

**Petition for Evaluation of Moxidectin for Inclusion on the National List of  
Substances Allowed in Organic Production and Handling**

*Introduction*

Moxidectin, a potent broad-spectrum endectocide (endo-and ectoparasiticide), is a semi-synthetic methoxime derivative of LL F-28249 $\alpha$  (F-alpha). F-alpha is a fermentation product of *Streptomyces cyaneogriseus* subsp. *noncyanogenus*. Structurally, moxidectin is a 16-member, second generation pentacyclic lactone of the milbemycin class of compounds. It is approved globally as an injectable for cattle and sheep, a pour-on for cattle and deer, an oral drench for sheep, an oral gel for horses, a tablet for dogs, and an injectable (sustained release) suspension for dogs.

Fort Dodge Animal Health hereby submits this petition for inclusion of moxidectin on the National List as a Synthetic substance allowed for use in organic livestock production. The required information, as stipulated in the Federal Register, Volume 65, No. 135 dated July 13, 2000, pp43259 – 43261, immediately follows.

1. **Common name:** (2aE,4E,5'R,6R,6'S,8E,11R,13S,15S,17aR,20R,20aR,20bS)-6'-[(E)-1,2-Dimethyl-1-butenyl]-5',6,6',7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5'6,8,19-tetra-methylspiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2'-[2H]pyrano]-4',17(3'H)-dione,4'-(E)-(O-methyloxime)

USAN designation: 23-(O-Methyloxime)-F28249- $\alpha$ , or 3-(O-Methyloxime)-F28249-alpha

Other names include: Moxidectin, Moxidectin Solid, Moxidectin Technical Material

2. **Manufacturer's name, address and telephone number:**

Moxidectin is manufactured at the Fort Dodge Animal Health facility in Catania, Italy:

Fort Dodge Animal Health  
Division of Wyeth-Lederle S.p.A.  
Via Franco Gorgone,  
Zona Industriale  
95030 Catania  
Italy  
Tel: 390-9559-8111

3. **Intended and current use:** Moxidectin is used as an endectocide, with demonstrated potent activity against a broad spectrum of internal and external parasites of cattle.
4. **A list of the crop, livestock or handling activities for which the substance will be used. If used for crops or livestock, the substance's rate and method of application must be described. If used for handling (including processing), the substance's mode of action must be described.**

Moxidectin is approved for use in both beef and dairy cattle for the treatment and control of various existing parasitic infections and infestations, including several species of gastrointestinal roundworms, lungworms, lice, mites, horn flies and cattle grubs. Moxidectin also effectively protects treated cattle from reinfection with several species of roundworms. The dose rate is 0.5 mg moxidectin/kg body weight, and is applied topically along the dorsal midline of the animal.

Moxidectin was approved for use in cattle by the Center for Veterinary Medicine, the veterinary arm of the FDA, in 1998 and is registered around the world, in all major markets, including the 15 member states of the European Union, Australia, New Zealand, Canada, and Japan. Moxidectin tolerances have been established for many edible tissues, including fat, muscle, liver, kidney and milk. When formulated into a Pour-On formulation for cattle in The United States, no withdrawal period prior to slaughter, and no milk withholding period, is required.

Moxidectin is a veterinary pharmaceutical product for the control of internal and external parasites of cattle. Moxidectin is not used in the handling or processing of livestock.

5. **The source of the substance and a detailed description of its manufacturing or processing procedures from the basic component(s) to the final product. Petitioners with concerns for confidential business information can follow the guidelines in the Instructions for Submitting Confidential Business Information (CBI) listed in Item #13.**

CBI

**6. A summary of any available previous reviews by State or private certification programs or other organizations of the petitioned substance.**

Moxidectin has not been reviewed by State or private certification programs.

**7. Information regarding EPA, FDA, and State regulatory authority registrations, including registration numbers.**

Moxidectin-containing products are regulated in the United States by the Center for Veterinary Medicine (CVM, the veterinary branch of FDA). The following products are approved for use in the United States, and their New Animal Drug Application designations (NADA numbers) are provided for each product.

<b>Product</b>	<b>NADA Number</b>
CYDECTIN® Pour-On for Cattle	141-099
QUEST® Gel for Horses	141-087
ProHeart® Tablets for Dogs	141-051
ProHeart® 6 Injectable for Dogs	141-189

CYDECTIN Pour-On and QUEST Gel are both over-the-counter products, whereas both ProHeart products are prescribed by veterinarians.

The above-referenced CVM-approved products are also approved world-wide in all major markets.

**8. CAS Registry Number or other product numbers of the substance and labels of products that contain the petitioned substance.**

CAS Registry number: 113507-06-5

Facsimile copies of the package inserts for moxidectin-containing products are provided in **Attachment 1**. These include:

CYDECTIN® Pour-On for Cattle  
QUEST® Gel for Horses  
ProHeart Tablets for Dogs  
ProHeart 6 Injectable for Dogs

Only the package inserts are provided, as this labeling component is the most comprehensive and inclusive of all labeling components (e.g., cartons, vials, syringes). The package insert that is the most relevant to this petition is that for CYDECTIN® Pour-On for Cattle.

9. The substance's physical properties and chemical mode of action including (a) chemical interactions with other substances, especially substances used in organic production; (b) toxicity and environmental persistence; (c) environmental impacts from its use of manufacture; (d) effects on human health; and, (e) effects on soil organisms, crops, or livestock.

The physico-chemical properties of moxidectin are described below.

Appearance	White to pale yellow powder
Melting point (liquefaction)	145 – 154°C
Vapor pressure	<3.2 x 10 <sup>-8</sup> Torr (limit of detection)
Bulk density	
Untapped	0.42 g/mL
Tapped	0.56 g/mL
Hygroscopicity	0.6 – 1.1%
Solvation	Non-hydrating
Octanol/water partition coefficient	58,300

These properties directly influence the fate of moxidectin in the environment. For instance, the high melting point and very low vapor pressure indicate that moxidectin is non-volatile and will not spread away from areas of use through the atmosphere. The large *n*-octanol/water partition coefficient of moxidectin indicates that the compound is lipophilic, thus confirming its poor water solubility.

- a) Chemical interactions with other substances, esp substances used in organic production

Moxidectin is slightly soluble in water, 0.51 mg/L; solubility is not affected by change in pH. It is readily soluble in a variety of organic solvents, as tabulated below.

Solvent	Solubility (mL solvent/g moxidectin)
Dichloromethane	1.64
Diethyl Ether	1.19
Ethanol (95%)	0.81
Acetonitrile	0.62
Ethyl Acetate	0.47

For the treatment of cattle, moxidectin is formulated into a pour-on formulation that is topically applied to animals individually. Therefore, there is no direct interaction of moxidectin with any other substances used in the organic production of cattle. The following two summaries of the fate of moxidectin when combined with soil provide information regarding its degradation half life, and its ability to bind to soil. The latter study demonstrates the strong binding of moxidectin to soil, resulting in the virtual elimination of its availability to the environment.

Soil degradation: A soil degradation study was conducted by adding  $^{14}\text{C}$ -moxidectin to each of three soils and aging them under aerobic conditions for 63 days. During the aging period the  $^{14}\text{C}$ -moxidectin was extensively degraded, with 5.24%, 1.59% and 1.16% of the applied dose being mineralized (converted) to  $^{14}\text{CO}_2$  in soils from Indiana, New Jersey and Wisconsin, respectively. After 63 days of incubation, moxidectin accounted for 47, 44, and 57% of the applied dose in the Indiana, New Jersey and Wisconsin soils. These findings indicate that moxidectin is biodegradable in soils. There were at least 10 degradation products formed, most of which were at trace levels. Half-lives of approximately two months under these conditions indicate that moxidectin is not expected to persist in the environment. The properties of the soils are given in the following table.

**Composition of Solids Tested**

Type & Texture	Composition					pH	C.E.C
	% Sand	% Silt	% Clay	% O.M.	% O.C.		
Sassafras sandy loam <sup>1</sup>	62.8	25.6	11.6	1.0	0.58	6.9	5.9
Piano loam <sup>2</sup>	32.8	47.6	19.6	2.4	1.39	7.1	7.46
Tippecanoe silt loam <sup>3</sup>	32.8	49.6	17.6	3.1	1.80	6.9	20.06

Soil origin: <sup>1</sup>New Jersey, <sup>2</sup>Wisconsin, <sup>3</sup>Indiana

O.M. = organic matter; O.C. = organic carbon; C.E.C. = cation exchange capacity

Soil adsorption: The adsorption of moxidectin onto four different soils was investigated using the batch equilibrium technique. Initial concentrations of  $^{14}\text{C}$ -moxidectin of 0.044, 0.084, 0.455 and 0.983 ppm in 0.01 M calcium chloride were used. The soil and the moxidectin solutions were mixed, shaken continuously for two days at room temperature, centrifuged and the concentration of moxidectin in the adsorption solution was measured. Fresh 0.01 M calcium chloride was added and the desorption of moxidectin from soil was studied using the same procedures used in the adsorption phase. After the desorption phase, the amount of  $^{14}\text{C}$ -moxidectin remaining in the soil was determined. The adsorption coefficients, normalized for the % organic carbon in the soil (Koc), are shown in the following table. The Koc values of these soil samples ranged from 18,000 to 41,000, indicating a strong binding of moxidectin to soils.

### Adsorption of Moxidectin to Soils

Type & Texture	Composition					pH	C.E.C	Koc
	% Sand	% Silt	% Clay	% O.M.	% O.C.			
Buelah loamy sand <sup>1</sup>	80.0	15.6	3.6	0.5	0.29	6.5	3.4	41379
Sassafras sandy loam <sup>2</sup>	62.8	25.6	11.6	1.0	0.58	6.9	5.9	28448
Piano loam <sup>3</sup>	32.8	47.6	19.6	2.4	1.39	7.1	7.46	20215
Tippecanoe silt loam <sup>4</sup>	32.8	49.6	17.6	3.1	1.80	6.9	20.06	18666

Soil origin: <sup>1</sup>Arkansas, <sup>2</sup>New Jersey, <sup>3</sup>Wisconsin, <sup>4</sup>Indiana

O.M. = organic matter; O.C. = organic carbon; C.E.C. = cation exchange capacity

#### b) Toxicity and environmental persistence

Please also refer to Section 9a).

*Soil mobility:* The mobility of moxidectin (<sup>14</sup>C-labeled) was assessed in four different soils using soil thin layer chromatography. Soil coated (1 mm) plates were used with water as the mobile phase. The very small Retardation Factor (RF) values indicated that moxidectin-soil complex could not be separated by the thin layer chromatography. All four soil types were given a 1 classification with moxidectin under the Helling method, indicating that the binding of moxidectin to soils is so tight that the complex is characterized as an immobile compound.

