Date of Approval: November 30, 2005

# FREEDOM OF INFORMATION SUMMARY

## *ORIGINAL NEW ANIMAL DRUG APPLICATION*

## NADA 141-247

CYDECTIN (moxidectin) Oral Drench for Sheep

"for the treatment and control of internal parasites of sheep"

Sponsored by:
Fort Dodge Animal Health
Division of Wyeth

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## *1. GENERAL INFORMATION:*

a. File Number: NADA 141-247

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 Names: CYDECTIN (moxidectin) Oral Drench for Sheep

e. Dosage Form: Ready-to-use drench solution

f. How Supplied: 1-liter and 4-liter polyethylene bottles

g. How Dispensed: OTC

h. Amount of Active Ingredients: 1 mg moxidectin/mL (0.1% w/v)

i. Route of Administration: Oral

j. Species/Class: Ovine

k. Recommended Dosage: 1 mL per 11 lb (1 mL per 5 kg) body weight to provide 0.2 mg moxidectin/2.2 lb (0.2 mg/kg) body weight

l. Pharmacological Category: Antiparasitic

m. Indications: CYDECTIN Oral Drench for Sheep, when administered at the recommended dose of 0.2 mg moxidectin/2.2 lb (0.2 mg/kg) body weight (BW), is effective in the treatment and control of the adult and larval ($L_4$) stages of the following internal parasites of sheep:

*Haemonchus contortus* - Adult and $L_4$ larvae
*Teladorsagia circumcincta* – Adult and $L_4$ larvae
*Teladorsagia trifurcata* - Adult and $L_4$ larvae
*Trichostrongylus axei* - Adult and $L_4$ larvae
*Trichostrongylus colubriformis* - Adult and $L_4$ larvae
*Trichostrongylus vitrinus* – Adult and $L_4$ larvae
*Cooperia curticei* - Adult and $L_4$ larvae
*Cooperia oncophora* – Adult and $L_4$ larvae
*Oesophagostomum columbianum* - Adult and $L_4$ larvae
*Oesophagostomum venulosum* – Adult and $L_4$ larvae
*Nematodirus battus* - Adult and $L_4$ larvae
*Nematodirus filicollis* - Adults and $L_4$ larvae
*Nematodirus spathiger* - Adults and $L_4$ larvae

## *2. EFFECTIVENESS*

### *a. Dosage Characterization:*

In a series of dose determination studies conducted in several locations outside of the U.S., a dose of 0.2 mg moxidectin/kg BW was demonstrated to be effective against the adult and larval stages of pathogenically important ovine parasites. Specifically, data from seven dose-titration studies conducted in Argentina, Australia, New Zealand, and the United Kingdom provided the critical data necessary to initially define the effective dose. All studies were designed to evaluate the effectiveness of the 0.1 mg, 0.2 mg, and/or 0.4 mg moxidectin/kg BW dose in sheep with either naturally-acquired or experimentally-induced parasite infections. The data from these studies demonstrated that treatment with the 0.1 mg moxidectin/kg BW dose did not in all instances provide an optimum level of control against the dose-limiting species: *Nematodirus* spp. and *Cooperia* spp. However, the 0.2 mg moxidectin/kg BW dose resulted in 99.5% or greater efficacy in all evaluations. Comparable therapeutic efficacy was reported for the test groups treated with 0.4 mg moxidectin/kg BW. These data resulted in the selection of the recommended 0.2 mg moxidectin/kg BW dose.

### *b. Substantial Evidence:*

CYDECTIN Oral Drench for Sheep was approved in various overseas locations in the early 1990s. Over 24 dose confirmation studies were conducted including one study in the U.S. for these approvals. Sheep are a minor species and to complement the available historical data, two additional dose confirmation studies were conducted in the U.S. These two studies included the gastrointestinal nematodes common to sheep raised in the U.S. The studies were designed to demonstrate the effectiveness of the product against adults (Study 0866-O-US-5-02) and larval stages (Study 0866-O-US-6-02) of six nematode genera including *Haemonchus* spp., *Teladorsagia* spp. *Cooperia* spp., *Nematodirus* spp., *Trichostrongylus* spp., and *Oesophagostomum* spp. They were conducted in accordance with Good Clinical Practices as outlined in the VICH GL 9 Final Guidance (May 9, 2001). A claim for all species found in the U.S. of each genera tested was allowed from these two studies.

