FREEDOM OF INFORMATION SUMMARY

1. General Information

New Animal Drug Application Number: 140-833

Sponsor: Merck Sharp & Dohme Research Laboratories
Division of MERCK & CO., Inc.
P. O. Box 2000
Rahway, New Jersey 07065

Generic Name of Drugs: Ivermectin and clorsulon

Trade Name: IVOMEC-F* Injection For Cattle

Marketing Status: Over-The-Counter (OTC)

2. Indications For Use

IVOMEC-F Injection For Cattle is indicated for the treatment and control of the following species of gastrointestinal nematodes, lungworms, liver flukes, grubs, sucking lice, and mange mites of cattle.

Gastrointestinal nematodes (adults and fourth-stage larvae):

Haemonchus placei
Ostertagia ostertagi (including inhibited L_4)
O. lyrata
Trichostrongylus axei
T. colubriformis
Cooperia oncophora
C. punctata
C. pectinata
Bunostomum phlebotomum
Nematodirus helvetianus (adults only)
N. spathiger (adults only)
Oesophagostomum radiatum

Lungworms (adults and fourth-stage larvae):

Dictyocaulus viviparus

Liver Flukes (adults only):

Fasciola hepatica

Cattle grubs (parasitic stages):

Hypoderma bovis
H. lineatum

Sucking Lice:

Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mites:

Psoroptes ovis (syn. *P. communis* var. *bovis*)
Sarcoptes scabiei var. *bovis*

3. Dosage

a. Form: A ready-to-use sterile formulation containing 1% ivermectin and 10% clorsulon.

b. Route Of Administration: Subcutaneous injection only.

c. Recommended Dosage: 1 ml of formulation (containing 10 mg ivermectin and 100 mg clorsulon) per 50 kg, or 200 mcg ivermectin and 2 mg clorsulon per kg.

4. Effectiveness

Clorsulon given in combination with ivermectin by the subcutaneous route is shown in the following trial summaries to be effective against adult *Fasciola hepatica* and not to interfere with the efficacy or spectrum of ivermectin. Dose selection was determined in five titration trials using clorsulon in IVOMEC Injection vehicle. Six dose-confirmation trials using clorsulon alone and in combination with ivermectin (formulated in IVOMEC Injection vehicle) also were conducted.

a. Dose Determination

Five dose-titration trials were conducted using clorsulon formulated in IVOMEC Injection vehicle. These trials were directed at 8-week-old F. hepatica since immatures are less susceptible to clorsulon than are adults. Efficacy in these trials against the immatures was 70% or less at 2 mg/kg and 94% at 4 mg/kg. Earlier, clorsulon formulated in a different vehicle resulted in 68% efficacy at 2 mg/kg against 8-week-old F. hepatica as well as 97% against adults at 2 mg/kg . Based on these data, the formulation selected for further development contained 1% ivermectin and 10% clorsulon dissolved in the same vehicle as used in IVOMEC Injection.

The following trials were conducted using clorsulon dissolved in IVOMEC Injection vehicle against 8-week-old F. hepatica.

1) Trial 10551 was conducted by Dr. T. A. Yazwinski (University of Arkansas, Fayetteville, AR). Twenty-eight cattle artificially infected were randomly allocated to four groups of equal size. When the F. hepatica infections were 8 weeks old, each animal was given either vehicle or clorsulon once subcutaneously. Necropsies were performed 37 or 38 days later. The reductions were 17% at 1 mg/kg, 90% at 2 mg/kg, and 98% at 4 mg/kg. No adverse reactions were observed.

2) Trial 10639 was conducted by Dr. R. L. Kilgore (Merck Farms, Inc., Springdale, AR). Twenty-four cattle artificially infected were randomly allocated to four groups of equal size. When the F. hepatica infections were 8 weeks old, each animal was given either vehicle or clorsulon once subcutaneously. Necropsies were performed six weeks later. The reductions recorded were 38% at 1 mg/kg, 87% at 2 mg/kg, and 97% at 4 mg/kg. No adverse reactions were observed.

