg/kg treatment group) had palpable injection site swellings at necropsy.

B3. Study Number 0693-B-US-30-98

1) Type of Study: Dose confirmation study in cattle with an experimentally-induced nematode infection

2) Investigators:

Edward G. Johnson, D.V.M.	Gary L. Zimmerman, D.V.M., Ph.D.
Johnson Research	Zimmerman Research
Parma, ID	Livingston, MT

3) General Design:

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

b. Animals: Forty-eight Holstein steer calves weighing between 156 and 245 kg were randomly assigned to six treatment groups of eight animals each. Two groups of animals were treated with moxidectin 1% nonaqueous injectable solution and two groups served as concurrent controls. The other two groups in this study were not relevant to the present NADA.

c. Housing: These cattle were maintained in separate outdoor pens by treatment group after experimental infections.

d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Cooperia* spp. and *Trichostrongylus colubriformis* on Day 0.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

f. Route of Administration: Single subcutaneous injection in the neck region

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 6 (L_4) or Day 23 (Adult) at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: Each treated group and a control group were necropsied 14 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The percent efficacy against the parasite pertinent to this supplement is summarized in Table 2.B3:

Table 2.B3 Study Number 0693-B-US-30-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin 0.2 mg/kg
Treatment during Adult Stage: *Cooperia pectinata*	145.3	95.5

5) Adverse Reactions: No adverse reactions to treatment were noted.

B4. Study Number 0693-B-US-31-98

1) Type of Study: Dose confirmation study in cattle with experimentally-induced nematode infections

2) Investigators: Larry L. Smith, D.V.M.
Larry Smith Research & Development
Lodi, WI

3) General Design:

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

b. Animals: Thirty Holstein male calves weighing between 80 and 194 kg were randomly assigned to three treatment groups of ten animals each.

c. Housing: These cattle were maintained in separate outdoor pens by treatment group after experimental infections.

d. Infection: On Day 0 all cattle were inoculated with a mixed population of L_3 larvae containing *Dictyocaulus viviparus*, *Haemonchus placei*, and *Trichostrongylus axei*. In addition, there were L_3 infective larvae of *Ostertagia* spp., *Cooperia* spp., and *Oesophagostomum* spp. present in the inoculum.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

f. Route of Administration: Single subcutaneous injection in the neck region

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 5 (L_4) and to a second group on Day 28 (Adult) at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: All cattle were necropsied on Days 42 or 43, 14 to 15 days after the second group was treated.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The percent efficacies against the parasites pertinent to this supplement are summarized in Table 2.B4:

Table 2.B4 Study Number 0693-B-US-31-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg
Treatment during Larval Stage:		
Ostertagia ostertagi	2849.1	100
Trichostrongylus axei	498.0	>99.9

5) Adverse Reactions: No adverse reactions to treatment were noted.

B5. Study Number 0693-B-US-8-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired nematode infections

2) Investigator: Craig R. Reinemeyer, D.V.M., Ph.D.

University of Tennessee
Knoxville, TN

3) General Design:

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

b. Animals: Thirty beef crossbred steer calves weighing between 191 and 274 kg were blocked by pretreatment fecal egg count and randomly assigned within blocks to three treatment groups of 10 animals each.

c. Housing: These cattle were maintained in separate pastures by treatment group.

d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

f. Route of Administration: Single subcutaneous injection in the neck region

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once on Day 0 at 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Controls: Injectable vehicle containing no moxidectin was administered at 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: All cattle were necropsied 12-16 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The percent efficacy against the parasite pertinent to this supplement at the approved dose is summarized in Table 2.B5:

Table 2.B5 Study Number 0693-B-US-8-97

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg:
Treatment during Adult Stage: *Cooperia pectinata*	97.5	77.2

5) Adverse Reactions: Eleven study animals (3 from the 0.2 mg/kg treatment group, and 8 from the 0.3 mg/kg treatment group) had injection site lesions (fibrosis, firmness, or inflammation) at necropsy.

