DATE OF APPROVAL LETTER: NOVEMBER 2, 1999

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-099

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

"When used according to label directions, neither a preslaughter drug withdrawal period nor a milk discard time are required. Meat and milk produced from cattle treated with CYDECTIN Pour-On may be used at any time following treatment."

Sponsored by

Fort Dodge Animal Health

®Registered trademark of American Cyanamid Company

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I. GENERAL INFORMATION

NADA Number:	141-099
Sponsor:	Fort Dodge Animal Health 800 Fifth St. NW Fort Dodge, Iowa 50501
Established Name:	moxidectin
Proprietary Name:	CYDECTIN® (moxidectin) Pour-On for Beef and Dairy Cattle
Marketing Status:	Over-the-counter (OTC)
Effect of Supplement:	The additional indication contained in this supplemental NADA is for the addition of dairy cattle with a zero-day milk discard time and, thus, the removal of the warning statement for female dairy cattle of breeding age. Meat and milk produced from cattle treated with CYDECTIN Pour-On may now be used at any time following treatment.

II. INDICATIONS FOR USE:

Effective in the treatment and control of the following internal and external parasites.

Gastrointestinal Roundworms

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

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 *Ostertagia ostertagi* for 28 days following 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

A series of effectiveness studies were presented in the original NADA 141-099 FOI Summary dated January 28, 1998, to establish the recommended effective dose of Cydectin Pour-On for the control of all ecto- and endoparasites as label claims. Because a withdrawal time in milk had not been established at the time of the original NADA approval, this product was labeled against use in female dairy cattle of breeding age. The following study confirms the effectiveness of Cydectin Pour-On at the recommended dose of 0.5 mg/kg body weight for use in lactating dairy cows.

Study Number 0863-B-US-24-98

1. Title: Dose Confirmation of Moxidectin 0.5% Pour-On Against Natural Nematode Infections in Lactating Dairy Cows

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

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose required for control of natural nematode infections in lactating dairy cows.

   b. Animals: Twenty Holstein cows ranging in age from two to twelve years of age and weighing between 402 to 581 kg, were assigned to the two treatment groups (10 animals per group) in a completely random fashion. Cows had freshened between two and 15 months prior to treatment.

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

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

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg moxidectin/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to cows at 1.0 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to cows on Day 0 at 1.0 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   i. Test Duration: Necropsies were conducted on Days 14 to 18 post-treatment

   j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control cows are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on
Ostertagia ostertagi, adult	1950	98.7
Ostertagia lyrata, adult	32	100
Ostertagia spp., adult females	2447	97.3
Ostertagia spp., inhibited EL_4	22,106	95.2
Ostertagia spp. L_4	400	93.2
Trichostrongylus axei, adult	3038	99.8
Cooperia punctata, adult	424	100
Cooperia spp., adult females	983	98.4

5. Statistical Methods:

Efficacy 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 efficacy or percent reduction was calculated using arithmetic 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, stage and sex 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). In order to demonstrate the effectiveness of Cydectin Pour-On, the following criteria were applied for each parasite claim: a) at least six control animals were infected with that specific stage and species of parasite; 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 $P<0.05$.

6. Conclusion:

This study demonstrated that Cydectin Pour-On, applied to lactating dairy cows at the recommended dose was safe and effective in the reduction of natural infections of adult *O. ostertagi*, adult *O. lyrata*, adult and larval stages (inhibited and late L_4) of *Ostertagia* spp., adult *T. axei*, adult *Cooperia* spp. and adult *C. punctata*.

7. Adverse Reactions:

No adverse reactions to treatment were observed.

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

A. Toxicology

Moxidectin was initially tested in a battery of four different short-term genetic toxicity experiments. Specific information pertaining to the conduct and outcome of these four studies is located on pages 73-75 of the original NADA 141-099 FOI Summary (January 1998). Three additional genotoxicity studies (chemical induction of chromosome aberration in cultured Chinese Hamster Ovary cells assay, *in vivo* test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells and L5178Y TK+/- mouse lymphoma mutagenesis assay) have been subsequently carried out with moxidectin. The moxidectin test article used in all three of these tests had a purity of 90.84%. Individual summaries of these three genotoxicity studies are presented below.