3) Trial 10775 was conducted by Dr. A. F. Batty (Merck Sharp and Dohme, Ltd., Highfield Farm, Nr. Hertford, Herts., U.K.). Twenty-four cattle artificially infected were randomly allocated to four groups of equal size. When the F. hepatica infections were 8 weeks old, each animal was given either vehicle or clorsulon once subcutaneously. Necropsies were performed three weeks later. The reductions recorded were 5% at 1 mg/kg, 0% at 2 mg/kg, and 89% at 4 mg/kg. No adverse reactions were observed.

4) Trial 10782 was conducted by Dr. A. F. Batty (Merck Sharp and Dohme, Ltd., Highfield Farm, Nr. Hertford, Herts., U.K.). Twenty-four cattle artificially infected were randomly allocated to four groups of equal size. When the F. hepatica infections were 8 weeks old, each animal was given either vehicle or clorsulon once subcutaneously. Necropsies were performed three weeks later. The reductions recorded were 0% at 1 mg/kg, 70% at 2 mg/kg, and 92% at 4 mg/kg. No adverse reactions were observed.

5) Trial 10851 was conducted by Dr. C. H. Courtney (University of Florida, Gainesville, FL). Twenty-four cattle artificially infected were randomly allocated to four groups of equal size. When the F. hepatica were eight weeks old, each animal was given either vehicle or clorsulon once subcutaneously. Necropsies were performed 21 to 24 days later. The reductions recorded were 0% at 1 mg/kg, 47% at 2 mg/kg, and 91% at 4 mg/kg. Other than minor, transient injection-site swellings observed in one to four animals in each group, no adverse reactions were observed.

b. Dose Confirmation

Six dose-confirmation trials were conducted using ivermectin, clorsulon, and ivermectin/clorsulon combination (each formulated in IVOMEC Injection vehicle). The purpose of the trials was to demonstrate that clorsulon given in combination with ivermectin by the subcutaneous route is effective against adult F. hepatica and has no effect on the efficacy or spectrum of ivermectin. In addition to F. hepatica, these trials tested activity against 11 species of parasitic nematodes, including the dose-limiting species Cooperia oncophora, Trichostrongylus colubriformis and Nematodirus helvetianus. Confirmation of efficacy against these species assures that there is no effect of clorsulon on the efficacy of ivermectin over its entire spectrum of antiparasitic activity, including ectoparasites.

1) Trial 10810 was conducted by Dr. A. F. Batty (Merck Sharp and Dohme, Ltd., Highfield Farm, Nr. Hertford, Herts., U.K.). Twenty-four cattle were artificially infected. When the parasites were in the adult stage, the animals were randomly allocated to four groups of equal size. Treatments administered once subcutaneously included vehicle (1 ml/50 kg), clorsulon (2 mg/kg), ivermectin (200 mcg/kg), and clorsulon (2 mg/kg) combined with ivermectin (200 mcg/kg). Necropsies were performed three weeks later. The reductions ($p<0.05$) listed below were recorded. No adverse reactions were observed.

	% Reduction		
Parasite	Clorsulon	Ivermectin	Combination
Fasciola hepatica	93	7 ns	93
Ostertagia ostertagi	15 ns	>99	>99
Cooperia oncophora	15 ns	82	97
Dictyocaulus viviparus	74	>99	>99

ns = Not significantly different from controls ($p>0.05$).

2) Trial 11074 was conducted by Dr. R. L. Kilgore (Merck Farms, Inc. Springdale, AR). Twenty-four cattle were artificially infected and randomly allocated to four groups of equal size. When the parasites were in the adult stage, each animal was given either vehicle (1 ml/50 kg), clorsulon (2 mg/kg), ivermectin (200 mcg/kg), or clorsulon (2 mg/kg) in combination with ivermectin (200 mcg/kg). Necropsies were performed three weeks later. The reductions ($p<0.01$) are listed below. Minor, transient injection-site swellings occurred in three animals; otherwise, no adverse reactions were observed.