### Mobility of Moxidectin in Soils

Type & Texture	Composition					pH	C.E.C	RF
	% Sand	% Silt	% Clay	% O.M.	% O.C.			
Buelah loamy sand <sup>1</sup>	80.8	15.6	3.6	0.5	0.29	6.5	3.4	0.07
Sassafras sandy loam <sup>2</sup>	62.8	25.6	11.6	1.0	0.58	6.9	5.9	0.08
Piano loam <sup>3</sup>	32.8	47.6	19.6	2.4	1.39	7.1	7.46	0.07
Tippecanoe silt loam <sup>4</sup>	32.8	49.6	17.6	3.1	1.80	6.9	20.06	0.07

Soil origin: <sup>1</sup>Arkansas, <sup>2</sup>New Jersey, <sup>3</sup>Wisconsin, <sup>4</sup>Indiana

O.M. = organic matter; O.C. = organic carbon; C.E.C. = cation exchange capacity

Retardation Factor (RF) = distance traveled by compound/distance traveled by water front

*Photodegradation:* The photodegradation of moxidectin in aqueous solutions was studied using both sunlight and a high-pressure xenon-arc lamp which was filtered to

remove light <290 nm to simulate sunlight. The sunlight study was conducted in NJ in late autumn (November). Due to the low solubility of moxidectin in water (i.e., < 1 ppm), acetonitrile (1%) was used as a cosolvent to help keep moxidectin in solution. Foil wrapped samples were used as dark controls. The initial concentration of moxidectin was measured and additional determinations made every two hours until termination of the study after 14 hours exposure. There was a reduction in the measured moxidectin concentration from 97% to 22% of the applied dose after 12 hour exposure to natural sunlight, and a reduction from 94% to 19% of the applied dose after 14 hour exposure to the xenon-arc lamp. The calculated half-lives were 6.8 hours and 5.6 hours, respectively. The half-life from the spring to early fall would be even more rapid due to the longer and more intense exposure to sunlight. This rapid photodegradation in water will rapidly degrade moxidectin entering the aquatic environment. Several photodegradation products were observed, but were not identified since each accounted for less than 10% of the applied dose.

Summary of environmental fate of moxidectin: Because of the very low water solubility, high n-octanol/water partition coefficient, high melting point, high degree of adsorption to soil, and biodegradation by microorganisms in soils, moxidectin is not expected to move from fields into surface water. Even being washed off from soil or feces, moxidectin will subsequently undergo photodegradation and bind to other suspended soil particles, plants and any materials in water. This secondary binding process will result in a continuous depletion of free moxidectin from the environment. In addition, because of the very strong binding to soil particles, the water bed would prevent the moxidectin from entering and contaminating groundwater.

### **Toxicity of Moxidectin to Dung Insects**

The dung ecosystem is comprised of a diverse population of invertebrates and microorganisms. It consists of a patchy and ephemeral habitat, characterized by severe competition, and complex behavior in many similar species living together. Dung beetles constitute one of the animal populations of importance in the dispersal and breakdown of dung. Dung beetles are often exceedingly abundant. Thousands of individuals and dozens of species may be attracted to single droppings in both temperate and tropical localities. A number of species of dung beetles (especially Scarabaeidae) have been introduced throughout the world to aid in the environmental recycling of the dung of domestic animals. The effects of moxidectin on dung insects has been extensively studied. The results of these studies are summarized herein; the references for many of these studies are provided in **Attachment 4**, in response to item #11 (Research information).

#### **Summary: Toxicity of Moxidectin to Dung Insects**

Two comprehensive studies were undertaken whose results demonstrate that moxidectin residues in dung of treated animals occur at levels below those that are toxic to indicator beetle and fly species which dwell or breed in dung. Two *in vitro* bioassays determined NOEL and toxic level for the dung beetles *Onthophagus*



*gazella* and *Euoniticellus intermedius*, and for the dung breeding fly *Haematobia irritans exigua*. The results of the *in vitro* bioassay studies are tabulated in the table below.

**Toxicity Assessment of Moxidectin on Two Dung Beetle Species**

Species	NOEC	EC <sub>50</sub>
<i>Onthophagus gazella</i> adult	> 500 ppb	Can not determine
<i>Onthophagus gazella</i> progeny	> 500 ppb	2567.7 ppb
<i>Euoniticellus intermedius</i> adult	> 500 ppb	Can not determine
<i>Euoniticellus intermedius</i> progeny	> 269 ppb	469.3 ppb

The results of the study assessing the comparative larvicidal effect of moxidectin and abamectin against *Onthophagus gazella* and the buffalo fly, *Haematobia irritans exigua* De Meijere (the fly species most sensitive to moxidectin) are displayed in the following table.

**Survival of larval and pupal *H. irritans exigua* and oviposition and larval survival of *Onthophagus gazella* in dung containing various concentrations of moxidectin and abamectin.**

Treatment	<i>H. i exigua</i> Mean % Pupation (SE)	<i>H. i exigua</i> Mean % Eclosion (SE)	<i>O. gazella</i> Mean No Brood Balls (SE)	<i>O. gazella</i> Mean % Survival to Adult (SE)
<b>Moxidectin ppb</b>				
4	38 (9.7)	99 (0.8)	48 (2.8)	89 (4.1)
8	55 (4.3)	98 (0.8)	49 (10.4)	81 (5.1)
16	50 (6.5)	99 (0.7)	44 (2.7)	89 (4.4)
32	50 (9.0)	98 (1.0)	56 (5.1)	87 (3.6)
64	47 (5.3)	97 (0.9)	56 (6.4)	87 (4.0)
128	24 (3.2)	92 (3.4)	61 (6.1)	81 (3.2)
256	13 (1.8)	96 (2.5)	64 (1.8)	61 (5.3)
512	0 (0)	na	70 (11.1)	7 (2.5)
<b>Abamectin ppb</b>				
4	1 (0.8)	83 (16.7)	42 (5.9)	57 (6.8)
8	0*	na	53 (3.2)	5 (1.9)
16	0*	na	44 (6.8)	0*
32	0*	na	49 (6.0)	0*
64	0*	na	nt	nt
128	0*	na	nt	nt
256	0*	na	nt	nt
512	0*	na	nt	nt
<b>Control</b>				
	62 (8.2)	96 (1.4)	46 (6.2)	72 (4.2)

\* excluded from analysis

na = not applicable

nt = not tested

Average dung residues exceeded the NOEL for *H. i. exigua*, the most sensitive fly species, immediately following treatment, but were below the EC<sub>50</sub> except for a period of approximately 24 hours two days after treatment. Average dung are estimated to be below the NOEL for *H. i. exigua* by approximately 16 days following treatment. Levels of moxidectin 64 fold higher than abamectin were needed to elicit a comparable toxic effect. These data are summarized in the table below.

**Toxicity of Moxidectin to Dung Insects**

Species	NOEC	EC <sub>50</sub>
<i>Onthophagus gazella</i> adult	> 500 ppb	Can not determine
<i>Onthophagus gazella</i> progeny	> 500 ppb	2567.7 ppb
<i>Euoniticellus intermedius</i> adult	> 500 ppb	Can not determine
<i>Euoniticellus intermedius</i> progeny	> 269 ppb	469.3 ppb
<i>H. irritans exigua</i>	64 ppb	134 ppb

Additional studies were conducted, using beetle and fly bioassays on dung from animals treated with commercial formulations of moxidectin, at the recommended commercial dose rate. Details are not included as these studies employed various formulated products, rather than the active substance, moxidectin, alone. The results of these studies are summarized herein. These studies also included one or more of the avermectins, not only for outright comparisons, but also to demonstrate that the assays used were sensitive enough to detect adverse effects of macrocyclic lactones, if they were present. In all cases the assays were valid, in that toxic effects were evident with the avermectins, and these were consistent with previously published literature. The effects of moxidectin residues generally were not significantly different from controls, although in a number of studies, a slight improvement in viability of dung dwelling insects was observed. The studies covered indicator species of the three main families of dung beetles, the Aphodiidae, Scarabaeidae and Geotrupidae. The studies also assessed a range of dung dwelling flies, including three species of *Musca inferior*, *Neomyia cornicina*, *Stomoxys calcitrans*, *Haematobia irritans exigua* and *Orthelia timorensis*. *Haematobia irritans* was determined to be the most sensitive to effects of macrocycle lactones. Bioassays were not conducted on the parasitic beetles such as Staphylinidae or Hydrophilidae, since unlike with avermectins, there was no detectable effect on the prey of these species.

Assessment of potential effects of moxidectin was not limited to juvenile and adult lethal effects, but also included measurement of sub-lethal effects which may affect the reproductive performance of beetles into a subsequent generation. The beetles exposed to dung from moxidectin treated cattle were indistinguishable from controls.

Field evaluations of dung colonization and degradation were conducted in two different climatic regions, the northern temperate zone, and a warm Mediterranean zone, as was a colonization study in a wet tropical zone in order to confirm that, as expected from the above results, there was no effect on either colonization or dung degradation in any type of climate. As expected, the colonization and degradation rates for dung from moxidectin treated animals was indistinguishable from controls.

A further evaluation was done, using a computer simulation model, to predict any potential disruption to dung beetle populations. The model was run to assess not only differing effects based on beetle breeding cycle (univoltine versus multivoltine species) but also the potential impact of the timing of treatment of cattle in relation to median emergence time of beetle species. The computer prediction based on multiple simulations is that effects of moxidectin dung are indistinguishable from untreated controls.

The differential activity observed between moxidectin and the avermectins is consistent with expectations, based on *in vitro* molecular binding studies, which show that avermectins bind to insect brain and thorax/abdomen receptors at much lower concentrations than moxidectin.

The evaluation of potential moxidectin residue effects has been conducted in keeping with published recommendations for the assessment of disruptions to soil ecosystems, and indicates that no adverse effects are expected on insects which dwell in, breed in or feed on dung and therefore there is no disruption to colonization numerically or in diversity. The colonization and degradation of such dung is not distinguishable from control dung.

### Toxicity of Moxidectin to Terrestrial Organisms

#### **Toxicity of Moxidectin to Avian Species**

Birds may ingest the components of cattle dung pats, dung insects, plants and/or earthworms which may be contaminated with moxidectin. Therefore, the toxicity of moxidectin to various avian species was investigated.

Bobwhite quail: The acute toxicity of moxidectin, when administered as a single oral dose, was determined for the bobwhite quail. The test was conducted in accordance with US EPA protocol FIFRA Guideline No. 71-1. Moxidectin was administered to 24-week old bobwhite quail (*Colinus virginianus*) at the dose range of 0 - 681 mg/kg body weight. Results concluded that the 21-day acute oral median lethal dose (LD<sub>50</sub>) was 278 mg/kg body weight.

Mallard duck: The acute toxicity of moxidectin, when administered as a single oral dose, was determined for the mallard duck. Moxidectin was administered to 33-week old mallard ducks (*Anas platyrhynchos*) at the dose range of 0 - 464 mg/kg body weight. The test was conducted in accordance with US EPA protocol FIFRA Guideline No. 71-1. The calculated 21-day acute oral median lethal dose (LD<sub>50</sub>) was 365 mg/kg.

Chicken: The acute toxicity of moxidectin, when administered as a single oral dose, was determined for the chicken. Moxidectin was administered to 2-5 week old Peterson x Arbor Acres chicken at the dose range of 0 - 400 mg/kg body weight. Results concluded that the 14-day oral lethal dose (LD<sub>50</sub>) was 283 mg/kg body weight.

Summary: Based on the LD<sub>50</sub> levels of moxidectin for these 3 representative avian species as summarized in the following table, birds would have to consume hundreds of kg of soil, feces and/or dung insects containing moxidectin in order to reach the toxic level through feeding. Therefore, moxidectin is highly unlikely to cause any adverse effects on birds when used according to the product label.

**Toxicity of Moxidectin on Avian Species**

Test Species	Test Parameter	Results
Bobwhite Quail	21 day acute oral LD <sub>50</sub>	278 mg/kg bw
Mallard Duck	21 day acute oral LD <sub>50</sub>	365 mg/kg bw
Chicken	14 day acute oral LD <sub>50</sub>	283 mg/kg bw

## Toxicity of Moxidectin to Aquatic Species

While moxidectin binds tightly to soil, it is theoretically possible that moxidectin can be washed off into ponds or waterways from the feces of treated cattle or from soil contaminated with moxidectin. Therefore, the potential toxicity of moxidectin to living aquatic organisms is discussed in this section.