1. Chromosome Aberration in Cultured Chinese Hamster Ovary (CHO) Cells Assay

   a. Identification: Study performed by Dr. Jing Xu and staff at SITEK Research Laboratories, Rockville, Maryland testing facility. Experimental period: October 13, 1998, to July 15, 1999. Fort Dodge No.: 971-98-131 (SITEK Study No.: 0504-3110).

   b. Procedure: Based on the results of initial range-finding work, the definitive phase of this chromosome aberration study was conducted at five concentrations between 1-30 mcg/mL in the absence and presence of a metabolic activation system that consisted of phenobarbital/β-naphthoflavone-induced rat liver homogenate (S9). The treatment period was three hours in both systems with a harvest time of 18 hours. The toxicity was assessed by the reduction in the Relative Cell Growth (RCG) and/or Relative Mitotic Index (RMI). Mitomycin-C at concentrations of 0.08 and 0.2 mcg/mL was used as the positive control in the non-activated system and cyclophosphamide at concentrations of 7.5 and 12.5 mcg/mL was used as the positive control in the activated system. Based on the negative results from the definitive phase of this study**,** a confirmatory test with an 18-hour treatment period was conducted using only the non-activated system. Two separate confirmatory tests were carried out to verify the results of the definitive phase of the study.

   c. Findings: The results of this testing showed that moxidectin did not induce a statistically significant increase in the percentage of cells with chromosome damage at any of the concentrations tested in both the definitive and confirmatory phases of this study.

d. Conclusion: The test material was negative in the *in vitro* chromosome assay with cultured Chinese Hamster Ovary (CHO) cells and is not considered to be clastogenic to the CHO cells under these test conditions.

2. *In Vivo* Mouse Bone Marrow Micronucleus Test

a. Identification: Study performed by Dr. Jing Xu and staff at SITEK Research Laboratories, Rockville, Maryland testing facility. Experimental period: October 13, 1998, to November 15, 1998. Fort Dodge Study No.: 971-98-132 (SITEK Study No.: 0504-1521).

b. Procedure: In this test, male and female CD-1 mice were administered a single treatment of either 7.5, 15 or 30 mg moxidectin/kg body weight by oral gavage and sacrificed at either 24, 48 or 72 hours post-treatment to assess the potential of moxidectin to induce chromosome damage in bone marrow cells. Vehicle controls, which received only corn oil, were also sacrificed at the same 1-, 2-, and 3-day time points. A single group of positive control animals, which received cyclophosphamide, was harvested as part of the 24-hour sacrifice. Toxicity of moxidectin to the treated animals was assessed by the clinical symptoms observed during the treatment period. The bone marrow exposure to the moxidectin was assessed by calculating the reduction in the percentage of polychromatic erythrocytes (PCE) in the total population of erythrocytes. The frequency of micronucleated polychromatic erythrocytes (MPCE) induced by moxidectin in the mouse bone marrow cells were determined in the PCE sub-population.

c. Findings: There were no statistically significant increases in the number of MPCEs at any dose level of moxidectin or harvest time when compared to the concurrently treated vehicle controls and no reductions (>20% of vehicle controls) in the percentage of PCE at any treatment level or harvest time except in the high-dose females at the 48-hour sacrifice point (23.8%).

d. Conclusion: The test material, moxidectin, was negative in the *in vivo* mouse micronucleus assay and is not considered to be a clastogenic agent in this test.

3. Mouse Lymphoma Mutagenesis Assay

a. Identification: Study performed by Kamala J. Pant and staff at SITEK Research Laboratories, Rockville, Maryland testing facility. Experimental period: September 23, 1998, to December 3, 1998. Fort Dodge Study No.: 971-98-147 (SITEK Study No.: 0504-2400).

b. Procedure: This *in vitro* test was performed to evaluate the potential for moxidectin to induce mutations at the thymidine kinase locus of the L5178Y TK+/- mouse lymphoma cells. Based on the results of the initial range-finding work, the definitive mutation assay was conducted at eight concentrations between 5 to 25 mcg/mL in a non-activated system and eight concentrations between 10 to 115 mcg/mL in the activated system. The activated system consisted of hepatic S9 from male Sprague Dawley rats treated with Arclor 1254. The cells were exposed to various concentrations of moxidectin for a period of four hours and after an expression period of 2-days, the cells were plated for determining the cloning efficiency and mutation frequency. The recommended toxicity levels necessary to qualify as a valid test were determined by assessing relative total growth (RTG) of the cultures. Based on the results of the definitive mutation assay, a confirmatory mutation assay with a 24-hour treatment was conducted in the absence of S9. The concentrations of the test material used in this confirmatory mutation assay ranged from 0.5 mcg/mL to 17.5 mcg/mL. Since the highest test article concentration of 17.5 mcg/mL had a RTG of 50% and 55% in replicate cultures, the assay was repeated at higher concentrations of 17.5 mg/mL to 20.5 mcg/mL of the test article. Vehicle controls (DMSO) and positive controls (Hycanthone without S-9 and DMBA with S-9) were concurrently run as part of each phase of this study.