Parasite	% Reduction		
	Clorsulon	Ivermectin	Combination
Fasciola hepatica	100	26 ns	100
Haemonchus placei	17 ns	100	100
Ostertagia ostertagi	0 ns	100	100
O. ostertagi L 4	15 ns	100	100
Trichostrongylus axei	13 ns	100	100
T. colubriformis	8 ns	>99	99
Cooperia oncophora	0 ns	>99	99
C. punctata	4 ns	>99	99
Nematodirus helvetianus	0 ns	30 ns	75 ns
Dictyocaulus viviparus	62 ns	100	100

n = Not significantly different from controls ($p>0.05$).

3) Trial 11251 was conducted by Dr. W. J. Foreyt (Washington State University, Pullman, WA). Twenty-four cattle were artificially infected and randomly allocated to four groups of equal size. When the parasites were in the adult stage, each animal was given subcutaneously either vehicle (1 ml/50 kg), clorsulon (2 mg/kg), ivermectin (200 mcg/kg), or clorsulon (2 mg/kg) in combination with ivermectin (200 mcg/kg). Necropsies were performed three weeks later. The reductions ($p<0.05$) recorded are listed below. No adverse reactions were recorded.

Parasite	% Reduction		
	Clorsulon	Ivermectin	Combination
Fasciola hepatica	>99	18[s]	98
Haemonchus placei	47 [ns]	100	100
Ostertagia ostertagi	0 [ns]	100	100
Trichostrongylus axei	0 [ns]	>99	100
T. colubriformis	0 [ns]	100	100
Cooperia oncophora	0 [ns]	92	100
C. punctata	0 [ns]	>99	>99
Nematodirus helvetianus	2 [ns]	100	100
Oesophagostomum radiatum	0 [ns]	100	100
Dictyocaulus viviparus	0 [ns]	100	100

ns = Not significantly different from controls ($p>0.05$).

4) Trial 11293 was conducted by Mr. R. G. Harvey (MSD Research Centre, Hennops River, Republic of South Africa). Ten cattle were artificially infected and allocated to two groups of equal size. When the parasites were in the adult stage, each animal was given subcutaneously either vehicle (1 ml/50 kg) or clorsulon (2 mg/kg) in combination with ivermectin (200 mcg/kg). Necropsies were performed 25 or 26 days later. The reductions ($p<0.01$) are listed below. No adverse reactions were observed.

Parasite	% Reduction
Fasciola hepatica	98
Ostertagia ostertagi	100

5) Trial 10858 was conducted by Dr. C. H. Courtney (University of Florida, Gainesville, FL). Twenty-four cattle naturally infected were randomly allocated to four groups of equal size. Each animal was given subcutaneously either vehicle (1 ml/50 kg), clorsulon (2 mg/kg), ivermectin (200 mcg/kg), or clorsulon (2 mg/kg) combined with ivermectin (200 mcg/kg). Necropsies were performed seven to nine days later. The reductions ($p<0.05$) are listed below. Minor, transient injection-site swellings were observed in two animals given the combination; otherwise, no adverse reactions were observed.

FOI Summary
Ivermectin and Clorsulon

Parasite	% Reduction Clorsulon	Ivermectin	Combination
Fasciola hepatica	87 ns	43 ns	100
Haemonchus placei	78 ns	100	100
Ostertagia ostertagi	77	100	100
O. ostertagi inhibited L_4	100	100	100
Trichostrongylus axei	78 ns	>99	>99
Cooperia pectinata	85 ns	100 ns	100 ns
C. punctata	94 ns	>99	>99
Oesophagostomum radiatum	82 ns	98	100

ns = Not significantly different from controls ($p>0.05$).

6) Trial 11336 was conducted by Dr. R. L. Kilgore (Merck Farms, Inc., Springdale, AR). Twenty-four cattle naturally infected were randomly allocated to four groups of equal size. Each animal was given subcutaneously either vehicle (1 ml/50 kg), clorsulon (2 mg/kg), ivermectin (200 mcg/kg), or clorsulon (2 mg/kg) combined with ivermectin (200 mcg/kg). Necropsies were performed seven to nine days later. The reductions ($p<0.05$) are listed below. No adverse reactions were recorded.