Green algae:: The effects of moxidectin on the growth of green algae (*Selenastrum capricornutum*) were studied over three days in accordance with OECD Guideline G 201. The effects were studied using a control, a solvent control and solution of moxidectin at nominal concentrations of 9.38, 18.8, 37.5, 75.0 and 150 µg ai/L in a synthetic algal assay nutrient medium. The mean measured concentration of moxidectin were 5.1, 10.0, 17.6, 39.5 and 86.9 µg ai/L, respectively. The highest concentration studied corresponding to the maximum solubility level in the test medium. The test was conducted under static, non-renewal conditions at 24±2°C with continuous illumination (4306 lux). Test vessels (500 mL Erlenmeyer flasks with 100 mL of test solution) were continually shaken. The effects on growth were evaluated by comparing the area under the growth curves in the treated solutions with the control groups. A statistical difference was noted between the blank and solvent controls. Therefore, the percentage growth inhibition was calculated against the growth in the solvent control. The 72-hour EC<sub>50</sub>, based on measured concentrations was > 87 ppb which was the highest concentration tested. The NOEC of moxidectin to the green algae was not determined due to its limit of solubility in the test conditions. During the study there were significant decreases in the concentration of moxidectin from the treatment solutions. This decrease is consistent with the finding that moxidectin is rapidly photodegraded.

Water flea: The toxicity of moxidectin to the water flea (*Daphnia magna*) was determined using a flow-through test over 48 hours of exposure. The test was conducted in accordance with US EPA guidelines, and used a control, a solvent control and solutions of moxidectin at nominal concentrations of 6.5, 11, 18, 30 and 50 ng ai/L. For each concentration studied, 20 daphnia were used with monitoring conducted at 24-hour intervals. The 48-hour LC<sub>50</sub> was 30.2 ppt (ng/L), while the NOEC was 11 ppt (ng/L).

Bluegill The toxicity of moxidectin to the bluegill (*Lepomis macrochirus*) was determined using a flow-through test over 96 hours of exposure. The test was conducted in accordance with US EPA guidelines, and used a control, a solvent control and solutions of moxidectin at nominal concentrations of 0.65, 1.1, 1.8, 3.0 and 5.0 µg ai/L. The mean measured concentrations of moxidectin were 0.52, 0.71, 1.1, 2.0 and 3.2 µg ai/L, respectively. For each concentration studied, 20 fish were used with monitoring conducted at 24-hour intervals. The 96-hour LC<sub>50</sub>, based on measured concentrations was 0.62 ppb (µg/L), while the NOEC was < 0.52 ppb, the lowest concentration tested.

Rainbow trout: The toxicity of moxidectin to the rainbow trout (*Oncorhynchus mykiss*) was determined using a flow-through test over 96 hours of exposure. The test was conducted in accordance with US EPA guidelines, and used a control, a solvent control and solutions of moxidectin at nominal concentrations of 0.26, 0.43, 0.72, 1.2 and 2.0 µg ai/L. The mean measured concentrations of moxidectin were 0.15, 0.22, 0.43, 0.71 and 1.2 µg ai/L, respectively. For each concentration studied, 20 fish were used with monitoring conducted at 24-hour intervals. The 96-hour LC<sub>50</sub>, based on measured concentrations was 0.16 ppb (µg/L), while the NOEC was < 0.15 ppb, the lowest concentration tested.

Summary: The toxicity of moxidectin to various aquatic species are summarized in the table below. The water flea (*Daphnia magna*) is the most sensitive species with its 48-hour EC<sub>50</sub> of 30 ppt and NOEC of 11 ppt. The concentrations at which toxicity is observed in these tests would be regarded as the "worst-case" values because several factors, such as binding to sediment and suspended particulate matter, and photo-degradation, which greatly reduces moxidectin exposure in field conditions, were not factored into these studies. Even under this worst case scenario and based on the US EPA Feedlot and Run-off Model, the maximum moxidectin PEC in water is 6.2 ppt (without adsorption) and 0.275 ppt (with adsorption), which is lower than all LC<sub>50</sub> values for these species including the water flea, the most sensitive aquatic species.

**Toxicity of Moxidectin on Aquatic Species**

Test Species	Test Parameter	Results
Green Algae	72-hour EC <sub>50</sub>	> 87 ppb
Water Flea	48-hour EC <sub>50</sub>	30 ppt
	NOEC	11 ppt
Bluegill	96-hour LC <sub>50</sub>	0.62 ppb
	NOEC	< 0.52 ppb
Rainbow Trout	96-hour LC <sub>50</sub>	0.16 ppb
	NOEC	< 0.15 ppb

The moxidectin PEC of 6.2 ppt (without adsorption) and 0.275 ppt (with adsorption) in water was estimated under the worst case scenario in which the metabolism and degradation of moxidectin are not factored into the calculation. In reality, the concentration of moxidectin would be much less than these calculated estimates. Therefore, it is extremely unlikely that there would be any significant toxic impact on aquatic living organisms in aquatic ecosystems as a result of using the moxidectin injectable solution according to the product label.

c) Environmental impacts from its use or manufacture

Approval by the FDA of the four moxidectin-containing products described in item #7 included a review and the publication of an Environmental Assessment (EA) for each product with regard to its use or manufacture. The publication of these EAs and the FDA review of these EAs is contained in the Freedom of Information Summary

for each product. In all cases, the FDA concluded that “the use of CYDECTIN® (moxidectin) 0.5% Pour-On for cattle is not expected to have a significant impact on the human environment.”

d) Effects on human health

The toxicological potential of moxidectin has been evaluated during numerous global regulatory processes since the first registration of a moxidectin based product. The most extensive toxicological review of moxidectin was during the 45<sup>th</sup> meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The studies reviewed by JECFA provide the basis for determining the amount of moxidectin (derived from residue in edible tissues from treated animals) that is safe for humans to consume (ADI, or *Acceptable Daily Intake*). A tabular summary of that review is listed in the following table and is the basis of this summary.

**Toxicity Studies with Moxidectin**

<b>Species, Study and Doses Tested (MKD)</b>	<b>NOEL mg/kg</b>
<b>Mouse (CD-1)</b> 28-Day – Diet (0, 6.9, 17.7, 23.2, 24.1, 32.2) 2-Year – Diet (0, 2.49, 5.10, 11.87/7.89)	6.9 5
<b>Rat (Crl:CD)</b> 28-Day – Diet (0, 12.2, 22.8, 26.4, 31.2) 90-Day – Diet (0, 1.95, 3.90, 7.99, 12.23) 2-Year – Diet (0, 0.8, 3.2, 9.8/5.1) Teratology – Gavage (0, 2.5, 5, 10, 12)  3-Generation – Diet (0, 0.07, 0.15, 0.41, 0.83)	<12 4 6 5 5 0.4 0.4
<b>Rabbit</b> Teratology – Gavage (0, 1, 5, 10)	1 10
<b>Dog</b> 28-Day – Diet (0, 0.5, 2, 4/1.25) 91-Day – Diet (0, 0.3, 0.9, 1.6) 52-Week – Diet (0, 0.25, 0.49, 1.12)	0.5 0.3 1.1

Genotoxicity

The genotoxicity of moxidectin has been evaluated in a variety of tests. Negative results were obtained when moxidectin was tested in the Ames test, in reverse and forward mutation assays with *E. coli*, or in a test using mammalian cells for chromosome aberrations in rat bone marrow cells. Moxidectin did not induce unscheduled DNA synthesis in primary rat hepatocytes.

### Acute Toxicity

Moxidectin was considered to be moderately toxic after oral and interperitoneal (IP) administration to rats and mice in acute toxicity testing. The main clinical sign in mice administered a toxic dose of moxidectin was decreased activity. Animals observed with decreased activity had recovered by 4 days after treatment. Post-mortem evaluation of animals that had died or were sacrificed after 14 days showed no gross abnormalities. In rats, toxic doses resulted in decreased activity, prostration, tremors, chromodacryorrhea, decreased respiration, diarrhea, hypersensitivity to touch and sound, and epistaxis. In post mortem examination, congestion of the liver, kidneys and lungs were observed in animals that died during the test, but for animals that survived to sacrifice at 14 days, no abnormalities were observed.

Dermal application of moxidectin to rabbits had overt toxicity.

### **Acute Toxicity Studies with Moxidectin**

Species	Sex	Route	LD <sub>50</sub> (mg/kg b.w.)
Mouse	M & F	Oral	84
	F	Oral	42
	F	Oral	50
	M & F	i.p.	86
	M & F	s.c.	263
Rat	M & F	Oral	106
	M & F	i.p.	394
	M & F	s.c.	>640
	M & F	inhal.	3.28 mg/l (5 h LC <sub>50</sub> )

### Subchronic Toxicity

In mice, the subchronic toxicity of moxidectin was evaluated in a 28-day study. Mice were given 0, 6.9, 18, 23, 24 or 32 mg moxidectin/kg BW/day. High mortality (80-100%) was observed in the 3 highest dose groups. Only 1 animal died in the 18 mg/kg BW group with no mortality observed in the remaining groups. Other signs of toxicity included tremors, hypersensitivity to touch and urine stained fur in the 18, 23 and 24 mg/kg BW groups. No effects were observed on hematology, relative or absolute organ weights, or in gross or microscopic evaluation of the tissues. The NOEL in this study was 6.9 mg/kg BW/day.

In rats, subchronic toxicity was evaluated at 28 days (0, 12, 23, 26 or 31 mg moxidectin/kg BW/day) and 13 weeks (0, 1.9, 3.9, 7.9 or 12 mg moxidectin/kg BW/day). Clinical observation, mortality, organ evaluation, feed intake, hematology, clinical chemistry and urinalysis were used to evaluate toxicity. In the



28-day study, mortality was seen in the 2 highest dose groups (100%). Two female rats died in the 23 mg moxidectin/kg groups. There was no mortality in the lowest dose group. No NOEL was assigned in this study due to hypersensitivity to touch which was observed in the lowest dose group. In the 13 week study, 3 females in the highest dose rate died or were sacrificed in moribund condition. Other signs of toxicity observed in some groups included decreased food intake, ataxia, tremors, salivation, piloerection, hypersensitivity to touch and diuresis. The assigned NOEL was 3.9 mg moxidectin/kg BW/day.

The toxicity of moxidectin in dogs was evaluated in a 28-day (0, 0.5, 2 or 4 mg moxidectin/kg BW/day), a 91-day (0, 0.3, 0.9 or 1.6 mg moxidectin/kg BW/day) and a 52-week study (0, 0.26, 0.52 or 1.15 mg moxidectin/kg BW/day). In the 28-day study, dogs developed anorexia, ataxia, prostration and diarrhea at the highest dose level and were changed to a dose of 1.25 mg moxidectin/kg BW/day at day 5. Toxicity signs were observed at the highest doses in the 28-day and the 91-day study with clinical signs, tissue effects and effects on food consumption, which were similar to those seen in mice and rats. The NOEL's assigned to these studies were 0.5, 0.3 and 1.15 mg moxidectin/kg BW/day for the 28-day, 91-day and 52-week studies, respectively.

#### Developmental and Reproductive Toxicity

The reproductive and developmental toxicity of moxidectin has been evaluated in rats and rabbits. In a preliminary single generation test, rats were fed 0, 1.8, 3.9 or 9.8 mg moxidectin/kg BW/day for a 9-week period prior to mating and through gestation and lactation to produce F1<sub>a</sub> litters. All pups died at the highest treatment level and parental animals had reduced weight gains, a decreased number of live pups at birth and an increased number of dead pups at birth. No parental adverse reactions were observed at the 2 mid-dose treatments. However, all pups died during lactation. Subsequently, dietary levels were reduced to 0, 0.4, 0.8 or 1.1 mg moxidectin/kg BW/day. In the F1<sub>b</sub> litters, no parental effects were observed with various pup effects in all but the lowest treatment level. The NOEL for this study was established as 0.4 mg moxidectin/kg BW/day. In a 3-generation study, treatment levels of 0, 0.07, 0.15, 0.41 or 0.83 mg moxidectin/kg BW/day were tested for a period of 70 days prior to mating. Randomly selected offspring (F1<sub>b</sub> and F2<sub>b</sub>) were selected to produce subsequent generations. Toxic signs were noted in parents and offspring at the highest dose rate only. The NOEL for this study was 0.4 mg moxidectin/kg BW/day for the F1<sub>b</sub> animals.

