I. GENERAL INFORMATION

A. File Number

NADA 131-392

B. Sponsor

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

C. Proprietary Name

IVOMEC® Liquid For Sheep

D. Established Name

ivermectin

E. Dosage Form

A ready-to-use liquid 0.08% w/v micellar formulation of ivermectin.

F. Dispensing Status

OTC

G. Dosage Regimen

IVOMEC Sheep Drench is administered orally at a dose of 3.0 mL (2.4 mg ivermectin) per 26 lbs body weight or 200 mcg ivermectin per kilogram of body weight.

H. Route of Administration

oral (by drench).

I. Species/Class

Species and class (if applicable)

J. Indication

For the control of the following parasites in sheep.

Gastrointestinal nematodes:

Haemonchus contortus (adults and fourth-stage larvae)
H. placei (adults)
Ostertagia circumcincta (adults and fourth-stage larvae)
Trichostrongylus axei (adults and fourth-stage larvae)
T. colubriformis (adults and fourth-stage larvae)
Cooperia curtitei (adults and fourth-stage larvae)
C. oncophora (adults)
Nematodirus spathiger (adults and fourth-stage larvae)

N. battus (adults and fourth-stage larvae)
Strongyloides papillosus (adults)
Oesophagostomum columbianum (adults and fourth-stage larvae)
Oes. venulosum (adults)
Trichuris ovis (adults)
Chabertia ovina (adults)

Lungworms:

Dictyocaulus filaria (adults and fourth-stage larvae) Nasal bots:
Oestrus ovis (first-, second- and third-instars)

II. EFFECTIVENESS

Ivermectin for the treatment of parasites affecting sheep was evaluated in 35 controlled efficacy trials. There were 748 sheep involved, of which 520 were given ivermectin and 228 served as controls.

A. Dose-Titration Trials

Dose-titration studies were carried out to determine the dose of ivermectin given once orally that would control gastrointestinal nematodes, lungworms, and nasal bots. Nineteen trials were conducted using ll9 control and 373 ivermectin-treated sheep. Dosages of 50 mcg/kg to 400 mcg/kg were employed. Local procedures were followed regarding animal husbandry during the trials as well as for allocating, dosing, collecting samples, enumerating and identifying parasites, and performing necropsies. The parasitisms were artificially induced in 13 of the trials, naturally acquired in two trials, and induced infections were superimposed in four trials. Based on the data collected, a minimum effective dose of 200 mcg ivermectin/kg bodyweight was determined.

Trial 4828 was conducted in the United States to establish the optimum effective level of ivermectin against nematodes. Sheep were given infective larvae on days 27 and 7 before treatment. Prior to treatment, 25 sheep were randomly allocated to four groups. Ten sheep were used as controls and the other groups had five sheep each. Control sheep were given propylene glycol vehicle, and ivermectin was given once orally to the sheep in the other groups at 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. Necropsies were performed seven days after treatment, and the reductions listed below were recorded. No adverse reactions occurred. Data from 15 additional sheep given another drug are irrelevant to this summary and have been deleted.

	% Reduction (mcg/kg)		
Nematodes	**50**	**100**	**200**
Haemonchus contortus	100	>99	>99
Ostertagia circumcincta	>99	100	>99
Trichostrongylus axei	100	100	100
T. colubriformis	>99	>99	>99
Cooperia spp.	100	100	>99
Immatures (abomasum)	100	100	100
Immatures (small intestine)	100	100	100

Investigator:

K. S. Todd, Jr., Ph.D., College of Veterinary
Medicine, University of Illinois,
Urbana, Illinois 61801.

Trial 4829 was conducted in the United States to establish the optimum effective level of ivermectin against nematodes. The sheep were naturally infected, but were given additional infective larvae 16 days prior to treatment. On the day before treatment, 25 sheep were randomly allocated to four groups. Ten sheep were used as controls and the other groups had five sheep each. Control sheep were given propylene glycol vehicle and ivermectin was given once orally to the sheep in the other groups at 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. Necropsies were performed six days after treatment, and the reductions listed below were recorded. No adverse reactions occurred. Data from an additional 15 sheep given another drug are irrelevant to this summary and have been deleted.