Each study was conducted in nematode-free sheep experimentally infected with a mixed inoculum of $L_3$ larvae from recent field isolates of six common genera of gastrointestinal nematodes found in the U.S. Counts were transformed by a $Y=Log_{10}$ (count +1). A one-way analysis of variance (ANOVA) was used to analyze log transformed count data. The geometric treatment means were tested for significance at alpha = 0.05. 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]. A claim was granted for the species found in the U.S. of each genera when the following were met: there was an adequate level of infection in six control animals, the treatment effect was significant at alpha = 0.05, and percent efficacy was 90% or greater using geometric means.

The infection was adequate for the dose limiting parasites, *Nematodirus spathiger*, *Cooperia oncophora*, and *Haemonchus contortus*, the most pathogenic intestinal parasites

of sheep. The infection was lower for *Teladorsagia circumcincta* and *Cooperia curticei*, however, they were present in at least six control animals in both studies. With the preponderance of supportive data for these genera from the earlier studies, claims for these genera were granted. The two trials are individually summarized below.

**b.1. Study Number 0866-O-US-5-02**

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

2) Clinical Investigator: Siva Ranjan, B.V.Sc., Ph.D
Fort Dodge Animal Health
Princeton, New Jersey

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of CYDECTIN Oral Drench for Sheep for the treatment and control of adult-stage nematode infections in sheep.

b. Animals: A total of 20 weaned Dorset wether lambs weighing between 28 and 35 kg body weight were randomly assigned to one of two, ten-animal treatment groups.

c. Housing: Test animals were maintained in separate pens by treatment group (10 sheep per pen).

d. Infection: All sheep were orally administered inocula of the infective $L_3$ larvae from recent field isolates of the following species of nematodes 32 days prior to treatment: ~5300 *Haemonchus contortus;* ~3300 *Teladorsagia circumcincta;* ~4900 *Cooperia* spp.; ~4800 *Trichostrongylus* spp.; ~3000 *Nematodirus spathiger; and* ~1000 *Oesophagostomum* spp. Only the *Nematodirus* infective larvae were obtained as a pure culture.

e. Dosage Form: CYDECTIN Oral Drench for Sheep; 1 mg/mL

f. Route of Administration: Oral drench

g. Dose: Treated sheep were administered 0.2 mg moxidectin/kg BW of CYDECTIN Oral Drench for Sheep. Sheep in the control group were administered a comparable volume of a placebo formulation containing no moxidectin.

h. Test Duration: All sheep were necropsied 14 to 15 days after treatment.

i. Pertinent Measurements/Observations: Nematodes recovered from test sheep at necropsy were counted and identified by genus and species.

4) Results: Percent efficacy against the adult stages of specific parasite species are summarized in Table 2.1:

Table 2.1: Study Number 0866-O-US-5-02 – Dose confirmation study – adult nematode parasites – percent efficacy of CYDECTIN Oral Drench for Sheep

| Nematode species | No. Lambs Infected | No. of Parasites Geometric mean in Controls | % Efficacy 0.2 mg moxidectin/kg |
|---|---|---|---|
| *Haemonchus contortus* | 10 | 874.8 | 99.8 |
| *Teladorsagia circumcincta* | 7 | 7.0 | 100.0 |
| *Cooperia curticei* | 6 | 4.7 | 100.0 |
| *Cooperia oncophora* | 10 | 970.6 | 99.9 |
| *Nematodirus spathiger* | 10 | 581.7 | 98.9 |
| *Trichostrongylus colubriformis* | 10 | 1731.6 | 100.0 |
| *Oesophagostomum venulosum* | 9 | 152.9 | 100.0 |

5) Adverse Reactions: No adverse signs related to treatment were observed.

6) Conclusion: The study demonstrated that CYDECTIN Oral Drench for Sheep is effective against the adult stage of the six genera of parasites tested.

**b.2. Study Number 0866-O-US-6-02**

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

2) Clinical Investigator: Siva Ranjan, B.V.Sc., Ph.D.
Fort Dodge Animal Health
Princeton, New Jersey

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of CYDECTIN Oral Drench for Sheep for the treatment and control of larval ($L_4$) stage nematode infections in sheep.

b. Animals: A total of 20 weaned Dorset wether lambs weighing between 21 and 28 kg body weight were randomly assigned to one of two, ten-animal treatment groups.

c. Housing: Test animals were maintained in separate pens by treatment group (10 sheep per pen).

d. Infection: All sheep were orally administered inocula of the infective $L_3$ larvae from recent field isolates of the following species of nematodes prior to treatment: ~1000 *Oesophagostomum* spp. 17 days before treatment; ~3000 *Nematodirus spathiger* 10 days before treatment; ~2000 *Teladorsagia circumcincta* 7 days before treatment;

and ~4800 *Haemonchus contortus*, ~3800 *Trichostrongylus* spp., and ~5000 *Cooperia* spp. 5 days before treatment. Only the *Nematodirus* infective larvae were obtained as a pure culture.