#### Chronic Toxicity

Two chronic toxicity/carcinogenicity studies have been conducted with moxidectin. Diets providing 0, 2.5, 5.1 or 12 mg moxidectin/kg BW/day were fed in a 2-year study in mice. After 9 weeks, the highest dose level was reduced to 7.9 mg moxidectin/kg BW/day due to mortality in the original high dose group. Clinical signs of toxicity were limited to the highest dose group in this study with no

increased incidence of tumors. The NOEL was 5.1 mg moxidectin/kg BW in this study. In rats, dose levels of 0, 0.8, 3.2 or 9.8 mg moxidectin/kg BW/ day were tested. After 8 weeks, the highest dose was reduced to 5.1 mg moxidectin/kg BW/day because of increased mortality at the original high dose level. After 2 years, there was no increase in the incidence or type of tumor. The NOEL was established at 5.1 mg moxidectin/kg BW/day. Based on these studies, moxidectin is considered to be non-carcinogenic.

e) Effects on soil organisms, crops or livestock

Low levels of moxidectin may migrate from dung pats of treated cattle to soil in the field. The toxicity of moxidectin to plants and earthworms is discussed in this section.

Plants: Moxidectin was applied to 12 different plants, at a rate of 4 kg active ingredient/hectare, either through the soil (pre-emergence) or directly onto the plants (post-emergence). This application rate is many orders of magnitude greater than the levels of moxidectin which could be expected in fields from treating cattle at pasture. Tested plants in this study included *Abutilon theophrasti* (velvetleaf), *Ambrosia artemisiifolia* (common ragweed), *Avena fatua* (wild oats), *Brassica kaber* (wild mustard), *Calystegia arvensis* (hedge bindweed), *Cyperus rotundus* (purple nutsedge), *Digitaria sanguinalis* (large crabgrass), *Echinochloa crus-galli* (barnyardgrass), *Elytrigia repens* (quackgrass), *Ipomoea* sp. (morningglory), *Setaria viridis* (green foxtail), and *Sida spinosa* (prickly sida). The absence of any visible effect of moxidectin on the ability of the plants to germinate or damage leaves of growing plants indicated that moxidectin caused no impact on plants when manure from treated animals is applied to field or pastures.

Earthworms: A subacute toxicity test was conducted on earthworms using a mixture of <sup>14</sup>C-labeled and non-labeled moxidectin. The toxicity of moxidectin to earthworms (*Eisenia foetida*) was evaluated in a 28-day test in a mixture of manure and artificial soil. After a range finding test, eight concentrations of moxidectin were used ranging from 1 to 1280 mg/kg (nominal). Samples were prepared by mixing a solution of moxidectin in acetone (11.8 mL) with cow manure (50 g) and deionized water (27.3 mL). The manure slurry was held in a fume hood overnight to evaporate the solvent. The slurry was then mixed with artificial soil (1000 g, dry weight) using a mechanical mixer. Samples were held in 2 L covered glass beakers with 10 earthworms per test container. Samples were kept at 20±2°C, with four replicates per concentration. Observations of mortality were taken at 7, 14, 21 and 28 days after application. Results showed that the Lethal Concentration 50 (LC<sub>50</sub>) was 37.2 ppm and the NOEC was 1 ppm. Behavioral and morphological changes were generally observed in earthworms at concentrations above 1 ppm, which also corresponded to the no effect level, as determined by observations of weight gain. These concentrations are much higher than the levels of moxidectin which could be expected in the soil.

Summary: When compared with the maximum moxidectin PEC of 1.31 ppb in soil under the “worst-case” situation, findings from the above toxicity studies (summarized in the table below) indicate that moxidectin residues in soil are highly unlikely to cause any adverse effects on plants or earthworms when the product is used according to the product label. This “worst-case” calculation is based on a feedlot situation, in which large numbers of animals are treated with moxidectin, and assumes that all moxidectin applied is excreted as moxidectin during the 130-day excreta holding period, and assumes no degradation occurs. The aged excreta is then spread is then applied to fields.

**Toxicity of Moxidectin on Plants and Earthworms**

Test Species	Test Parameter	Results
Plant	4 kg/ha	No effects
Earthworm	28-day subacute LC <sub>50</sub>	37.2 ppm
	NOEC	1 ppm

**10. Safety information about the substance including a Material Safety Data Sheet (MSDS) and a substance report from the National Institute of Environmental Health Studies.**

The Material Safety Data Sheet (MSDS) for moxidectin is provided in **Attachment 2**. A report on moxidectin from the National Institute of Environmental Health Studies is not required by the FDA for registering moxidectin-containing products. Thus, a report has never been written and is therefore not available. Comprehensive safety data with respect to human health and the environment are supplied in Item #s 4 and 9.

**11. Research information about the substance, which includes comprehensive substance research reviews and research bibliographies, including reviews and bibliographies which present contrasting positions to those presented by the petitioner in supporting the substance’s inclusion on or removal from the national List.**

A comprehensive literature search was conducted, in which seven databases (AGRICOLA, EMBASE, International Pharmaceutical Abstracts, Derwent Drug File, Current Contents, CAB Abstracts, BIOSIS Previews) were searched. The time period the searches spanned was from 1979 to October, 2002. The publication references resulting from searching these databases that pertain to human and environmental safety are provided in **Attachment 4**. Numerous publications compare the effects of moxidectin and other endectocides, such as ivermectin and doramectin, on dung flora and fauna. In these studies, moxidectin is demonstrated to be less toxic to these environmental species than the other endectocides. These database searches were not biased towards publications with a favorable position regarding moxidectin, yet failed to uncover publications that were unfavorable towards moxidectin with respect to these aspects of moxidectin safety.

12. A “Petition Justification Statement” which provides justification for one of the following actions requested in the petition: Inclusion of a synthetic substance on the National List. The petition should state why the synthetic substance is necessary for the production or handling of an organic product. The petition should also describe the nonsynthetic substances or alternative cultural methods that could be used in place of the petitioned synthetic substance. Additionally, the petition should summarize the beneficial effects to the environment, human health, or farm ecosystem from use of the synthetic substance that support the use of it instead of the use of a nonsynthetic substance or alternative cultural methods.

#### Justification

Strategic parasite management programs are an integral part of livestock production. For the animal, parasite control ensures the health and well-being of species susceptible to parasitic infection and infestation. It also ensures limiting the spread of disease in situations where a number of animals, either in a pasture or a feedlot, are maintained. For the producer, because parasite control results in healthier animals, carcass weights are greater and have greater economic value than do those from diseased carcasses. Moxidectin is a very potent, broad spectrum endectocide and is indicated for treatment and control of existing infections/infestations and also provides persistent activity against a number of internal parasites. Therefore, one treatment with moxidectin provides sufficient treatment and protection versus numerous treatments that are effective for either endoparasites or ectoparasites, but not both. For these reasons, inclusion of moxidectin on the National List is justified.

#### Alternatives

One nonsynthetic or alternate cultural method was evaluated in sheep and cattle. In Niezen et alia’s International Journal for Parasitology article entitled “Controlling internal parasites in grazing ruminants without recourse to anthelmintics – approaches, experiences and prospects”, the authors describe several years of experience of raising cattle and sheep without the use of anthelmintics. Parasite control was strictly dependent on integrated grazing management of sheep and cattle. Strict systems of grazing management were required. The authors conclude that “developing effective and acceptable systems for raising stock without using anthelmintics presents a considerable challenge, to parasitologists, as well as to plant breeders, agronomists and farming systems researchers”. Therefore, effective alternatives to the use of anthelmintics do not appear to be currently available.

#### Beneficial effects

The data presented in Item #9 clearly demonstrate that moxidectin is not harmful to either human health or the environment when the formulated product is administered at the recommended dose rate. The safety to human health is further underscored by the fact that 1) beef cattle treated with moxidectin, when administered in the pour-on

formulation, can be slaughtered and enter the human food chain immediately after treatment (zero day meat withdrawal period) and 2) milk from moxidectin-treated lactating dairy cattle can be used immediately after treatment (zero day milk withholding period) when moxidectin is administered as a pour-on at the recommended dose rate.

As previously stated, the data presented in Item #9 attest to the environmental safety of moxidectin. In fact, with regard to dung flora and fauna, moxidectin is the treatment of choice as it is the least harmful to this important ecosystem when compared to other endectocides. Therefore, moxidectin provides a clear benefit to the environment in general and to this ecosystem in particular.

### **13. Commercial Confidential Information Statement**

The applicant considers that the information contained in Item #5 of this petition, namely, the description of the chemical reactions and steps required to manufacture moxidectin, is proprietary. In the context of this petition, such information falls under all three of the criteria in the category of "Trade secrets". That is, the information has commercial value as proprietary products containing moxidectin are manufactured by Fort Dodge Animal Health. The information is used in the applicant's business as moxidectin is formulated into a number of products that are marketed globally. This information has been, and must continue to be, maintained in secrecy.

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# ATTACHMENT 1

## Package Inserts

Facsimile copies of package inserts for the following four moxidectin-containing products that are approved and marketed in the United States are provided.

CYDECTIN® Pour-On for Cattle  
QUEST® Gel for Horses  
ProHeart® Tablets for Dogs  
ProHeart® Sustained Release Injectable for Dogs

A copy of the material safety data sheet (MSDS) which provides more detailed occupational safety information can be obtained by calling 1-888-339-6761. To report adverse reactions attributable to exposure to this product, call 1-800-477-1365.

#### RESIDUE WARNING

When used according to label directions, neither a pre-slaughter drug withdrawal period nor a milk discard time are required. Meat and milk from cattle treated with CYDECTIN (moxidectin) Pour-On may be used for human consumption at any time following treatment. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

#### PRECAUTIONS

For external use only. Do not apply to areas of skin with mange scabs, skin lesions, mud or manure. CYDECTIN Pour-On is not recommended for use in species other than cattle. This product has been formulated specifically for topical use in cattle and should not be used in other animal species or by other routes of administration as adverse reactions may occur.

CYDECTIN Pour-On is effective against the migrating stage of cattle grubs (*Hypoderma* larvae). Treatment with CYDECTIN Pour-On during the period when grubs are migrating through vital areas may cause undesirable host-parasite reactions. Killing *H. lineatum* when they are located in peri-esophageal tissues may cause bloat. Killing *H. bovis* when they are in the vertebral canal may cause staggering or hindlimb paralysis. Cattle should be treated as soon as possible after heel fly (warble fly) season to avoid this potential problem. Cattle treated with CYDECTIN Pour-On at the end of fly season can be re-treated during the winter without danger of grub-related reactions. Consult your veterinarian for more information regarding these secondary grub reactions and the correct time to treat with CYDECTIN Pour-On.

#### ENVIRONMENTAL SAFETY

Studies indicate that when moxidectin comes in contact with the soil it readily and tightly binds to the soil and becomes inactive. Free moxidectin may adversely affect fish and certain aquatic organisms. Do not contaminate water by direct application or by improper disposal of drug containers.

#### STORAGE

Store product at or below room temperature. Avoid prolonged exposure above 25°C (77°F). If product becomes frozen, thaw completely and shake well prior to use.

#### DISPOSAL

Dispose of containers in an approved landfill or by incineration.