Nematodes	% Reduction (mcg/kg)		
	50	**100**	**200**
Haemonchus spp.	96	86	100
Ostertagia spp.	81	34	100
Trichostrongylus axei	96	98	100
T. colubriformis	75	93	>99
Nematodirus spp.	93	97	>99
Trichuris ovis	80	100	100

Investigator:

A.C. Todd, Ph.D.,
Department of Veterinary Science,
University of Wisconsin,
Madison, Wisconsin 53715.

Trial 5748 was conducted in Australia to establish the optimum effective level of ivermectin against nematodes. Twenty sheep were artificially infected and randomly allocated to groups of equal size. After the nematodes had reached adulthood, each sheep was given either propylene glycol vehicle or ivermectin once orally at 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. Necropsies were performed seven to nine days after treatments, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred. Data from an additional 15 sheep given another drug are irrelevant to this summary and have been deleted.

Nematodes	% Reduction (mcg/kg)		
	50	**100**	**200**
Haemonchus contortus	99	100	100
Trichostrongylus colubriformis (adults)	89ns	>99	100
Nematodirus spathiger (L4)	98ns	>99ns	100ns
Oesophagostomum columbianum (adults)	>99	100	100

ns - Reductions were not significantly different from controls.

Investigators: R. W. Butler, B.V.Sc., and B. M. Thomson, Merck Sharp & Dohme (Australia) Pry Ltd., Campbelltown Road, Ingleburn, N.S.W., Australia

Trial 5759 was conducted in Australia as a dose-titration trial and to compare the efficacy of the individual ivermectin components formulated in propylene glycol against immature nematodes. Forty sheep were artificially infected and randomly allocated to eight groups of equal size. The sheep in both control groups were given vehicle, 22,23-dihydroavermectin B1a was given once orally to the sheep in three groups at 25 mcg/kg, 70 mcg/kg, or 200 mcg/kg, and 22,23-dihydroavermectin B1b was given once orally to the sheep in the other three groups at 25 mcg/kg, 70 mcg/kg, or 200 mcg/kg. Treatments were administered when the nematodes were in the fourth larval stage (L4) of development. Necropsies were performed 13 to 15 days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

	% Reductions (mcg/kg)					
	22,23-dihydroavermectin B1a			**22,23-dihydroavermectin B1b**		
Nematodes	**25**	**70**	**200**	**25**	**70**	**200**
Haemonchus contortus (L4)	12ns	0ns	85	47ns	34ns	86
Osteragia circumcinctal L4	63ns	92	>99	68ns	96	100
Tichostrongyluscolubriformis L4	0ns	98	>99	96ns	>99	100
Nematodirus spathiger L4	0ns	98	>99	37ns	>99	>99

ns - Reductions were not significantly different from controls.

Investigators: R.W. Butler, B.V.Sc., and B.M. Thomson,
Merck Sharp & Dohme (Australia) Pty Ltd,
Campbelltown Road,
Ingleburn, N.S.W.,
Australia

Trial 6074 was conducted in South Africa to establish the optimum effective level of ivermectin against nematodes. Twenty sheep were artificially infected and randomly allocated to four groups of equal size. When the nematodes were in the fourth larval stage (L4), each sheep was given propylene glycol vehicle or ivermectin once orally at 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. Necropsies were performed 14 to 17 days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred. Data from an additional 15 sheep given another drug are irrelevant to this summary and have been deleted.