Parasite	% Reduction Clorsulon	Ivermectin	Combination
Fasciola hepatica	100	58 ns	98
Haemonchus placei	32 ns	100	100
Ostertagia ostertagi	28 ns	>99	100
O. ostertagi inhibited L_4	47 ns	97	>99
Trichostrongylus axei	54 ns	>99	>99
T. colubriformis	64 ns	>99	>99
Cooperia spp.*	24 ns	>99	>99
Cooperia spp. L_4	79 ns	100	100
Bunostomum phlebotomum	100 ns	100	100
Oesophagostomum radiatum	86 ns	100	100
Oes. radiatum L_4	94	100	100

ns = Not significantly different from controls ($p>0.05$).
*Cooperia punctata, C. pectinata, and C. mcmasteri.

c. Field Trials

Field trials were conducted in Louisiana, Oregon, and Florida using the clorsulon/ivermectin combination at the therapeutic use level to demonstrate efficacy and safety under practical conditions. Cattle in each trial were randomly allocated to groups based on presentation of replicates at the time of treatment. Control cattle were given vehicle (1 ml/50 kg) while the others were given clorsulon (2 mg/kg) and ivermectin (200 mcg/kg) in combination. Fecal samples were examined for helminth ova per gram of feces at the time of treatment and again three weeks later. Other than a few minor, transient injection-site swellings, no adverse reactions were observed. Numbers of cattle utilized are listed below and the results are listed on the next page.

Trial Number	Location	Last Day of Observation After Treatment	Number of Cattle Control	Number of Cattle Medicated
11654	Louisiana	20	30	119
11673	Oregon	21	25	100
11691	Florida	23	26	104

Trial Number	Number of Cattle With Fluke Eggs/Number Sampled				Number of Cattle With Nematode Eggs/Number Sampled			
	Before Treatment		After Treatment		Before Treatment		After Treatment	
	Control	Medicated	Control	Medicated	Control	Medicated	Control	Medicated
11654	23/24	37/37	22/24	8/37	11/24	18/34	11/24	5/34
11673	15/25	21/33	13/25	2/33	12/25	15/34	19/25	0/34
11691	1/12	0/54	0/12	0/54	6/12	19/55	2/12	2/55

5. Safety

a. Tolerance

Tolerance trial 11334 was conducted by Dr. R. Alva-Valdes (Merck Farms, Inc., Fulton, MO) to investigate the response of cattle given clorsulon alone or clorsulon/ivermectin combination in three consecutive daily administrations. Five groups of eight animals each were formed. One group was given vehicle at three times the comparable therapeutic dose level on each occasion. Other groups were given either clorsulon alone or the combination at their therapeutic use levels (2 mg clorsulon/kg or 2 mg clorsulon/kg in combination with 200 mcg ivermectin/kg, respectively) or at three times use level on each occasion. Body weights and feed consumption were measured starting a week before initial treatments and continuing for three weeks thereafter, but no significant ($p>0.10$) differences were detected. A few minor, transient swellings were observed in cattle given either product at the proposed use levels, but after 21 days these had resolved as areas of fibrosis in the form of plaques, nodules or tracts in the subcutaneous tissue or underlying musculature, and as sterile caseous debris surrounded by fibrosis. These changes were all judged to be clinically acceptable.

b. Toxicity

Toxicity trial 11235 was conducted by Dr. J. D. Pulliam (Merck Farms, Inc., Springdale, AR) to investigate the response of cattle to clorsulon and ivermectin in combination given once at elevated dose levels. Four groups of six animals each were formed randomly. One group of cattle was given vehicle at 25 ml/50 kg (or 25 times the equivalent use level); cattle in the other three groups were given clorsulon/ivermectin combination at the therapeutic use level (2 mg clorsulon and 200 mcg ivermectin/kg), 10 times the therapeutic use level, and 25 times the use level. Each treatment was given once subcutaneously with no more than 10 ml being injected into any one site. The cattle were acclimated to trial conditions for 16 days