#### PACKAGE INFORMATION

CYDECTIN Pour-On is available in five convenient container sizes. The 16.91 fl oz/500 mL (NDC 0856-2680-01) and 33.81 fl oz/1 L (NDC 0856-2680-02) are packaged in specially-designed squeeze-measure-pour polyethylene bottles. When treating larger numbers of cattle, 84.54 fl oz/2.5 L (NDC 0856-2680-03), 169 fl oz/5 L (NDC 0856-2680-04), or 338 fl oz/10 L (NDC 0856-2680-05) conventional polyethylene containers are available for use with most commercially-available topical applicators.

U.S. Patent No. 4,916,154

NADA 141-099, Approved by FDA

# CYDECTIN<sup>®</sup> moxidectin

## Pour-On for Beef and Dairy Cattle

Antiparasitic

Contains 5 mg moxidectin/mL

For Treatment of Infections and Infestations Due to  
Internal and External Parasites of Beef and Dairy Cattle

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism. If animals are likely to be reinfected following treatment, a strategic parasite control program should be established.

#### MODE OF ACTION

Moxidectin is an endectocide in the milbemycin chemical class which shares the distinctive mode of action characteristic of macrocyclic lactones. CYDECTIN (moxidectin) Pour-On is specially formulated to allow moxidectin to be absorbed through the skin and distributed internally to the areas of the body affected by endo- and/or ectoparasitism. Moxidectin binds selectively and with high affinity to glutamate-gated chloride ion channels which are critical to the function of invertebrate nerve and muscle cells. This interferes with neurotransmission resulting in paralysis and elimination of the parasite.

#### INDICATIONS

CYDECTIN Pour-On when applied at the recommended dose level of 0.5 mg/2.2 lb (0.5 mg/kg) body weight is effective in the treatment and control of the following internal [adult and fourth-stage larvae (L<sub>4</sub>)] and external parasites of cattle:

#### Gastrointestinal Roundworms

*Ostertagia ostertagi* - Adult and L<sub>4</sub> (including inhibited larvae)  
*Haemonchus placei* - Adult and L<sub>4</sub>  
*Trichostrongylus axei* - Adult and L<sub>4</sub>  
*Trichostrongylus colubriformis* - Adult and L<sub>4</sub>  
*Cooperia oncophora* - Adult and L<sub>4</sub>  
*Cooperia pectinata* - Adult  
*Cooperia punctata* - Adult and L<sub>4</sub>  
*Cooperia spatulata* - Adult  
*Cooperia surrabadana* - Adult and L<sub>4</sub>  
*Bunostomum phlebotomum* - Adult  
*Nematodirus helvetianus* - Adult and L<sub>4</sub>  
*Oesophagostomum radiatum* - Adult and L<sub>4</sub>

#### Lungworms

*Dictyocaulus viviparus* - Adult and L<sub>4</sub>

#### Cattle Grubs

*Hypoderma bovis*  
*Hypoderma lineatum*

#### Mites

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

#### Lice

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

#### Horn Flies

*Haematobia irritans*

#### Management Considerations for External Parasites

For most effective external parasite control, CYDECTIN Pour-On should be applied to all cattle in the herd. Cattle entering the herd following this administration should be treated prior to introduction. Consult your veterinarian or a livestock entomologist for the most appropriate time to apply CYDECTIN Pour-On in your location to effectively control horn flies and external parasites. CYDECTIN Pour-On provides seven days of persistent activity against horn flies. For optimal control of horn flies, the product should be used as part of an integrated control program utilizing other methods to provide extended control.

#### Persistent Activity

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. Efficacy below 90% was observed in some *Ostertagia ostertagi* persistent activity studies at 21 and 28 days posttreatment.

Fort Dodge Animal Health  
Fort Dodge, Iowa 50501 USA

Revised March 2001

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## DOSAGE

CYDECTIN (moxidectin) Pour-On is a ready-to-use topical formulation intended for direct application to the hair and skin in a narrow strip extending along the top of the back from the withers to the tailhead (see Figure 1). Due to the angular topline characteristic of most dairy breeds, it is recommended that all pour-on products be applied slowly to dairy cows. Apply to healthy skin avoiding any mange scabs, skin lesions, mud or manure. Treated cattle can be easily recognized by the characteristic purple color, which will remain for a short period of time after treatment. The recommended rate of administration is 1 mL for each 22 lb (10 kg) body weight which provides 0.5 mg moxidectin for each 2.2 lb (0.5 mg/kg) body weight. The table below will assist in the calculation of the appropriate volume of pour-on which must be applied based on the weight of animal being treated.

Body Weight Lb (kg)	Dose mL	Body Weight Lb (kg)	Dose mL
88 (40)	4	330 (150)	15
110 (50)	5	440 (200)	20
132 (60)	6	550 (250)	25
154 (70)	7	660 (300)	30
176 (80)	8	770 (350)	35
198 (90)	9	880 (400)	40
220 (100)	10	990 (450)	45
242 (110)	11	1100 (500)	50
264 (120)	12	1210 (550)	55
286 (130)	13	1320 (600)	60
308 (140)	14	1430 (650)	65

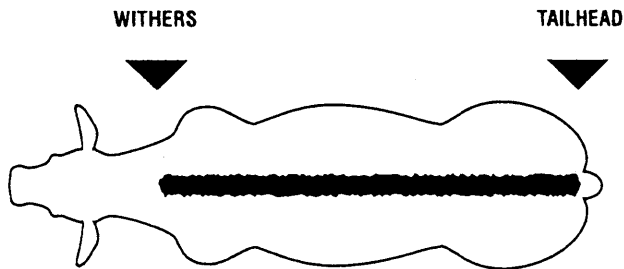


Figure 1. Where to Apply CYDECTIN Pour-On

### Use Conditions

Varying weather conditions, including rainfall, do not affect the efficacy of CYDECTIN Pour-On.

### ADMINISTRATION

CYDECTIN Pour-On is available in three convenient package styles designed for ease of administration and the number of cattle to be treated. Directions for use of each container type follow:

#### Squeeze-Measure-Pour System (16.91 fl oz/500 mL and 33.81 fl oz/1 L Bottles)

Determine the weight of the animal, calculate the recommended volume of CYDECTIN Pour-On and locate the volume marker equivalent to this dose on the dosing chamber of the bottle. Remove the dosing chamber cap and squeeze the main chamber of bottle until the desired level of solution is present in the dosing chamber. Release pressure on the container to avoid further filling. Holding the dosing chamber as shown below, pour this measured volume of solution evenly along the backline of the animal from the withers to the tailhead (see Figure 1).

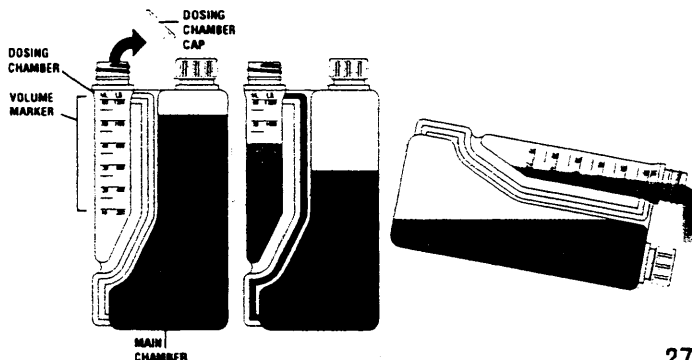


Figure 2. Squeeze-Measure-Pour System  
(16.91 fl oz/500 mL and 33.81 fl oz/1 L Bottles)

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#### Large Conventional Containers (84.54 fl oz/2.5 L and 169 fl oz/5 L Bottles and 338 fl oz/10 L Cubetainer)

These bottles are designed for use with the CYDECTIN (moxidectin) Pour-On applicators. Simply remove the transient cap and seal and replace with the vented cap. Attach the applicator feeder hose to the vented cap. Invert the container prior to use (2.5 L and 5 L containers only). Apply the recommended volume of CYDECTIN Pour-On evenly along the backline of the animal from the withers to the tailhead (see Figure 1).

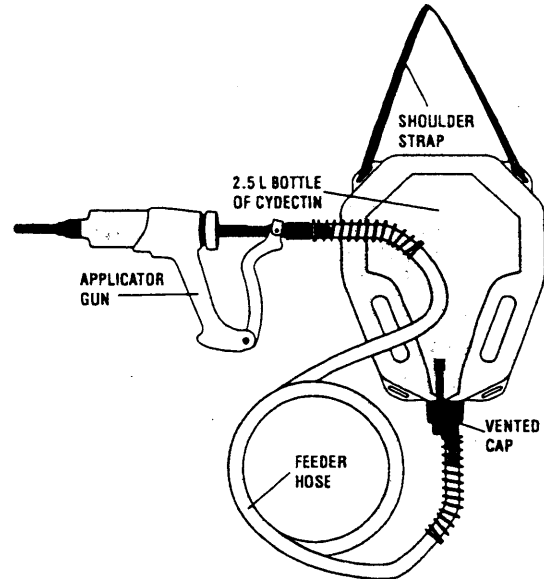


Figure 3. Large Conventional Containers  
(84.54 fl oz/2.5 L and 169 fl oz/5 L Bottles)

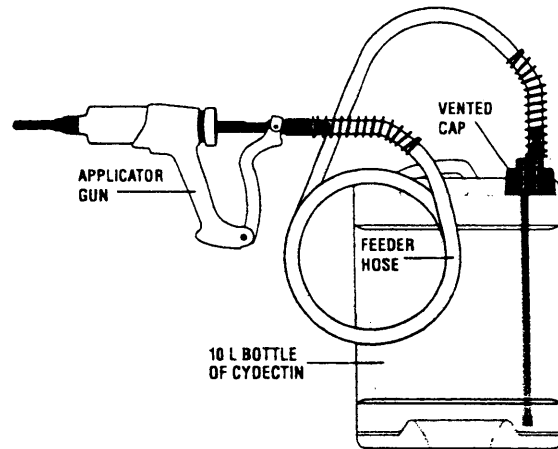


Figure 4. Large Conventional Container  
(338 fl oz/10 L Cubetainer)

### ANIMAL SAFETY

Tolerance and toxicity studies have demonstrated an adequate margin of safety to allow treatment of cattle of all ages with CYDECTIN Pour-On. No toxic signs were seen in cattle given up to 25 times the recommended dose level. Newborn calves similarly showed no toxic signs when treated with up to three times the recommended dose level within 12 hours of birth and nursing from cows concurrently treated with the recommended dose level of CYDECTIN Pour-On. In breeding animals (bulls and cows in estrous and during early, mid and late pregnancy), treatment with three times the recommended dose level had no effect on breeding performance.

### WARNING

**Not For Use In Humans. Keep this and all drugs out of the reach of children.** This product can cause irritation to skin, eyes, or mucous membranes. In case of accidental skin contact and/or clothing contamination, wash skin thoroughly with soap and water and launder clothing with detergent. In case of accidental eye contact, flush eyes with copious amounts of water. When direct inhalation occurs, cleanse lungs and respiratory passages with fresh air. In case of ingestion do not induce vomiting and seek medical attention immediately. If irritation or any other symptom attributable to exposure to this product persists, consult your physician.