e. Dosage Form: CYDECTIN Oral Drench for Sheep; 1 mg/mL

f. Route of Administration: Oral drench

g. Dose: Treated sheep were given 0.2 mg moxidectin/kg BW of CYDECTIN Oral Drench for Sheep. Sheep in the control group were administered a comparable volume of a placebo formulation containing no moxidectin.

h. Test Duration: All sheep were necropsied 14 to 15 days after treatment.

i. Pertinent Measurements/Observations: Nematodes recovered from test sheep at necropsy were counted and identified by genus and species.

4) Results: Percent efficacy against the larval stages of specific parasite species is summarized in Table 2.2.

Table 2.2: Study Number 0866-O-US-6-02 – dose confirmation study – larval nematode parasites – percent efficacy CYDECTIN Oral Drench for Sheep.

| Nematode species | No. Lambs Infected | No. of Parasites Geometric Mean in Controls | % Efficacy 0.2 mg/ moxidectin/kg |
|---|---|---|---|
| *Haemonchus contortus* | 10 | 1310.5 | >99.9 |
| *Teladorsagia circumcincta* | 10 | 145.7 | 100.0 |
| *Cooperia curticei* | 10 | 92.0 | 100.0 |
| *Cooperia oncophora* | 10 | 639.8 | 100.0 |
| *Nematodirus spathiger* | 10 | 961.7 | 99.8 |
| *Trichostrongylus colubriformis* | 10 | 1857.6 | 100.0 |
| *Oesophagostomum columbianum* | 10 | 53.1 | 100.0 |
| *Oesophagostomum venulosum* | 10 | 52.9 | 100.0 |

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

6) Conclusion: The study demonstrated that CYDECTIN Oral Drench for Sheep is effective against the larval stage of the six genera of parasites tested.

## *3. TARGET ANIMAL SAFETY*

A multiple dose target animal safety study was conducted to demonstrate the margin of safety, after administering CYDECTIN Oral Drench for Sheep to growing lambs at levels up to five times the recommended 0.2 mg moxidectin/kg BW dose three times at 14-day intervals. This study was performed in full compliance with the Good Laboratory Practice (GLP) regulations as specified in 21 CFR 58.

**Drug Toxicity - Study Number 0866-O-US-7-02**

1) Type of Study: Laboratory Safety Study

2) Study Director: Cathy Ann Ball, VMD
Fort Dodge Animal Health
Princeton, New Jersey

3) General Design:

a. Purpose**:** To evaluate possible clinical effects in growing lambs treated with either 1X, 3X, or 5X the recommended dose level (0.2 mg/kg BW) of CYDECTIN Oral Drench for Sheep on three successive occasions 14 days apart.

b. Animals: Thirty-two intact (16 males and 16 females) 4 to 6 month old growing lambs were used, weighing between 27 to 48 kg at the time of the initial treatment.

c. Dosage Form: CYDECTIN Oral Drench for Sheep; 1 mg/mL

d. Control: Physiologic saline

e. Route of Administration: Oral drench

f. Doses: Test lambs in Groups B, C, and D received CYDECTIN Oral Drench for Sheep at 0.2, 0.6, or 1.0 mg moxidectin/kg BW (1X, 3X and 5X the recommended dose), respectively, three times at 14-day intervals. Lambs in Group A (control) were administered a volume of saline equivalent to the 5X group (1 mL/kg body weight) at the same time intervals.

g. Test Duration: 35 days

h. Pertinent Measurements/Observations: All test animals were observed for clinical signs of adverse reaction at approximately 3, 12, and 24 hours following each treatment, and then daily for the next 13 days. Although any abnormality or behavioral change was recorded, the observer was specifically instructed to look for the following potential signs of toxicity: ocular discharge, nasal discharge, hypersalivation, coughing, rapid or labored breathing, muscle tremors, convulsions, impaired mobility, depression, recumbency, reluctance to move, and ataxia and/or dragging of the front or hind limbs. Daily ocular exams to monitor pupil size were

also performed. In addition, each test animal was given a complete physical exam on the day prior to treatment, the day after treatment, and seven days post-treatment. All observations and exams were performed by the Study Director, who was masked to treatment. Animals were weighed on a digital hanging scale on Study Days -5, -1, 13, and 27.