	% Reduction (mcg/kg)		
Nematodes	**50**	**100**	**200**
Haemonchus contortus (L4)	98	98	100
Trichostrongylus colubriformis (L4)	97	98	100
Nematodirus spathiger (L4)	97	>99	100
Oesophagostomum columbianum (L4)	98	98	100

Investigator:

J. Schroder, B.V.Sc., Merck Sharp & Dohme (Pty) Ltd, Private Bag 3, Halfway House 1685, Transvaal, South Africa.

Trial 6637 was conducted in the United Kingdom to establish the optimum effective level of ivermectin in propylene glycol vehicle against immature nematodes. Twenty-five sheep on a betamethasone regimen were artificially infected and randomly allocated to five groups of equal size. Control sheep were given propylene glycol vehicle and ivermectin was given once orally to the sheep in the other groups at 25 mcg/kg, 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. Treatments were administered when the nematodes were in the fourth larval stage (L4) of development. Necropsies were performed seven days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

	% Reduction (mcg/kg)			
Nematodes	**25**	**50**	**100**	**200**
Nematodirus battus L4	57ns	>99	>99	100
Dictyocaulus filaria L4	>99	>99	>99	>99

ns - Reductions were not significantly different from controls.

Investigators:

J.M. Preston, B.V.Sc., M.R.C.V.S., Ph.D., and A.F. Batty, B.V.Sc., M.R.C.V.S., Highfield Farm, Goose Green, Hertford, Hefts, SG13 8QL, United Kingdom.

Trial 6639 was conducted in the United Kingdom to establish the optimum effective level of ivermectin in propylene glycol vehicle against adult nematodes. Twenty sheep on a betamethasone regimen were artificially infected and randomly allocated to four groups of equal size. Control sheep were given propylene glycol vehicle and ivermectin was given once orally to the sheep in the other groups at 50 mcg/kg, 100 mcg/kg, and 200 mcg/kg. Treatments were administered when the nematodes had been allowed to develop to the adult stage. Necropsies were performed ten days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

	% Reduction (mcg/kg)		
Nematodes	**50**	**100**	**200**
Haemonchus contortus	100	100	100
Ostertagia circumcincta	>99	100	100
O. circumcincta L4	69	>99	100
T. colubriformis	95	100	100
Strongyloides papillosus	97ns	100	100
Dictyocaulus filaria	100	>99	>99

ns - Reductions were not significantly different from controls.

Investigators: J.M. Preston, B.V.Sc., M.R.C.V.S., Ph.D., and A.F. Batty, B.V.Sc., M.R.C.V.S., Highfield Farm, Goose Green, Hertford, Herts, SG 13 BQL, United Kingdom.

Trial 6640 was conducted in the United Kingdom to establish the optimum effective level of ivermectin against nematodes. Twenty-five sheep were artificially infected and randomly allocated to five groups of equal size. Each sheep was given propylene glycol vehicle or ivermectin once orally at 25 mcg/kg, 50 mcg/kg, l00 mcg/kg, or 200 mcg/kg when the nematodes were in the fourth larval stage (L4) of development. Necropsies were performed 12 days after treatment, and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

	% Reduction (mcg/kg)			
Nematodes	**25**	**50**	**100**	**200**
Haemonchus contortus L4	65ns	56ns	97	100
Ostertagia spp.* L4	64	90	99	>99
Trichostrongylus colubriformis L4	45ns	94	>99	100

**Ostertagia circumcincta* and *O. trifurcata* ns - Reductions were not significantly different from controls.

Investigators:

J.M. Preston, B.V.Sc., M.R.C.V.S., Ph.D.,
and A.F. Batty, B.V.Sc., M.R.C.V.S.,
Merck Sharp & Dohme, Highfield Farm, Goose Green,
Hertford, Herts, SG 13 8QL, United Kingdom.