before treatment; clinical observations, physical examinations, hematologic values, blood chemistry profiles, and body temperatures were measured before and during the trial. Feed consumption and weight gain were measured before and after dosing. All animals were necropsied 14 to 16 days after treatment and histopathologic evaluations were conducted on the control and high-dose groups. Statistically significant ($p<0.05$) treatment-by-day interaction was seen in 16 of the 36 analyses performed. However, for only one of these variables (aspartate transaminase) was there any suggestion that the interaction might be related to treatment with the clorsulon/ivermectin combination. Average daily feed consumption decreased with increasing dose levels. Signs of transient injection pain were evident in some animals from all treatment groups. Clinically, subcutaneous injection-site swellings were seen in all animals except one vehicle control animal. At necropsy, the injection-site lesions included necrosis of subcutaneous connective tissue and muscle, edema, fibrosis and inflammation. Similar reactions with tissue necrosis are seen with other injectable products and these reactions have been clinically acceptable. Expected larger site reactions were seen at doses greater than the proposed use level.

c. Irritancy

Irritancy trial 11233 was conducted by Dr. J. D. Pulliam (Merck Farms, Inc., Fulton, MO) to determine the injection-site acceptability of clorsulon alone and in combination with ivermectin. Sixteen cattle were given clorsulon at 2 mg/kg once subcutaneously in one side of the neck and the combination (2 mg clorsulon and 200 mcg ivermectin/kg) once subcutaneously in the other side. Each injection site was examined clinically on Days 1, 3, 7, 14, 21, 28, and 35 after treatment, or until necropsy. Eight of the cattle were necropsied 21 days after treatment and eight were necropsied 35 days after treatment. Minor injection-site reactions were observed and these were

usually of the greatest dimensions on Day 3. The swellings gradually resolved and most were gone by Day 21. At necropsy, injection-site lesions 21 days after injection ranged from no visible changes to minor fibrous dermal plaques and/or fibrotic tracts in the underlying muscle. At 35 days after treatment, injection-site lesions ranged from no visible changes to minor tracts in the underlying muscle. These fibrotic scars in the muscle would probably not be noticed at slaughter. The reactions were slightly greater with the combination than with clorsulon alone. Similar reactions with tissue necrosis are seen with other injectables and these reactions have been clinically acceptable.

d. Breeding Animal Safety

Breeding animal safety trials were not conducted with the clorsulon/ivermectin combination. Safety of either component alone has already been demonstrated in prior submissions. However, in the case of clorsulon, the prior data submitted were developed using an oral suspension given at 14 mg/kg (twice the use level). To use these data in support of injectable clorsulon, a bioavailability trial was conducted to compare plasma levels following subcutaneous administration of clorsulon at 3 mg/kg (or 1.5 times the recommended use level) compared to oral administration of the suspension at 14 mg/kg.

Bioavailability trial 11012 was conducted by Dr. R. K. Fulton (Merck Farms, Inc., Springdale, AR) to determine the plasma concentrations of clorsulon following oral administration at 14 mg/kg versus subcutaneous administration at 3 mg/kg. Fourteen cattle were used in a cross-over study. Two animals were chosen randomly as controls and half the remaining animals were given either clorsulon orally at 14 mg/kg or clorsulon subcutaneously at 3 mg/kg on Days 0 and 28. Blood samples were collected repeatedly after treatments and assayed for clorsulon. Cattle given

clorsulon injection had significantly ($p<0.01$) lower areas under the curve, observed peak plasma levels, and time to peak than did cattle given clorsulon orally, as listed below. No adverse reactions were observed in any of the cattle.

Variable	Route of Administration	
	Oral	Subcutaneous
Area under the curve (ng-ml/day)	9.37	4.79
Observed peak plasma level (ng/ml)	4.50	3.85
Time to peak plasma level (days)	1.04	0.33

6. Human Food Safety

A. Toxicity Tests

No additional toxicity testing was done with the combination drug ivermectin and clorsulon.