c. Findings: All responses in both the definitive and confirmatory tests were negative and adequate mutagenic responses were achieved with the positive controls. In the definitive test the RTGs ranged from 7 to 93% and 25 to 88% with and without S-9 activation, respectively, and 17 to 53% in the confirmatory assay. The vehicle and positive controls in each portion of the assay produced acceptable colony size distributions.

d. Conclusion: The test material was negative in the *in vitro* Mouse lymphoma mutation assay and is not considered to be a mutagenic agent in this test.

B. Safe Concentration of Residues

The Acceptable Daily Intake (ADI) for moxidectin has been established as 0.004 mg moxidectin/kg/day. The studies that support the establishment of that ADI were presented in the original FOI Summary for NADA 141-099 dated January 28, 1998. The portion of the ADI to be set aside for milk is 37.5%.

The safe concentration (SC) for a drug in an edible tissue is generally determined using the ADI (in milligrams/kg body weight/day), the weight in kg

of an average adult (60 kg) and the estimated amount of each edible tissue consumed per day in kg according to the following relationship.:

SC (ppm) = ADI (mg/kg/day) x 60 kg ÷ edible tissue consumption (kg/day)

In consideration of the 37.5% set-aside for milk, the SC's for milk and tissues are given in equations (1) and (2), respectively.

(1) SC (ppm) = ADI (mg/kg/day) x 60 kg x 0.375 ÷ milk consumption (kg/day)
(2) SC (ppm) = ADI (mg/kg/day) x 60kg x 0.625 ÷ edible tissue consumption (kg/day)

The resulting SC's are shown below.

Food	Daily Consumption (kg)	Safe Concentration (ppm)
Milk	1.5 L	0.06 (or 60 ppb)
Muscle	0.3	0.5
Liver	0.1	1.5
Kidney	0.05	3.0
Fat	0.05	3.0

C. Total Residue and Metabolism

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. The following study defines the levels of total drug-related residues and metabolic profile of moxidectin in the milk of lactating cows treated with the pour-on formulation using [^{14}C]-moxidectin.

Study Number M97A423NM1

1. Title: Moxidectin (CL 301423): Residue Profile in the Milk of Cows Treated Topically with [^{14}C]-Moxidectin

2. Identification: In-life experimentation conducted by John Campbell, Ph.D., and staff at Southwest Bio-Labs, Inc., Las Cruces, New Mexico. Analytical component performed by Jalees Afzal, Ph.D., and staff at American Cyanamid's Princeton, New Jersey, testing facility. Experimental period: January 22, 1998, to September 10, 1998. Report MET 98-006.01.

3. Purpose: The purpose of this study was to determine the [^{14}C]-moxidectin residue profile and the ratio of parent compound to the total radioactive residues in the milk of cows following a single topical administration of moxidectin pour-on at the rate of 0.75 mg [^{14}C]-moxidectin/kg body weight, 1.5 times the approved use level for the pour-on formulation.

4. Design: Six lactating Holstein cows, three in the first trimester of lactation and three in the third trimester, were individually dosed one time at 1.5 mL/10 kg body weight with moxidectin pour-on containing radiolabeled moxidectin. Milk samples were collected at approximately 12 hour intervals twice immediately pretreatment and through 10 days post-treatment. Milk production for each cow was recorded at each milking. Total radioresidues (TRR) were determined in each sample by direct scintillation counting (limit of quantification: 4 ppb). Radioresidues were extracted from the samples with the highest TRR for four of the six treated cows and the TRR was partitioned by HPLC; peak TRR for two of the cows was too low to provide reliable partitioning data. The major components of the TRR were identified.

5. Findings: Peak TRR for individual milk samples ranging from 5 to 31 ppb were recorded at 5 to 7 days post-treatment for five of the cows, with residues peaking on Day 9 for the sixth cow.

   Because milk is pooled in the dairy industry before being marketed, daily averages of total residue levels were calculated in order to simulate drug residues in marketed milk. The pooled daily average residue peaked at 10.9 ppb total residues (moxidectin and structurally related compounds) at 8 days after administration of a 1.5X dose of moxidectin pour-on.