# QUEST<sup>®</sup> GEL

## moxidectin



**2% Equine Oral Gel**  
**Contains 20 mg moxidectin/mL**  
**(2.0% w/v)**

**DEWORMER & BOTICIDE**

**FOR ORAL USE IN HORSES AND  
PONIES FOUR MONTHS OF AGE  
AND OLDER**

#### INDICATIONS

QUEST (moxidectin) 2% Equine Oral Gel when administered at the recommended dose level of 0.4 mg moxidectin/kg (2.2 lb) body weight is effective in the treatment and control of the following stages of gastrointestinal parasites in horses and ponies:

#### Large strongyles

- Strongylus vulgaris* – (adults and L<sub>1</sub>/L<sub>2</sub> arterial stages)
- Strongylus edentatus* – (adults and tissue stages)
- Triodontophorus brevicauda* – (adults)
- Triodontophorus serratus* – (adults)

#### Small strongyles

- Cyathostomum* spp. – (adults)
- Cylicocyclus* spp. – (adults)
- Cylicostephanus* spp. – (adults)
- Gyalocephalus capitatus* – (adults)
- Undifferentiated luminal larvae

#### Encysted cyathostomes

- Late L<sub>3</sub> and L<sub>4</sub> mucosal cyathostome larvae

#### Ascarids

- Parascaris equorum* – (adults and L<sub>4</sub> larval stages)

#### Pin worms

- Oxyuris equi* – (adults and L<sub>4</sub> larval stages)

#### Hair worms

- Trichostrongylus axei* – (adults)

#### Large-mouth stomach worms

- Habronema muscae* – (adults)

#### Horse stomach bots

- Gasterophilus intestinalis* – (2<sup>nd</sup> and 3<sup>rd</sup> instars)
- Gasterophilus nasalis* – (3<sup>rd</sup> instars)

One administration of the recommended dose rate of QUEST (moxidectin) 2% Equine Oral Gel also suppresses strongyle egg production through 84 days.

QUEST is indicated for use in horses and ponies, including breeding mares and stallions, and foals four months of age and older.

#### STRATEGIC PROTECTION PROGRAMS

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism. For best control of parasites, all horses and ponies should be included in a strategic treatment program, with particular attention given to high performance animals, brood mares, stallions and foals. In foals, initial treatment is recommended at 4 months of age, after which they should be included in a recurrent treatment program. Because QUEST provides effective control of the mucosal stages of small strongyles (encysted cyathostomes), it is useful in reducing the frequency of treatment required for successful strategic equine parasite control. A veterinarian can assist in preparing the best program for your needs.

QUEST 2% Equine Oral Gel when used at the recommended dose rate suppresses strongyle egg production through 84 days following a single oral administration. This residual strongyle control reduces pasture contamination and provides a period of protection from reinfection for horses and ponies maintained on the same pasture.

#### MODE OF ACTION

QUEST 2% Equine Oral Gel acts by interfering with chloride channel-mediated neurotransmission in the parasite. This results in paralysis and elimination of the parasite. Moxidectin is safe for use in horses and ponies because it does not have the same injurious effect on the mammalian nervous system.

(continued on opposite side)

#### ADMINISTRATION AND DOSAGE

QUEST (moxidectin) 2% Equine Oral Gel is specially formulated as a palatable gel which is easily administered to horses and ponies.

QUEST Gel is packaged in ready-to-use SURE-DIAL™ syringes (see diagram of the SURE-DIAL™ syringe below). The syringe is calibrated in 50-pound increments, up to 1150 pounds. This enables the administration of the recommended dose level of 0.4 mg moxidectin/kg body weight by choosing a setting consistent with the animal's weight.

#### HOW TO SET THE DOSE

Since the dose is based on the weight of the animal, you need to use a scale or weight tape to find each animal's weight before treating with QUEST Gel. Once the weight is known, set the dose for each horse or pony as follows.

1. Hold the syringe with the capped end pointing to the left and so that you can see the weight measurements and tick marks (small black lines) as shown in the diagram below. Each tick mark relates to 50 lbs. of body weight.
2. Turn the green dial ring until the left side of the ring lines up with the weight of the animal. In the diagram below, the dial ring is set to dose a 500 lb. animal.

#### HOW TO GIVE QUEST GEL TO A HORSE OR PONY

1. Make sure there is no feed in the animal's mouth.
2. Remove the cap from the end of the syringe. Save the cap for reuse.
3. Place the tip of the syringe inside the animal's mouth at the space between the teeth.
4. Gently push the plunger until it stops, depositing the gel on the back of the tongue.
5. Remove the syringe from the animal's mouth and raise the animal's head slightly to make sure it swallows the gel.
6. Replace the syringe cap.

#### ANIMAL SAFETY

QUEST (moxidectin) 2% Equine Oral Gel can be safely administered at the recommended dose of 0.4 mg moxidectin/kg body weight to horses and ponies of all breeds at least 4 months of age or older. Transient depression, ataxia and recumbency may be seen when very young or debilitated animals are treated. In these instances, supportive care may be advisable. Reproductive safety studies demonstrate a wide margin of safety when the product is used in the treatment of estrual and pregnant mares and breeding stallions.

To report adverse drug reactions or to obtain a copy of the Material Safety Data Sheet (MSDS) call (800)477-1365.

#### ENVIRONMENTAL SAFETY

Care should be taken to avoid the release of significant volumes of moxidectin into either ground or free-running water since moxidectin may be injurious to aquatic life. SURE-DIAL™ syringes and their contents should be disposed of in an approved landfill or by incineration.

#### PRECAUTION

QUEST 2% Equine Oral Gel has been formulated specifically for use in horses and ponies only. **This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.**

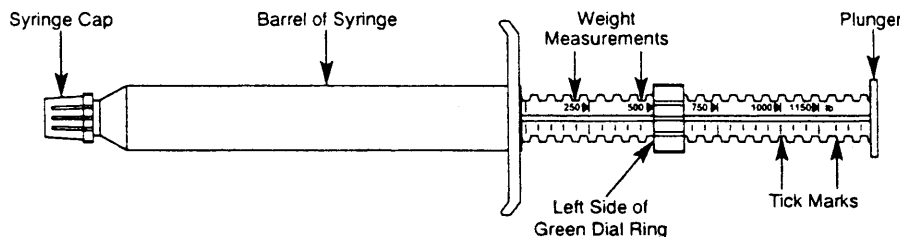
#### WARNING

**Extreme caution should be used when administering the product to foals, young and miniature horses, as overdosage may result in serious adverse reactions. Do not use in horses or ponies intended for food.**

#### HUMAN WARNING

Do not ingest. If swallowed, induce vomiting. Wash hands and contaminated skin with soap and water. If accidental contact with eyes occurs, flush repeatedly with water. If irritation or any other symptom attributable to exposure to this product persists, consult your physician. Keep this and all drugs out of reach of children.

### SURE-DIAL™ Syringe



#### TREATING A SECOND HORSE OR PONY WITH THE SAME SYRINGE

If the first animal you treat weighs less than 1150 lbs., there will be gel left in the syringe. You can use this gel to treat other horses or ponies. To set the next dose, add the weight of the animal you want to treat to the dose setting already on the syringe. For example, if the syringe was first used to treat a 250 lb. animal, the green dial ring is set on 250 lbs. To treat a 500 lb. animal next, move the green dial ring to the 750 lb. marking (250+500=750). You need more than one syringe to treat horses weighing more than 1150 lbs.

Each syringe of QUEST 2% Equine Oral Gel may be used to treat more than one animal especially when dosing foals, ponies and growing and lighter breeds of horses. The table below will help estimate the number of horses or ponies the contents of each syringe will treat.

Age	Ponies			Light Horses			Heavy Horses		
	Weight (lbs)	(kg)	Treated Animals (per syringe)	Weight (lbs)	(kg)	Treated Animals (per syringe)	Weight (lbs)	(kg)	Treated Animals (per syringe)
4 months	150	(68)	7	250	(113)	4	350	(159)	3
8 months	200	(91)	5	350	(159)	3	550	(249)	2
Mature	450	(204)	2	850	(386)	1	1100+	(499+)	1

#### HOW SUPPLIED

QUEST 2% Equine Oral Gel is available in one syringe applicator size. Each SURE-DIAL™ syringe contains 0.4 oz (11.3 g) of QUEST 2% Equine Oral Gel which is sufficient to treat a single horse weighing up to 1150 lb. or two or more lighter animals with a combined body weight of up to 1150 lb.

NDC 0856-7441-03 — 0.4 oz (11.3 g) syringe - 20 mg moxidectin per mL. Store at or near room temperature 15° to 30°C (59° to 86°F). Avoid freezing. If frozen, thaw completely before use. Store partially-used syringes with the cap tightly secured.

U.S. Patent No. 4,916,154

QUEST® is a registered trademark of American Cyanamid Company

**Fort Dodge Animal Health**  
Fort Dodge, Iowa 50501 USA

93569

7440H



# ProHeart® 6 (moxidectin)

Sustained Release Injectable for Dogs

### CAUTION

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

### DESCRIPTION

ProHeart 6 (moxidectin) Sustained Release Injectable consists of two separate vials. Vial 1 contains 10% moxidectin sterile microspheres and Vial 2 contains a specifically formulated sterile vehicle for constitution with Vial 1. No other diluent should be used. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 3.4 mg moxidectin, 3.1% glyceryl tristearate, 2.4% hydroxypropyl methylcellulose, 0.87% sodium chloride, 0.17% methylparaben, 0.02% propylparaben and 0.001% butylated hydroxytoluene. Hydrochloric acid is used to adjust pH.

### PHARMACOLOGY

Moxidectin is a semi-synthetic methoxime derivative of nemadectin which is a fermentation product of *Streptomyces cyaneogriseus* subsp *noncyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrolide.

Moxidectin has activity resulting in paralysis and death of affected parasites. The stage of the canine heartworm affected at the recommended dose rate of 0.17 mg moxidectin/kg body weight is the tissue larval stage. The larval and adult stages of the canine hookworms, *Ancylostoma caninum* and *Uncinaria stenocephala*, are susceptible.

Following injection with ProHeart 6, peak moxidectin blood levels will be observed approximately 7-14 days after treatment. At the end of the six month dosing interval, residual drug concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

### INDICATIONS

ProHeart 6 is indicated for use in dogs six months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis*.

ProHeart 6 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

### DOSAGE AND ADMINISTRATION

**Frequency of Treatment:** ProHeart 6 prevents infection by *D. immitis* for six months. It should be administered within one month of the dog's first exposure to mosquitoes. Follow-up treatments may be given every six months if the dog has continued exposure to mosquitoes. When replacing another heartworm preventive product, ProHeart 6 should be given within one month of the last dose of the former medication.

ProHeart 6 eliminates the larval and adult stages of *A. caninum* and *U. stenocephala* present at the time of treatment. However, persistent effectiveness has not been established for this indication. Re-infection with *A. caninum* and *U. stenocephala* may occur sooner than 6 months.

**Dose:** The recommended subcutaneous dose is 0.05 mL of the constituted suspension/kg body weight (0.0227 mL/lb.). This amount of suspension will provide 0.17 mg moxidectin/kg bodyweight (0.0773 mg/lb.). To ensure accurate dosing, calculate each dose based on the dog's weight at the time of treatment. Do not overdose growing puppies in anticipation of their expected adult weight. The following dosage chart may be used as a guide.

### DOSAGE CHART

Dog Wt.			Dose Volume		
lb	kg	mL/Dog	lb	kg	mL/Dog
11	5	0.25	77	35	1.75
22	10	0.50	88	40	2.00
33	15	0.75	99	45	2.25
44	20	1.00	110	50	2.50
55	25	1.25	121	55	2.75
66	30	1.50	132	60	3.00

**Injection Technique:** The two-part sustained release product must be mixed at least 30 minutes prior to the intended time of use (See **CONSTITUTION PROCEDURES** for initial mixing instructions). Once constituted, swirl the bottle gently before every use to uniformly re-suspend the microspheres. Withdraw 0.05 mL of suspension/kg body weight into an appropriately sized syringe fitted with an 18G or 20G hypodermic needle. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

Using aseptic technique, inject the product subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3 mL should be administered in a single site. The location(s) of each injection (left or right side) should be noted so that prior injection sites can be identified and the next injection can be administered on the opposite side.

### CONTRAINDICATIONS

ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug.