B6. Study Number 0863-B-US-26-98

1) Type of Study: Dose confirmation study in cattle with experimentally-induced nematode infections

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

3) General Design:

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

b. Animals: Forty-eight Holstein steer calves weighing between 112 and 172 kg were randomly assigned to six treatment groups of eight animals each. Two groups of animals were treated with moxidectin 1% nonaqueous injectable solution and two groups served as concurrent controls. The other two groups in this study were not relevant to the present NADA.

c. Housing: These cattle were maintained in separate indoor pens by treatment group with 4 animals per pen.

d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Cooperia* spp. and *Trichostrongylus colubriformis* on Day 0. In addition, half of the groups were also infected with *Dictyocaulus viviparus* infective larvae.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

f. Route of Administration: Single subcutaneous injection in the neck region

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 5 (L4) or Day 26 (Adult) at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: Groups infected with *D. viviparus* and treated on Day 5 were necropsied 19 to 20 days post-treatment. The groups treated on Day 26 were necropsied 14 to 15 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The percent efficacy against the parasite pertinent to this supplement is summarized in Table 2.B6:

Table 2.B6 Study Number 0693-B-US-26-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin 0.2 mg/kg
Treatment during Adult Stage: *Cooperia spatulata*	1608.6	99.6

5) Adverse Reactions: No adverse reactions to treatment were noted.

C. New Effectiveness Claims

Table 2.C lists the studies (with corresponding efficacy results) that support the effectiveness of 1% moxidectin nonaqueous injectable solution against the new parasite claims granted in this supplemental NADA.

Table 2.C: Effectiveness Studies

Parasite	**Treatment Stage**	**Study**	**Study % Efficacy**
Trichostrongylus colubriformis	Adult	**0693-B-US-37-00** 0693-B-US-9-97	**100** 100
Cooperia pectinata	Adult	**0693-B-US-37-00** 0693-B-US-30-98 0693-B-US-8-97	**99.7** 95.5 77.2
Cooperia spatulata	Adult	**0693-B-US-37-00** 0863-B-US-26-98	**94.5** 99.6
Nematodirus helvetianus	Adult	**0693-B-US-37-00** 0693-B-US-9-97	**99.3** 95.9
Ostertagia ostertagi	L4	**0693-B-US-37-00** 0693-B-US-31-98	**>99.9** >99.9
Trichostrongylus axei	L4	**0693-B-US-37-00** 0693-B-US-31-98	**100** 100

***Bold** indicates supplemental data from the new study

3. TARGET ANIMAL SAFETY

The Center for Veterinary Medicine (CVM) did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-220 (approved May 20, 2005) contains a summary of target animal safety studies for cattle.

4. HUMAN FOOD SAFETY

CVM did not require human food safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-220 (approved May 20, 2005) contains a summary of human food safety studies.

5. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle at the dose rate of 0.2 mg moxidectin/2.2 lb (0.2 mg/kg) body weight is effective for the treatment and control of three additional parasite species and additional life stages for three previously approved parasites of cattle.

An Acceptable Daily Intake (ADI) of 0.004 mg/kg/day has been established for moxidectin. A tolerance of 900 ppb for residues of parent moxidectin (marker residue) in fat (target tissue) of cattle has been established. A withdrawal period of 21 days is required for this use of moxidectin in cattle. Tolerances of 50 ppb and 200 ppb have also been established for residues of moxidectin in muscle and liver of cattle, respectively.

The data submitted for the CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle support the marketing of the product as an over-the-counter new animal drug. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, CVM has concluded that this product shall have over-the-counter marketing status.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. This exclusivity is based on 5 previously submitted dose confirmation studies and one new dose confirmation study submitted in this application. The three years of marketing exclusivity applies only to the new indications of treatment and control of adult *Trichostrongylus colubriformis, Cooperia pectinata, Cooperia spatulata,* and *Nematodirus helvetianus* and L_4 *Ostertagia ostertagi* and *Trichostrongylus axei*.

CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle is under the following US patent numbers:

U.S. Patent Number	Date of Expiration
4,916,154	April 10, 2007
5,965,603	July 8, 2018

6. ATTACHMENTS

Facsimile labeling is attached as indicated below:

A. Insert Label

B. Bottle Labels: 200 mL and 500 mL

C. Carton Labels: 200 mL (40% reduction) and 500 mL (50% reduction)