B. Safe Concentration of Residues

The lowest no observable effect level (NOEL) for the drugs in this combination was for ivermectin in a mouse oral teratogenic study where cleft palate was observed above levels of 0.2 mg/kg/day. Thus using a 1000 times safety factor, an acceptable daily intake of up to two tenths micrograms (0.2 mcg) per kilogram of ivermectin residue by an individual in food.

i.e., 0.2 mg ÷ 1000 safety factor = 0.2 mcg.

A safe level in the muscle tissues of cattle is calculated from the acceptable daily intake, assuming the average weight of man to be 60 kg and the daily human intake of muscle to be 500 g, as follows:

$$\text{safe concentration in muscle} = \frac{(60\text{ kg})\ (0.2\text{ mcg/kg})}{500\text{ g}} = 24\text{ ppb.}$$

When rounded to the nearest 5 ppb the safe concentration in muscle then becomes 25 ppb. The safe concentration of residues in liver, kidney and fat are determined from this number using appropriate food consumption values (food factor) for these tissues. Therefore, the safe concentrations are:

Liver:	25 ppb x 2 (food factor) =	50 ppb
Kidney:	25 ppb x 3 (food factor) =	75 ppb
Fat:	25 ppb x 4 (food factor) =	100 ppb

C. Metabolism and Total Residue Depletion Studies

No additional metabolism or total residue depletion studies were conducted with ivermectin or clorsulon.

D. Studies Demonstrating a Withdrawal Time

A study was performed to determine residues in bovine tissues resulting from dosing the cattle with a subcutaneous injection combination of ivermectin at 0.2 mg/kg B.W. and clorsulon at 2 mg/kg. The vehicle contained 10 mg/ml ivermectin and 100 mg/ml clorsulon in 40% v/v glycerol formal and propylene glycol to make 100% v/v. Three steers and two heifers were sacrificed at each withdrawal time. The withdrawal times were 3, 7, 14, 21, 28 and 35 days. An additional set of five animals served as controls.

Determinative tissue residue assays using high pressure liquid chromatography with fluorescence detection for ivermectin were run on all livers (the target tissue) from this study. Average residues found were as follows:

Days post dose:	3	7	14	21	28	35	Control
ppb found:	160	220	87	63	11	6	0

The analytical method used for these determinations of ivermectin has a lower limit of reliable measurement of 10 ppb. The limit of detection is 1-2 ppb.

Determinative tissue residue assays using high pressure liquid chromatography with ultraviolet detection for clorsulon were run on the kidneys (the target tissue for clorsulon)) from this study. Average residues were as follows:

Days post dose:	3	7	14	21	28	35	Control
ppm found:	.54	.08	.01	.01	0	not assayed	0

The analytical method used for these determinations of clorsulon has a lower limit of reliable measurement of .05 ppm and a detection limit of .01 ppm.

The tolerance (Rm) for ivermectin in cattle has been determined to be 15 ppb in liver, while the Rm for clorsulon has been determined to be 1 ppm in kidneys. Both determinations have been derived experimentally from toxicity and metabolism data. Since the ivermectin tolerance is lower and the residues are more persistent, withdrawal calculations are based on the ivermectin data to estimate the withdrawal time.

Statistical analysis of the depletion data using the upper tolerance limit containing 99 percentile of the population with 95% confidence yields a withdrawal period of 49 days.

E. Regulatory Methods

Ivermectin Determinative Assay Scheme

The determinative assay measures the marker substance, 22,23-dihydroavermectin B_{1a}, by high pressure liquid chromatography of a fluorescent derivative. The marker substance is extracted into isooctane from an aqueous acetone homogenate of liver tissue. The isooctane is removed by evaporation and the extract purified by a series of acetonitrile-hexane-water distributions. The fluorescent derivative is formed by heating with an acetic anhydride/methylimidazole reagent. A chloroform solution is purified over a silica column and concentrated by evaporation; reverse phase liquid chromatography is carried out using 5:95 water/methanol and fluorescence detection. Quantitation is obtained using a standard curve for the marker substance carried through the derivatization and subsequent steps. Recoveries are in the range of 75-95%, and Lm is estimated to be a 10 ppb with a limit of detection of 1-2 ppb.