Trial 6647 was conducted in Australia to establish the optimum effective level of ivermectin against nematodes. Twenty sheep were artificially infected and randomly allocated to five groups of equal size. Each sheep was given propylene glycol vehicle or ivermectin once orally at 25 mcg/kg, 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg when the nematodes were in the fourth larval stage (L4) of development. Necropsies were performed 12 or 13 days after treatment, and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

	% Reduction (mcg/kg)			
Nematodes	**25**	**50**	**100**	**200**
Haemonchus contortus L4	67ns	89	77ns	94
Ostertagia circumincta L4	66ns	93	99	100
Trichostrongylus axei L4	86ns	100	100	100
T. colubriformis L4	82ns	99	100	100
Nematodirus spathtiger L4	46ns	94	100	100
Oesophagostomum columbianum L4	98ns	100ns	100ns	99ns

ns - Reductions were not significantly different from controls.

Investigators:

R.W. Butler, B.V.Sc., and B.M. Thomson,
Merck Sharp & Dohme (Australia) Pty Ltd.,
Campbelltown Road, Ingleburn, N.S.W.,
Australia.

Trial 6666 was conducted in Australia to establish the optimum effective level of ivermectin against nematodes. Twenty sheep naturally infected were randomly allocated to four groups of equal size. Each sheep was given propylene glycol vehicle or ivermectin once orally at 100 mcg/kg, 200 mcg/kg, or 400 mcg/kg. Necropsies were performed six or seven days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred. Data from an additional ten sheep given other drugs are irrelevant to this summary and have been deleted.

	% Reduction (mcg/kg)		
Nematodes	**100**	**200**	**400**
Haemonchus contortus adults	>99	>99	100
H. contortus L4	>99	100	100
Ostertagia spp.(a) adults	100	100	100
Trichostrongylus axei adults	100	100	>99
T. colubriformis adults	>99	100	100
T. colubriformis L4	100	100	100
Cooperia spp.(b) adults	100	100	100
Cooperia spp. L4	100ns	100ns	100ns
Nematodirus spp.(c) adults	>99	100	100
Nematodirus spp. L4	>99	100	100
Oesophagostomum venulosum adults	100	100	100
Trichuris ovis adults	97	93	97

(a)*Ostertagia* spp. were predominantly *O. circumcincta*.
(b)*Cooperia oncophora* and *C. punctata*.
(c)*Nematodirus spathiger* and *N. filicollis*.
ns - Reductions were not significantly different from controls.

Investigators:

R.W. Butler, B.V.Sc., and B.M. Thomson,
Merck Sharp & Dohme (Australia) Pry Ltd.,
Campbelltown Road, Ingleburn, N.S.W.,
Australia.

Trial 6676 was conducted in Australia to establish the optimum effective level of ivermectin against immature nematodes, and to compare the responses of two ivermectin component formulations (i.e., 80% dihydroavermectin B1a and 20% B1b versus 95% dihydroavermectin B1a and 5% B1b). Forty-five sheep artificially infected were randomly allocated to nine groups of equal size. Control sheep were given propylene glycol vehicle and sheep in the other groups were given 50 mcg/kg, 100 mcg/kg, 200 mcg/kg, or 400 mcg/kg of either ivermectin formulation (80% B1a or 95% B1a). necropsies were performed 12 to 14 days after treatment, and the

reductions (P<0.05) listed below were recorded. The two formulations were considered to be equivalent. No adverse reactions occurred.

Formulation: 80% B1a (mcg/kg)	**% Reduction**	
	H contortus	***T. colubriformis***
50	98	82
100	>99	>99
200	100	>99
400	>99	>99

Formulation: 95% B1a (mcg/kg)	**% Reduction**	
	H contortus	***T. colubriformis***
50	98	96
100	99	99
200	>99	>99
400	>99	>99

Investigators:

R.W. Butler, B.V.Sc., Merck Sharp & Dohme (Australia) Pty Ltd., Campbelltown Road, Ingleburn, N.S.W., Australia.