### HUMAN WARNINGS

**Not for human use. Keep this and all drugs out of the reach of children.**

May be slightly irritating to the eyes. May cause slight irritation to the upper respiratory tract if inhaled. May be harmful if swallowed. If contact with the eyes occurs, rinse thoroughly with water for 15 minutes and seek medical attention immediately. If accidental ingestion occurs, contact a Poison Control Center or a physician immediately. The material safety data sheet (MSDS) contains more detailed occupational safety information.

### PRECAUTIONS

**Use with caution in sick, debilitated or underweight animals (see SAFETY).**

ProHeart 6 should not be used more frequently than every 6 months.

The safety and effectiveness of ProHeart 6 has not been evaluated in dogs less than 6 months of age.

Prior to administration of ProHeart 6, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. ProHeart 6 is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, ProHeart 6 is not effective for microfilariae clearance.

No adverse reactions were observed in dogs with patent heartworm infections when ProHeart 6 was administered at three times the labeled dose. Higher doses were not tested.

## ADVERSE REACTIONS

In field studies, the following adverse reactions were observed in approximately 1% of 280 dogs treated with ProHeart 6: vomiting, diarrhea, listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature.

*Post-Approval Experience:* Although not all adverse reactions are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toxic reactions, depression/lethargy, urticaria, and head/facial edema. As with anaphylaxis/toxic reactions resulting from the use of other injectable products, standard therapeutic intervention should be initiated immediately.

To report suspected adverse reactions or to obtain technical assistance, call (800) 533-8536.

## ANIMAL SAFETY

*General Safety:* ProHeart 6 has been safely administered to a wide variety of healthy dogs six months of age and older, including a wide variety of breeds, pregnant and lactating females, breeding males, and ivermectin-sensitive collies. However, in clinical studies, two geriatric dogs with a history of weight loss after the initial ProHeart 6 injection died within a month of the second 6 month injection. A third dog who was underweight for its age and breed and who had a history of congenital problems experienced lethargy following the initial injection of ProHeart 6. The dog never recovered and died 3 months later (see **PRECAUTIONS**).

ProHeart 6 administered at 3 times the recommended dose in dogs with patent heartworm infections and up to 5 times the recommended dose in ivermectin-sensitive collies did not cause any adverse reactions. ProHeart 6 administered at 3 times the recommended dose did not adversely effect the reproductive performance of male or female dogs. ProHeart 6 administered up to 5 times the recommended dose in 7-8 month old puppies did not cause any systemic adverse effects.

In well controlled clinical field studies, ProHeart 6 was safely used in conjunction with a variety of veterinary products including vaccines, anthelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics and flea control products.

*Injection Site Reactions:* Injection site observations were recorded during effectiveness and safety studies. In clinical studies, ProHeart 6 was administered at six-month intervals to client-owned dogs under field conditions. There were no reports of injection site reactions in these field studies and evaluations of the injection sites revealed no abnormalities.

In a laboratory safety study, ProHeart 6 was administered at 1, 3 and 5 times the recommended dose to 7-8 month old puppies. Injection sites were clipped to facilitate observation. Slight swelling/edema at the injection site was observed in some dogs from all treated groups. These injection site reactions appeared as quickly as 8 hours post injection and lasted up to 3 weeks. A three-year repeated injection study was conducted to evaluate the safety of up to 6 injections of ProHeart 6 administered at the recommended dose (0.17 mg/kg) every 6 months. Mild erythema and localized deep subcuticular thickening were seen in dogs that received four injections in the same area on the neck and in one dog that received two injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous panniculitis with microvacuolation. The only adverse reaction seen that was not related to the injection site was weight loss in one dog.

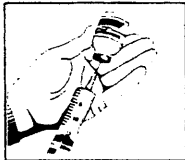
Some dogs treated with ProHeart 6 in laboratory effectiveness studies developed transient, localized inflammatory injection site reactions. These injection site reactions were visible grossly for up to 3 weeks after injection. Histologically, well-defined granulomas were observed in some dogs at approximately 5 months after injection.

## CONSTITUTION PROCEDURES

The two-part ProHeart 6 product must be mixed at least 30 minutes prior to the intended time of use.

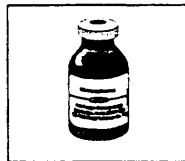
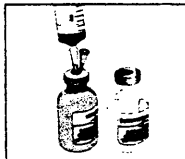
Items needed to constitute ProHeart 6:

- Microspheres (vial 1)
- Enclosed vent needle (25G)
- Vehicle (vial 2)
- Sterile 20 mL syringe for transfer
- Transfer needle (18G or 20G)



Constitution of the 20 mL vial product.

1. Shake the microsphere vial to break up any aggregates prior to constitution.
2. Using an 18G or 20G needle and sterile syringe withdraw 17.0 mL of the unique vehicle from the vial. **There is more vehicle supplied than the 17.0 mL required.**
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the vehicle has been added, remove the vent and transfer needles from the microsphere vial. Discard unused vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.
7. Record the time and date of mixing on the microsphere vial.
8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
9. Before **every** use, gently swirl the mixture to achieve uniform suspension. The microspheres and vehicle will gradually separate on standing.
10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.
11. Refrigerate the unused product. The constituted product remains stable for 4 weeks in a refrigerator. Avoid direct sunlight.



## STORAGE INFORMATION

Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After constitution, the product is stable for 4 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

## HOW SUPPLIED

ProHeart 6 is available in the following two package sizes.

### 1. 5-Pack

NDC 0856-3670-25 – 20 mL vial product:  
5 - 10% moxidectin sterile microspheres - 598 mg/vial  
5 - Sterile vehicle - 17 mL/vial

### 2. 10-Pack

NDC 0856-3670-29 – 20 mL vial product:  
10 - 10% moxidectin sterile microspheres - 598 mg/vial  
10 - Sterile vehicle - 17 mL/vial

For customer service, product information or to obtain a copy of the MSDS, call (800) 685-5656.

U.S. Patent No. 4,916,154 and 6,340,671

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**Fort Dodge Animal Health**  
**Fort Dodge, Iowa 50501 USA**

target species. When fed at levels in excess of 300 times the recommended monthly dose, moxidectin was determined to be safe for dogs.

**HUMAN WARNING**

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN. In case of human consumption, contact a Poison Control Center or a physician immediately.

**HOW SUPPLIED**

ProHeart (moxidectin) Heartworm Prevention Tablets — Packs containing 6 tablets each are packaged 10 packs per display carton.

NDC 0856-8851-01 — 30 µg per tablet

NDC 0856-8852-01 — 68 µg per tablet

NDC 0856-8853-01 — 136 µg per tablet

Store at room temperature up to 25°C (77°F). Do not store at temperatures greater than 25°C or expose to light for extended periods of time.

NADA 141-051, Approved by FDA



**ProHeart™  
MOXIDECTIN**

Heartworm Prevention Tablets for Dogs

**CAUTION**

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**INDICATIONS**

ProHeart (moxidectin) heartworm prevention tablets are indicated for once-a-month use in dogs to prevent infections by the canine heartworm, *Dirofilaria immitis*, and the subsequent development of canine heartworm disease.

**DESCRIPTION**

Each ProHeart heartworm prevention tablet is formulated to provide 1.36 µg moxidectin/lb body weight (3 µg/kg). Moxidectin is a semi-synthetic methoxime derivative of nemadectin which is a fermentation product of *Sireptomycetes cyaneogriseus* subsp *non-cyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrolide.

**PHARMACOLOGY**

Moxidectin has activity resulting in paralysis and death of affected parasites. The stage of the canine heartworm affected at the recommended dose rate of 3 µg/kg body weight is the tissue larval (L3) stage. There is no effect against the adult heartworm at this dose rate.

**ADMINISTRATION AND DOSAGE**

Administer tablets orally at one-month intervals during the time when the intermediate host (the mosquito) is present. Dosing should start within one month after the first exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. To establish a routine, it is recommended that the same day or date be used each month to administer the tablet to the dog.

U.S. Patent No. 4,916,154

Manufactured by

**Fort Dodge Animal Health**  
Fort Dodge, Iowa 50501 USA

Packaged by  
Sharp  
Conshohocken, PA 19428

92639

Revised September 1999

8850C



ProHeart (moxidectin) is recommended for dogs eight weeks of age and older. The recommended minimum dose rate is 1.36 µg moxidectin/lb (3 µg/kg) body weight which is achieved by using tablets as follows:

Dog Weight	Tablets per Month	Tablet Weight	Moxidectin per Tablet
Up to 22 lbs.	1	112 mg	30 µg
23 to 50 lbs.	1	412 mg	60 µg
51 to 100 lbs.	1	824 mg	136 µg

Dogs weighing over 100 pounds should be given the appropriate combination of these tablets. For example, a dog weighing 120 pounds should be given one large tablet containing 136 µg moxidectin and one small tablet containing 30 µg moxidectin each month.

The whole dosage should be swallowed. This may be achieved by manually placing the tablet(s) over the back of the tongue or by wrapping the tablet(s) in the dog's food. The dog should be observed closely for several minutes to insure that the dosage has been swallowed. If it is thought that the entire dosage has not been swallowed, the dog should be redosed. After administering the proper dose, as stated above, return the card with the remaining tablets to the package to protect the product from both moisture and light.

#### PRECAUTIONS

ProHeart heartworm prevention tablets should only be used in dogs testing negative for the presence of heartworm infection. Infected dogs should be treated to remove adult heartworms and microfilaria prior to initiating treatment with ProHeart tablets.

A complete heartworm disease prevention program includes a periodic physical examination and a test for the presence of adult heartworm by a licensed veterinarian. All dogs not currently on an approved heartworm prevention program should be tested for the presence of adult heartworms before using ProHeart heartworm prevention tablets.

If replacing another preventative medication, the first dosage of ProHeart heartworm prevention tablets must be administered within one month of cessation of the original program.

If a dosage of ProHeart heartworm prevention tablets is forgotten for a period of less than 1 month (not

more than 1 full month), give the full dosage immediately and then revert to the regular dosing routine. If a dosage is forgotten by a period exceeding one month (more than two months have passed since the last dose), a test for the presence of adult heartworms should be performed before re-establishing the monthly dosing routine. A follow-up test within the next year is also recommended.

Hypersensitivity reactions have not been observed in trials where animals were administered moxidectin up to five times the recommended dose level. Transient inappetence, decreased motor activity, and increased respiration were observed in microfilaria-positive animals administered moxidectin at 10 times the recommended dose level. Consult a veterinarian immediately if any adverse reaction is suspected.

#### ADVERSE REACTIONS

The following adverse reactions may be observed following the use of ProHeart (moxidectin): lethargy, vomiting, ataxia, anorexia, diarrhea, nervousness, weakness, increased thirst, and itching.

#### TARGET ANIMAL SAFETY

ProHeart heartworm prevention tablets have been safely administered to a wide variety of dog breeds. The target animal safety testing program for ProHeart heartworm prevention tablets includes field tests at the recommended dose level, tests with sensitive collie dogs, tests with dogs known to have patent heartworm infections, reproductive studies with breeding bitches and stud dogs, and safety studies with puppies eight weeks of age. These studies showed that ProHeart tablets were safe at the recommended dose level, at three times the recommended dose level in the breeding safety studies, at five times the recommended dose level in the collie and patent heartworm infection safety studies, and up to 10 times the recommended dose in puppies eight weeks of age. Mild signs of depression, ataxia and salivation were seen in one collie dog at 30 times the recommended dose.

As part of the field-testing program, ProHeart tablets were safely used in conjunction with a variety of veterinary products commonly used with dogs. These products included vitamins and nutritional supplements, steroid and antibiotic medications, shampoos, and other ectoparasite treatments.