   The four samples with the highest radioresidues were extracted with acetonitrile and analyzed by HPLC using a gradient system. The extractabilities of the total carbon-14 residues in milk ranged from 88% to 99% for the four samples. Parent moxidectin accounted for an average of 77% of the TRR. Two metabolites were observed as minor components (<5%) of the residue. These have been identified in previous work as monohydroxylated derivatives of moxidectin: the C-29/C-30 hydroxymethyl metabolite and the C-14 hydroxymethyl metabolite. The metabolic profile for moxidectin in milk is very similar to that previously demonstrated in fat, the target tissue for moxidectin in cattle. These same samples were also analyzed by a method specific for moxidectin residues using HPLC with fluorescence detection. Using this technique, parent moxidectin accounted for an average of 68% of the total radioresidue.

6. Conclusions: Pooled daily average moxidectin-related residues in the milk of cows dosed at 1.5X the use level of moxidectin pour-on peak at 10.9 ppb, approximately six-fold below the safe concentration of 60 ppb. The parent molecule, which accounts for approximately 68% of the total residue in milk, is established as the marker residue. The primary metabolites in milk are monohydroxylated derivatives of the parent molecule, similar to those seen in tissues.

D. Selection of Marker Residue, Target Tissue, and Determination of Tolerances

The parent compound, moxidectin, was established as the marker residue and fat as the target tissue in the original NADA 141-099 FOI Summary dated January 28, 1998. As demonstrated in the previously summarized [^{14}C]-moxidectin metabolism study in lactating dairy cows, moxidectin is also the marker residue for milk.

For purposes of monitoring by the FSIS/USDA, tolerances of 50 ppb and 200 ppb for parent moxidectin in muscle and liver, respectively, of cattle were

established by FDA in the original NADA 141-099 FOI Summary dated January 28, 1998. These tolerances are unchanged. The ratio of parent moxidectin to total moxidectin-related residues in milk is 0.68. Therefore, a tolerance of 40 ppb for moxidectin in milk is obtained by multiplying the milk Safe Concentration of 60 ppb by this ratio.

E. Cold Residue Depletion Studies

The depletion of the marker residue in the edible tissues of cattle was described in the original NADA 141-099 FOI Summary dated January 28, 1998. Pivotal studies were conducted to determine the peak moxidectin residues in milk following the treatment of lactating cows and to determine the moxidectin residues in the tissues of offspring and in the milk of cows treated just prior to parturition.

Moxidectin Residues in the Milk of Cows Treated during Lactation

1. Title: Milk Residue Depletion in Lactating Dairy Cows Following Treatment with CYDECTIN® Moxidectin 0.5% Pour-on at a Dose Rate of 0.5 mg Moxidectin/kg Body Weight

2. Identification: Study performed by W. B. Epperson, DVM, and staff at American Cyanamid's Princeton, New Jersey, testing facility. Experimental Period: July 5, 1994 to August 5, 1995. Study No. 0863-B-US-1-94. Report No. GASD 02-40.00.

3. Purpose: The purpose of this study was to determine moxidectin residues in milk of cows treated with moxidectin pour-on at the recommended dose level of 0.5 mg moxidectin/kg body weight.

4. Design: Four multiparous and four primiparous lactating Holstein dairy cows (two high producers averaging 30 kg of milk per day and two low producers averaging 19.2 kg per day from each parity) were treated with a single application of moxidectin pour-on to provide the recommended dose of 0.5 mg moxidectin/kg body weight. The moxidectin pour-on formulation used in this trial was identical to that of the commercial product. Milk samples were obtained at each milking starting immediately prior to treatment and continuing for 28 days. Samples from the first 10 days post-treatment were analyzed for moxidectin using a validated HPLC method with a Limit of Quantification of 10 ppb. Pooled daily residues for each cow and for each post-treatment day were calculated.

5. Findings: Daily residues for individual cows peaked two to five days following dosing at levels ranging from 10 to 22 ppb. Measurable residues ($\leq$ 10 ppb) were found in the milk of only one cow by the 6^{th} day after treatment. Pooled daily average residues for the 8 cows peaked at 14.2 ppb on the second day of the study.

6. Conclusions: In this group of cows representing various parities and production levels and treated at the use level with moxidectin pour-on, the pooled daily average moxidectin

residue in milk peaked two days post-treatment at a level of 14.2 ppb, well below the tolerance for moxidectin in milk.

Moxidectin Residues in the Tissues of Neonatal Calves and in the Milk of Cows Treated prior to Parturition.