Trial 6731 was conducted in South Africa to establish the optimum effective level of ivermectin against immature nematodes. Twenty-five sheep were artificially infected and randomly allocated to five groups of equal size. When the nematodes were in the fourth larval stage (L4) of development, the sheep were given either propylene glycol vehicle or ivermectin at 25 mcg/kg, 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. Necropsies were performed 17 to 19 days after treatment, and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction (mcg/kg)**			
	25	**50**	**100**	**200**
Haemonchus contortus L4	19ns	65	86	>99
Trichostrongylus colubriformis L4	39ns	95	>99	>99
Oesophagostomum columbianum L4	87	95	100	100

ns - Reductions were not significantly different from controls.

Investigator:

J. Schroder, B.V.Sc., Merck Sharp & Dohme (Pry) Ltd., Private Bag 3, Halfway House 1685, Transvaal, South Africa.

Trial 6734 was conducted in South Africa to establish the optimum effective dose of ivermectin, primarily against the nose bot *(Oestrus ovis)* but also against

Haemonchus contortus. Twenty-four sheep naturally infected were randomly allocated to four groups of equal size. The sheep were given either propylene glycol vehicle or ivermectin at 100 mcg/kg, 200 mcg/kg, or 400 mcg/kg. Necropsies were performed five days after treatment and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

Parasites	% Reduction (mcg/kg)		
	100	**200**	**400**
Haemonchus contortus	98	>99	>99
Oestrus ovis	100	100	100

Investigator:

J. Schroder, B.V.Sc., Merck Sharp & Dohme
(Pty) Ltd., Private Bag 3, Halfway House 1685,
Transvaal, South Africa.

Trial 7076 was conducted in the United States to establish the optimum effective level of ivermectin against nematodes. The sheep were naturally infected, but were given additional larvae 29 days prior to treatment. Twenty sheep were randomly allocated to four groups of equal size. Control sheep were given propylene glycol vehicle and ivermectin was given once orally to the sheep in the other groups at 100 mcg/kg, 200 mcg/kg, or 400 mcg/kg. Necropsies were performed seven days after treatment and the reductions listed below were recorded. No adverse reactions occurred.

Nematodes	% Reduction (mcg/kg)		
	100	**200**	**400**
Haemonchus contortus	100	100	100
H. placei	100	100	100
Ostertagia circumcincta	100	100	100
Trichostrongylus axei	>99	100	100
T. colubriformis	>99	100	100
Cooperia oncophora	100	100	100
C. mcmasteri	100	100	100
C. curticei	100	100	100

Investigator:

A.C. Todd, Ph.D., Department of Veterinary
Science, University of Wisconsin, Madison,
Wisconsin 53715.

Trial 7077 was conducted in the United States to establish the optimum effective level of ivermectin against nematodes. The sheep were naturally infected, but were given additional larvae seven days prior to treatment. Twenty sheep were randomly allowed to four groups of equal size. Control sheep were given propylene glycol vehicle and ivermectin was given once orally to the sheep in the other groups at 100 mcg/kg, 200 mcg/kg, or 400 mcg/kg. Necropsies were performed seven days after

treatment, and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	% Reduction (mcg/kg)		
	100	**200**	**400**
Haemonchus contortus adults	92	100	94
H. placei, adults	96	>99	>99
Haemonchus spp. L4	96	100	100
Ostertagia circumcincta adults	100	99	100
Ostertagia spp. L4	100	>99	100
Trichostrongylus axei adults	100	100	99
Trichostrongylus spp. L4 (abomasum)	100	100	96
Trichostrongylus colubriformis adults	100	100	100
Trichostrongylus spp. L4 (small intestine)	>99	>99	100
Cooperia oncophora adults	100	92	100

Investigator:

A.C. Todd, Ph.D., Department of Veterinary Science, University of Wisconsin, Madison, Wisconsin 53715.

Trial 7078 was conducted in the United States to establish the optimum effective level of ivermectin in propylene glycol vehicle against immature nematodes. Twenty-four sheep were artificially infected and randomly allocated to four groups of equal size. Control sheep were given propylene glycol vehicle and ivermectin was given once orally to the sheep in the other groups at 100 mcg/kg, 200 mcg/kg, or 300 mcg/kg. Treatments were administered when the nematodes were in the fourth larval stage (L4) of development. Necropsies were performed 12 days after treatment, and the reductions listed below were recorded. No adverse reactions occurred.