Moxidectin was fed to dogs daily for a period of one year to determine the safety of the product in the

## **ATTACHMENT 2**

The Material Safety Data Sheet (MSDS) for Moxidectin is provided in this attachment.

# MATERIAL SAFETY DATA SHEET


**FORT DODGE**

## Moxidectin Technical

Fort Dodge Animal Health  
800 5<sup>th</sup> Street NW  
PO Box 518  
Fort Dodge, IA 50501

Emergency Telephone No.: (515) 955-6033  
General Information No.: (515) 955-4600  
Preparation Date: 12 June, 1992  
Revision Date: 31 March, 2000

### 1. PRODUCT AND COMPANY IDENTIFICATION

- 1.1 **PRODUCT NAME:** Moxidectin Technical
- 1.2 **USE:** An active ingredient used in the manufacture of anthelmintics.
- 1.3 **SIZE:** NA
- 1.4 **SYNONYMS/TRADE NAMES:** CL 301,423

### 2. COMPOSITION / INFORMATION ON INGREDIENTS (\*Indicates active ingredient)

INGREDIENT NAME	SYNONYMS	CAS NO.	CONC.	OSHA PEL/STEL	ACGIH PEL/STEL	OTHER PEL/STEL
Moxidectin	NA	113507-06-5	85 - 95%	Not Established	Not established	0.05 mg/m <sup>3</sup>

### EMERGENCY OVERVIEW

- 3.1 **POTENTIAL HEALTH EFFECTS:** This material is considered to be toxic through ingestion in single doses. The acute oral LD<sub>50</sub> in rats is 106 mg/kg b.w. Inhalation or ingestion of material may cause gastrointestinal distress, vomiting, and central nervous system effects.
- 3.1.1 **ACUTE EFFECTS:**
- INHALATION:** May be toxic through inhalation. Remove victim to fresh air and seek medical attention immediately.
- INGESTION:** Ingestion may cause gastrointestinal distress and central nervous system effects. Seek medical attention immediately.
- SKIN:** Contact with skin is not expected to produce irritation. If irritation occurs, seek medical attention.
- EYE:** May be irritating to the eyes. Rinse thoroughly with water for 15 minutes and seek medical attention immediately.
- 3.1.2 **TARGET ORGAN EFFECTS (SUBCHRONIC/CHRONIC):** Gastrointestinal system, central nervous system. No chronic effects are associated with exposure to this product.
- 3.1.3 **CARCINOGENIC EFFECTS:** This product is not considered to be carcinogenic.
- 3.1.4 **REPRODUCTIVE/TERATOGENIC EFFECTS:** There are no reproductive or teratogenic effects associated with exposure to this product. May cause harm to the unborn fetus at doses considered to be maternally toxic.

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Product Name: Moxidectin Technical

3.2	<b>CARCINOGENICITY STATUS:</b>	This product is not listed as a carcinogen or suspected carcinogen by OSHA, IARC, or other organizations.	
3.3	<b>MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:</b>	None known.	
<b>4. FIRST AID MEASURES</b>			
<b>INHALATION:</b> Remove victim to fresh air. Seek medical attention immediately.			
<b>INGESTION:</b> Seek medical attention immediately.			
<b>SKIN:</b> Wash affected area thoroughly with soap and water. If irritation persists seek medical attention.			
<b>EYE:</b> Rinse eyes thoroughly with water for 15 minutes, holding eyelids open with fingers. Seek medical attention immediately.			
<b>5. FIRE FIGHTING MEASURES</b>			
5.1	<b>FLASH POINT:</b>	Not applicable	<b>METHOD:</b> NA
5.2	<b>AUTOIGNITION TEMPERATURE:</b>	351° C	
5.3	<b>FLAMMABILITY LIMITS:</b>	LOWER LIMIT: Not established. UPPER LIMIT: Not established.	
5.4	<b>UNUSUAL FIRE AND EXPLOSION HAZARDS:</b>	Fires involving this product may release toxic vapors and smoke. Material is a Class 2 dust explosion hazard.	
5.5	<b>COMMON EXTINGUISHING METHODS:</b>	Water, foam, dry chemical, or carbon dioxide extinguishers.	
5.6	<b>FIRE FIGHTING PROCEDURES:</b>	Wear full protective gear, including SCBA. Use as little water as possible, and dike area to prevent runoff. If water enters a drainage system, advise authorities downstream. Use spray or fog - solid stream may cause spreading. Conduct fire fighting and rescue operations from upwind of the fire area. Evacuate people downwind who may come in contact with smoke, fumes, or contaminated surfaces. Do not decontaminate personnel or equipment or handle broken packages or containers without protective equipment described in Section 8, Exposure Controls. Decontaminate emergency personnel with soap and water before leaving the fire area.	
<b>6. ACCIDENTAL RELEASE MEASURES</b>			
Wear appropriate protective gear as described in Section 8, Exposure Controls. For small spills, such as those that would be associated with normal use of this product, do not wash spilled material to a drain. Collect spilled tablets and place into a container for future disposal. Wash affected areas with soap and water. For large spills, contain the spill immediately using dikes, spill booms, or other appropriate containment devices. Collect the spill using shovels or other appropriate tools, and place into containers for future disposal. Do not use water, and do not allow the spill to enter rivers, lakes, streams, or sewer systems.			
<b>7. HANDLING AND STORAGE</b>			
Store product in a secure, dry, cool, well-ventilated area. Do not contaminate water, food, or feed by storage or disposal. Keep out of the reach of children. Not for use or storage in or around the home. Keep away from sources of ignition and protect from exposure to fire and heat.			
<b>8. exposure controls / personal protection</b>			
8.1	<b>VENTILATION:</b>	In situations where this material is being handled (i.e., transferred from the original container), local exhaust ventilation is recommended.	
8.2	<b>RESPIRATORY PROTECTION:</b>	If sufficient ventilation cannot be provided to maintain exposures within acceptable limits, use a NIOSH/MSHA approved full face or half mask respirator fitted with HEPA filter cartridges.	
8.3	<b>PROTECTIVE GLOVES:</b>	Nitrile or other impervious gloves are recommended.	
8.4	<b>EYE PROTECTION:</b>	Safety glasses are recommended.	
8.5	<b>OTHER:</b>	Protective (e.g., Tyvek) coveralls, head cover, and shoe covers.	
Continued on Page 3			
<b>Product Name: Monidectin Technical</b>			
Page 3			
<b>9. PHYSICAL AND CHEMICAL PROPERTIES</b>			

9.1	<b>APPEARANCE AND ODOR:</b>	White/Yellow Powder
9.2	<b>MELTING POINT:</b>	145° - 154° C
9.3	<b>BOILING POINT:</b>	Not Applicable
9.4	<b>SPECIFIC GRAVITY / DENSITY:</b>	Not Available
9.5	<b>VAPOR DENSITY:</b>	Not Applicable
9.6	<b>VAPOR PRESSURE:</b>	<3.2 X10 <sup>8</sup> TORR
9.7	<b>SOLUBILITY</b>	
	•	0.51 mg/L @ 25° C
	<b>WATER:</b>	
	•	Soluble in some organic solvents.
	<b>OTHER SOLVENTS:</b>	
9.8	<b>DECOMPOSITION TEMPERATURE:</b>	140° C
9.9	<b>VISCOSITY:</b>	Not Available.
9.10	<b>pH:</b>	Not Available
<b>10. STABILITY AND REACTIVITY</b>		
10.1	<b>STABILITY:</b>	This product is considered to be stable under normal conditions.
10.2	<b>HAZARDOUS DECOMPOSITION PRODUCTS:</b>	This product may release toxic vapors when subjected to fire conditions.
10.3	<b>CONDITIONS TO AVOID:</b>	Avoid high heat, flame, and other sources of ignition.
10.4	<b>MATERIALS AND SUBSTANCES TO AVOID (INCOMPATIBILITY):</b>	Strong acids or bases.
<b>11. TOXICOLOGICAL INFORMATION</b>		
11.1	<b>ACUTE DATA:</b>	This product is considered to be toxic through ingestion or inhalation. It may be slightly irritating to the skin, and may be irritating to the eyes.
	<b>INHALATION:</b>	May be harmful if inhaled. If inhalation occurs, seek medical attention immediately.
	<b>INGESTION:</b>	Material is considered toxic through ingestion. Oral LD <sub>50</sub> (Rat) – 106 mg/kg
	<b>EYES:</b>	May be irritating to the eyes.
	<b>SKIN:</b>	May be slightly irritating to the skin. Dermal LD <sub>50</sub> (Rabbit) >2,000 mg/kg
11.2	<b>TARGET ORGAN EFFECTS DATA (SUBCHRONIC/CHRONIC):</b>	Gastrointestinal system, central nervous system. No adverse chronic health effects are associated with exposure to this product.
11.3	<b>CARCINOGENIC EFFECTS DATA:</b>	This product is not considered to be carcinogenic.
Continued on Page 4		
<b>Product Name: Moxidectin Technical</b>		

11.4 **MUTAGENIC EFFECTS DATA:** There are no mutagenic effects associated with exposure to this product.

11.5 **REPRODUCTIVE / TERATOGENIC EFFECTS DATA:** There are no adverse reproductive or teratogenic effects associated with exposure to this product. This material may be harmful to the unborn fetus at levels considered to be maternally toxic.

**12. ECOLOGICAL INFORMATION**

12.1 **ECOTOXICOLOGICAL INFORMATION:** This product is considered to be highly toxic to fish and other aquatic life.

12.2 **CHEMICAL FATE INFORMATION:** Not available.

**13. DISPOSAL CONSIDERATIONS**

Persons seeking to dispose of this product should contact a commercial hazardous waste disposal firm for specific waste disposal procedures. Incineration in a licensed and approved hazardous waste incinerator is recommended.

**14. TRANSPORT INFORMATION**

14.1 **U.S. DEPARTMENT OF TRANSPORTATION (DOT):** Classified as a hazardous material (Class 6.1, Group III, UN 2811, "Poisonous Solid, N.O.S. (Moxidectin Technical)) under DOT regulations.

14.2 **INTERNATIONAL TRANSPORTATION REGULATIONS:** Classified as a hazardous material (Class 6.1, Group III, UN 2811, "Poisonous Solid, N.O.S. (Moxidectin Technical)) under International Transport regulations.

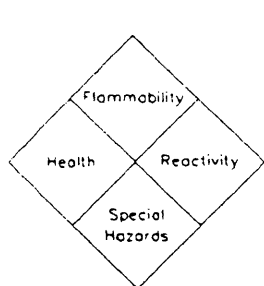
**15. REGULATORY INFORMATION**

15.1 **FEDERAL REGULATIONS:** None applicable.

15.2 **STATE REGULATIONS:** None applicable.

**16. OTHER INFORMATION**

**16.1 HAZARD RATINGS**



**NFPA\*:**  
**Health - 3**  
**Flammability - 0**  
**Reactivity - 0**  
**Special Hazards - 0**

**HMS:**

Health
Flammability
Reactivity
Personal Protection

**Health - 3**  
**Flammability - 0**  
**Reactivity - 0**  
**Personal Protection - See Section 8**

\* A hazard rating has not been developed by NFPA for this product. NFPA-derived rating is based on NFPA hazard evaluation criteria.

**16.2 PREPARATION AND REVISION INFORMATION**

**Fort Dodge Animal Health, Department of Safety**

The information and recommendations presented in this MSDS are based on sources believed to be accurate. However, Fort Dodge Laboratories, its Divisions and/or Subsidiaries assumes no liability for the accuracy, completeness, or suitability of this information. It is the product user's responsibility to determine the suitability of the information for their particular purposes.

This product should only be used by, or under the supervision of, a person trained and qualified to administer the product. Please refer to the package insert for indications or contraindications for use, and for dosage information.

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