4) Analysis: A repeated measures analysis was performed on the individual quantitative parameters [body weights and physical exam parameters (heart rate, body temperature, respiratory rate, and capillary refill time)] using the PROC MIXED procedure. The mixed model included pre-treatment as a covariate, and treatment, sex, treatment by sex, day, sex by day, treatment by day, and treatment by sex by day as the fixed effects; and block within sex as a random effect.

   Categorical variables (clinical observations-including breathing, nasal discharge, locomotion, ocular discharge, salivation, convulsions, recumbency, muscle tremors, mobility, ataxia, and depression) were conducted and measured as a "Yes/No." "Present/Absent" or "Normal/Abnormal." A 2-sided Fisher's Exact test was used for categorical variables for each observation period.

5) Results: All groups gained weight and grew similarly throughout the study. Food consumption levels were also comparable. The physical and ocular exam parameters were within normal limits for all test animals during the study. Lameness related to minor injury was observed in one control and one 1X treatment group animal. The control group had a significant number of rapid breathing observations on three occasions. This was attributed to a combination of high ambient temperature and increased activity associated with catching and restraining this group of sheep on these three occasions. While these were statistically significant, there was no clinical relevance, and therefore these observations were not attributed to treatment effect. In accordance with the study protocol, the observation schedule was terminated seven days after the third treatment based on the absence of any signs of toxicity up to that point in the study.

6) Conclusion: Under the conditions of this study, treatment of lambs with 0.2, 0.6, or 1.0 mg/kg BW (1X, 3X, or 5X levels) of CYDECTIN Oral Drench for Sheep did not cause clinical signs of toxicity in any of the test animals when treated three times at 14-day intervals.

## *4. HUMAN FOOD SAFETY*

### a. Toxicity

The toxicology of moxidectin has been extensively evaluated in conjunction with the use of moxidectin in cattle. Complete summaries of these toxicology studies were presented in the original NADA 141-099 (CYDECTIN Pour-On for Beef and Dairy Cattle) FOI Summary dated January 28, 1998 and the supplemental NADA 141-099 FOI Summary dated November 2, 1999. No additional toxicology data were required for the approval of this NADA.

### b. Safe Concentration of Total Residues

An acceptable daily intake (ADI) of up to 0.004 mg moxidectin/kg body weight/day has been determined as part of the prior evaluation of the safe use of moxidectin. The safe concentrations for moxidectin in edible tissues of cattle have been established in supplemental NADA 141-099 FOI Summary dated November 2, 1999 as follows: 0.5 ppm in muscle, 1.5 ppm in liver, 3.0 ppm in kidney and fat, and 0.6 ppm in milk. Because sheep are classified as a minor species for NADA approval purposes, the same safe concentrations established for edible cattle tissues are applicable to sheep, a related small ruminant species.

### c. Total Residue Depletion and Metabolism Studies

Total residues and the metabolic transformation of moxidectin in the edible tissues of cattle, and the metabolism of moxidectin in laboratory rats were presented in the original NADA 141-099 FOI Summary dated January 28, 1998. No additional data were required for the approval of this NADA.

### d. Comparative Metabolism Studies

Comparative metabolism studies for moxidectin were presented in the original NADA 141-099 FOI Summary dated January 28, 1998. No additional toxicology data were required for the approval of this NADA.

### e. Residue Depletion - Study Number A-267-866-AU-02-91

A study was conducted to determine the depletion of the marker residue in the edible tissues of sheep following treatment with the recommended dose level of the final 0.1% moxidectin oral drench formulation.

1. Type of Study: Residue Depletion Study

2. Investigator: B. F. Chick, B.V.Sc. (Syd)
   Agrisearch Services Pty. Ltd.,
   Orange, New South Wales, Australia

3. Design: A total of 34 weaned Border-Leicester/Merino crossbred sheep (17 females and 17 castrated males) weighing approximately of 25-35 kg each were randomly assigned to two, 12-animal treated groups and a 10-animal untreated control group. All groups had equal sex distribution. The two groups of treated sheep were given a single administration of the appropriate volume of either a 0.1% or 0.2% moxidectin oral drench formulation, resulting in the same 0.2 mg moxidectin/kg body weight dose. Two control sheep were sacrificed on the day of treatment. Sets of two control sheep and three sheep from each treatment group were sacrificed 7, 14, 20, and 28 days following treatment. Samples of muscle, liver, kidney, and fat were taken post mortem and moxidectin residue content was determined with a validated analytical procedure.