1. Title: Determination of Tissue Moxidectin Residues in Neonatal Calves Following the Treatment of Pregnant Cows with CYDECTIN® Pour-on

2. Identification: In-life phase conducted by Kim Ankenbauer-Perkins, DVM, and staff at Massey University, Palmerston North, New Zealand. Analytical component performed by Ms. B. Tierney, National Chemical Residue Laboratory, Upper Hutt, New Zealand. Study No. 0863-B-NZ-02-97. Report Nos. GASD 05-17.00 and GASD 05-17.01

3. Purpose: The purpose of this study was to determine whether treatment of cows in late pregnancy with Cydectin moxidectin Pour-on results in detectable moxidectin residues in edible tissues of newborn calves. Residues in the milk of periparturient cows were also determined.

4. Design: Dairy cows in late gestation were treated with moxidectin 0.5% pour-on at a rate to provide the approved dose of 0.5 mg moxidectin/kg body weight. The moxidectin pour-on formulation used in this trial was identical to that of the commercial product except that it did not contain a dye. A total of 18 calves born 3 to 21 days after the cows were treated were selected for this study. Calves were removed from their dams within 24 hours of birth and fed pooled colostrum from treated cows until sacrifice, generally at three to four days of age (one calf sacrificed at five days of age). Samples of liver and fat were collected and analyzed for moxidectin using a validated HPLC/fluorometric detection method with a limit of detection of 2 ppb. Milk samples were collected from 9 cows, calving between 3 and 11 days post-treatment, within 24 hours of calving (colostrum, Day 1) and once daily on Days 2, 3, 4 and 7 post-calving and analyzed for moxidectin residues using a similar assay method.

5. Findings: The highest moxidectin residue in both fat (146 ppb) and liver (10 ppb) were found in calves born three days after cows were treated. Residue levels declined steadily as the time between treatment and birth increased. Liver residues were ≤ 2 ppb (LOQ) in all calves born 11 to 21 days after the cows were treated while residues in fat were down to 11 ppb for the calf born 21 days after dam treatment.

   Log transformed residue data for both fat and liver were regressed over time. The predicted residue levels in fat and liver of calves born 3 days after cow dosing are 108 ppb and 8.4 ppb, respectively.

   The highest moxidectin levels in milk were detected over the period of three to six days post-treatment. The residue in the Day 1 milk (colostrum) of one cow that calved 3 days post-treatment was 16 ppb. Moxidectin residues averaged approximately 11 ppb during the 4 to 6 day post-treatment period when colostrum/milk samples from four to six cows were available for moxidectin analysis.

6. Conclusions: Residues in the tissues of calves born to cows treated with moxidectin pour-on present no human health risk. Predicted residues in fat are approximately 40-fold below the safe level for moxidectin in fat tissue. The predicted residue for liver is approximately

25-fold below the established tolerance of 200 ppb for moxidectin in liver. Peak average residues in milk from periparturient cows are well below the safe concentration of moxidectin in milk.

F. Assignment of Zero Tissue and Milk Withdrawal Periods

The original NADA 141-099 FOI Summary dated January 28, 1998, established that no withdrawal period is required for edible tissues of cattle treated with Cydectin Pour-on at the approved use level. The partitioning of 37.5% of the ADI for moxidectin (90 mcg of the total 240 mcg for the average 60 kg person) away from tissues for milk does not change the withdrawal time for tissues. Based on statistical analysis of the data in Study No. 0863-B-US-1-94, peak moxidectin residues in the milk of lactating cows treated with Cydectin Pour-on at the approved use level are below the tolerance of 40 ppb moxidectin in milk. Therefore, no withdrawal time is required for milk from cows treated according to label directions with Cydectin Pour-on.

G. Regulatory Methods

Since no post-treatment withdrawal time is necessary for the edible tissues or milk from cattle treated at the approved level of 0.5 mg moxidectin/kg body weight with Cydectin Pour-on, no official regulatory methods for tissues or milk are required. A sponsor-validated research method for moxidectin in milk is on file with the Center for Veterinary Medicine.

H. User Safety Statement

User safety information appears in the original NADA 141-099 FOI Summary dated January 28, 1998. 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 dairy cattle, when administered topically at a dose of 500 mcg/kg bodyweight.

For cattle, tolerances of 200 ppb for parent moxidectin (marker residue) in liver (target tissue) and 50 ppb in muscle are codified at 21 CFR 556.426. Neither a per-slaughter drug withdrawal period nor a milk discard time are required. As described in Section IV., a tolerance of 40 ppb is established for parent moxidectin in milk.

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 considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and an environmental impact statement is not required. The Agency's finding of no significant impact and the evidence supporting the finding are contained in an environmental assessment that may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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.