Nematodes	% Reduction (mcg/kg)		
	100	**200**	**300**
Haemonchus contortus L4	99	>99	>99
Ostertagia circumcincta L4	>99	100	100
Trichostrongylus axei L4	>99	100	100
T. colubriformis L4	>99	100	100

Investigator:

K.S. Todd, Jr., Ph.D., College of Veterinary Medicine, University of Illinois, Urbana, Illinois 61801.

Trial 7088 was conducted in the United States to establish the optimum effective level of ivermectin against nematodes. Three weeks after inoculation with infective larvae, twenty sheep (also naturally infected) were randomly allocated to five groups of equal size. Control sheep were given propylene glycol vehicle and ivermectin was

given once orally to the sheep in the other groups at 50 mcg/kg, 100 mcg/kg, 200 mcg/kg, or 400 mcg/kg. necropsies were performed seven days after treatment, and the reductions listed below were recorded. No adverse reactions occurred.

Nematodes	% Reduction (mcg/kg)			
	50	**100**	**200**	**400**
Haemonchus contortus	97	>99	>99	>99
Trichostronqylus colubriformis	>99	>99	>99	100
Nematodirus filicollis	95	93	98	100

Investigator:

H.E. Jordan, D.V.M., Ph.D., College of
Veterinary Medicine, Oklahoma State University,
Stillwater, Oklahoma 74074

Trial 7098 was conducted in the United States to establish the optimum effective level of ivermectin against the nasal bot, *Oestrus ovid.* Twenty-four naturally infected sheep were randomly assigned to five groups. Four sheep were used as untreated controls, five were given propylene glycol vehicle, and ivermectin was given to the sheep in the other groups (n=5/group) at 50 mcg/kg, 100 mcg/kg, or 200 mcg/Kg. Necropsies were performed seven or eight days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

Parasite	% Reduction (mcg/kg)		
	50	**100**	**200**
Oestrus ovis L2(a)	100	100	100
Oestrus ovis L3(b)	86ns	86ns	100

ns - Reductions were not significantly different from controls.
(a)Second-stage larvae (instars).
(b)Third-stage larvae (instars).

Investigator:

J.M. Cheney, D.V.M., College of Veterinary
Medicine and Biomedical Sciences,
Colorado State University, Ft. Collins,
Colorado 80523.

Trial 7937 was conducted in Australia to establish the optimum effective level of ivermectin in either propylene glycol or micelle vehicles against immature nematodes. Fifty sheep were artificially infected and randomly allocated to ten groups of equal size. Control sheep in one group were given propylene glycol vehicle, control sheep in another group were given micelle vehicle, and sheep in the other groups were given ivermectin formulated in propylene glycol vehicle or in micelle vehicle at 25 mcg/kg, 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. necropsies were performed 12 to 14 days after treatment, and the reductions ($P<0.05$) listed below were recorded. No differences between the formulations were detected. No adverse reactions occurred.

Nematodes	% Reduction (mcg/kg)							
	Propylene glycol				Micelle			
	25	50	100	200	25	50	100	200
Haemonchus contortus L4	90ns	0ns	97	92	0ns	88ns	96	97
Ostertagia circumincta L4	53ns	53	96	99	30ns	92ns	94	98
Trichostrongylus colubriformis L4	25ns	84ns	99	>99	12ns	87	97	>99

ns - Reductions were not significantly different from the controls.