Ivermectin Confirmatory Assay Scheme

The sample preparation and purification steps of the confirmatory assay are essentially the same as the determinative assay. The specificity is obtained by the production of two new species just prior to derivatization. The new species are produced by removing one of the saccharide groups with 1% sulfuric acid in isopropanol to form the monosaccharide or removing both saccharide groups with 1% sulfuric acid in methanol to form the aglycone of 22,23-dihydroavermectin B_{1a}. Since these two treatments are so similar, the formation of the two new species and their chromatographic properties is unique and hence confirmation of the presence of 22,23-dihydroavermectin B_{1a}.

In the actual test, the sample is split in three parts. One part is used for each of the sulfuric acid treatments. These samples are separated from the sulfuric acid by extractions, and fluorescent

derivatives of the two new compounds are made. The third aliquot is derivatized without pretreatment. All three derivatives are then extracted into hexane with a small amount of isobutyl alcohol present. The liquid chromatographic determination is made as in the determinative assay. Three separate peaks are observed at separate retention times which are compared to standards run through the procedure from the point of adding the sulfuric acid onward. Presence of and quantitation of the three peaks is confirmation that ivermectin is present.

Validation

The determinative and confirmatory methods have been validated satisfactorily by FDA and USDA laboratories. The validated regulatory analytical methods for detection of residues of ivermectin are filed in the Food Additives Manual on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

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7. Agency Conclusions:

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Act and demonstrate that ivermectin and clorsulon (IVOMEC-F) when administered to cattle by subcutaneous injection at doses of 200 mcg ivermectin and 2 mg clorsulon per kg are safe and effective for the indications stated on the product labeling.

Tolerances for ivermectin residues are published in 21 CFR 556.344. The safe concentrations for total residues of ivermectin in uncooked edible tissues of cattle are 25 parts per billion in muscle, 50 parts per billion in liver, 75 parts per billion in kidney, and 100 parts per billion in fat. Tolerances for clorsulon are published in 21 CFR 556.163. The safe concentrations for total clorsulon residues in uncooked edible cattle tissues are: muscle, 1.0 part per million; liver, 2.0 parts per million: kidney, 3.0 parts per million: and fat, 4.0 parts per million. The tissue residue study submitted demonstrated that residues of each drug in combination depleted below its safe concentration by the proposed withdrawal period of 49 days.

Because this drug contains a combination of two previously approved active ingredients, this application is treated as if it were a category II application under CVM's supplemental policy. The sponsor demonstrated via residue depletion studies using the approved regulatory methods that the depletion characteristics of the marker residue for each drug in the combination are not significantly modified. Based on the lack of significant change in depletion characteristics, CVM concluded that the composition of the residue for each drug is not changed. The sponsor also demonstrated that the existing regulatory method for each drug is not interfered with by residues of the other drug. Based on the foregoing, it was not necessary to reevaluate the underlying toxicity tests supporting the separate approvals, or to require additional metabolism and total residue depletion studies.

Adequate directions for over-the-counter use of this combination product have been written. Approved products containing ivermectin and clorsulon alone, for the same claims as are on the label for the combination product, are on the market. CVM is not aware of any reason why the combining of the two products would require restriction of the new product to prescription use.

Dose confirmation trials conducted with ivermectin, clorsulon, and ivermectin/clorsulon combination demonstrated that clorsulon given in combination with ivermectin by the subcutaneous route is effective against adult F. hepatica and has no effect on the efficacy or spectrum of ivermectin.

Section 512(c)(2)(F)(ii) of the act provides a three-year period of exclusivity to NADAs for previously approved active ingredients because reports of new clinical trials, field investigations and human food safety studies was required for approval.

Donald A. Gable

Donald A. Gable, D.V.M.
Director, Division of
Therapeutic Drugs for Food

Dianne T. McRae

Dianne T. McRae, D.V.M.
Branch Chief, Antiparasitic
and Physiologic Drugs(HFV-135)