4. Findings: No detectable residues were found in the control animals. Because the two treatment groups received the same moxidectin dose level, moxidectin residue values for all treated sheep were combined for reporting purposes. The mean values of moxidectin (marker residue) concentrations in tissues of treated sheep at each of the posttreatment sacrifice times are summarized in the table below.

| Days After Treatment | Moxidectin Residues (ppb)[a] | | | |
|---|---|---|---|---|
| | Fat | Muscle | Liver | Kidney |
| 7 | 65.7 ± 14.6 | <10 | <10 | <10 |
| 14 | 79.7 ± 19.6 [b] | <10 | <10 | <10 |
| 20 | 44.4 ± 19.5 | NA[c] | NA[c] | NA[c] |
| 28 | 28.6 ± 15.4 | NA[c] | NA[c] | NA[c] |

[a]Based on six animals per time point; values are mean ± standard deviation.
[b]Mean ± standard deviation moxidectin residue for five treated sheep.
[c]Because moxidectin residues were <10 ppb in muscle, liver and kidney samples from all treated sheep sacrificed 7 and 14 days posttreatment, samples of these tissues from treated sheep sacrificed 20 and 28 days posttreatment were not analyzed (NA).

5. Conclusions: There were no differences between males and females in tissue residues. This study confirmed omental fat as the target tissue for monitoring residue depletion in sheep and provided adequate data for the calculation of an appropriate posttreatment withdrawal.

## f. Tolerance and Withdrawal Time

**Tolerance:** The parent compound (moxidectin) has been established as the marker residue and fat as the target tissue in the original NADA 141-099 FOI Summary dated January 28, 1998. Data in the referenced NADA demonstrate that the extractablility of radiolabeled residues from fat is ≥ 99%, indicating the absence of bound residues. Moxidectin accounts for >80% of the total residues in fat. Based on a safe concentration in fat of 3 ppm, a tolerance for parent moxidectin in fat could be set as high as 2.4 ppm (3ppm x 0.8). However, in keeping with the Agency's policy of not establishing a tolerance at a level higher than reflected by the permitted use of the drug, a value of 900 ppb unchanged moxidectin is assigned as the tolerance in fat of sheep.

Because USDA/FSIS assays muscle and liver samples of sheep with a multi-residue method capable of detecting and measuring moxidectin in its monitoring program, FDA has established tolerances of 50 ppb and 200 ppb for parent moxidectin in muscle and liver, respectively, of sheep (21 CFR 556.426).

**Withdrawal Time:** Statistical analysis of the marker residue, moxidectin, in fat, the target tissue, from the residue depletion study indicated that a 7-day posttreatment slaughter withdrawal period is appropriate for this drug when used in accordance with label directions.

## g. Regulatory Method for Residues

Descriptions of the official determinative and confirmatory assay procedures for moxidectin in cattle fat and the sponsor-monitored trial conducted to validate the determinative procedure are described in the original NADA 141-220 (CYDECTIN Injectable Solution for Beef and Nonlactating Dairy Cattle) FOI Summary dated May 20, 2005. These assay procedures are also suitable for the analysis of sheep fat. The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

## h. User Safety

Not for use in humans. Keep this and all other drugs out of the reach of children. The material safety data sheet (MSDS) provides more detailed occupational safety information. A copy of the MSDS can be obtained by calling the 1-888 number on the product label. The product label will instruct users who experience adverse reactions to report these using the 1-800 number provided on the product label.

## *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 514 of the implementing regulations. The data demonstrate that CYDECTIN (moxidectin) Oral Drench for Sheep at the dose rate 0.2 mg moxidectin/2.2 lb (0.2 mg/kg) BW is effective for the treatment and control of various internal parasites in sheep.

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 sheep has been established. A withdrawal period of 7 days is required for this use of moxidectin in sheep. Tolerances of 50 ppb and 200 ppb have also been established for residue of moxidectin in muscle and liver of sheep, respectively.

The data submitted for CYDECTIN (moxidectin) Oral Drench for Sheep 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 of use prescribed on the labeling are likely to be followed in practice. Therefore, CVM has concluded that this product shall have over-the-counter status.

Under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the Act), this approval qualifies for SEVEN years of exclusive marketing rights beginning on the date of approval because the new animal drug has been declared a designated new animal drug by FDA under section 573(a) of the Act.

CYDECTIN (moxidectin) Oral Drench for Sheep is under the following U.S. Patent number:

| U.S. Patent Number | Date of Expiration |
|---|---|
| 4,916,154 | April 10, 2007 |

## *6. ATTACHMENTS:*

Facsimile Labeling is attached as indicated below:

A. One-Liter (1 L) Bottle Label (front and back panels)

B. Four-Liter (4 L) Bottle Label (front and back panels)