Investigators:

R.W. Butler, B.V.Sc., and B.M. Thomson
Merck Sharp & Dohme (Australia) Pty Ltd
Campbelltown Road, Ingleburn, N.S.W., Australia

B. Formulation Trials

Ivermectin is defined as a combination of two homologues, including not less than 80% 22,23-dihydroavermectin B1a and not more than 20% 22,23-dihydroavermecttn B1b (MK-933). Some of the trials early in the developmental program were conducted with a combination containing not less than 95% of the B1a homologue (MK-932). The definition of ivermectin includes both combinations but, nonetheless, a comparison was conducted (trial 6676, p. 15) and the efficacy of each was determined to be equivalent. An additional comparison (trial 5759, p.7) was made of the efficacy of the two homologues separately, and each was determined equally efficacious.

The vehicle (propylene glycol) used in the dose-titrations trials caused the sheep to cough more than was clinically acceptable. Hence, a micelle formulation was evaluated (trial 7937, p.23) and, with one minor change in components, was adopted for commercial use following further comparison in two other trials (7452, p.32; 8451, p.43).

C. Dose-Confirmation Trials

Confirmation of the dose selected for gastrointestinal and pulmonary nematodes was accomplished in 16 controlled trials. The confirmation data were obtained using a total of 147 sheep treated with ivermectin at 200 mcg/kg bodyweight and 109 controls. Infections were acquired naturally in four trials, induced in lO trials, and superimposed in two trials. All the sheep were killed 7 to 14 days after treatment for parasite recoveries.

Trial 6665 was conducted in Australia to confirm the efficacy of ivermectin against nematodes. Ten sheep with natural infections were randomly allocated to two groups of equal size. Control sheep were untreated and sheep in the other group were given ivermectin in propylene glycol once orally at 200 mcg/kg. Necropsies were performed eight days after treatment, and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus	64ns
Ostertagia spp.(a)	99
Ostertagia spp. L4	100
Trichostrongylus axei	>99
Oesophagostomum columbianum	100
O. venulosum	100

(a)*Ostertagia circumcincta* and *O. trifurcata*

Investigators:

R.W. Butler, B.V.Sc., and B.M. Thomson,
Merck Sharp & Dohme (Australia) Pry Ltd,
Campbelltown Road, Ingleburn, N.S.W.,
Australia.

Trial 6699 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Twenty sheep were artificially infected and randomly allocated to 3 groups (1 indicator, 7 controls and 12 treated with ivermectin). Control sheep were untreated and sheep in the other group were given ivermectin in propylene glycol once orally at 200 mcg/kg when the nematodes were in the third *(Haemonchus contortus, Trichostrongylus colubriformis,* and *Chabertia ovina)* or fourth *(Strongyloides papillosus)* larval stage of development. Necropsies were performed on the 34th, 35th and 3?th days after treatment. The reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus L3	>99
Trichostrongylus colubriformis L3	>99
Strongyloides papillosus L4	>99
Chabertia ovina L3	97
Trichuris sp. adult	70

Investigator:

J. Schroder, B.V.Sc., Merck Sharp & Dohme
(Pry) Ltd., Private Bag 3, Halfway House 1685,
Transvaal, South Africa.

Trial 6700 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Twenty sheep were artificially infected and randomly allocated. One group of seven sheep was used as untreated controls, a second group of 12 sheep was given ivermectin in propylene glycol once orally at 200 mcg/kg, and one sheep was an infectivity indicator control. The nematodes were in the fourth larval stage (L4) of development on the day of treatment. Necropsies were performed 23 to 25 days after treatment, and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus L4	99
Trichostrongylus colubriformis L4	100
Nematodirus spathiger L4	>99
Oesophagostomum columbianum L4	100
Trichuris spp. adults	>99
Dictyocaulus filaria L4	>99

Investigator:

J. Schroder, B.V.Sc., Merck Sharp & Dohme (Pty) Ltd., Private Bag 3, Halfway House 1685, Transvaal, South Africa.

Trial 6854 was conducted in Brazil to confirm the efficacy of ivermectin against *Oestrus ovis.* Ten sheep with natural infections were randomly allocated to two groups of equal size. Control sheep were untreated, and sheep in the other group were given ivermectin in propylene glycol once orally at 200 mcg/kg. Necropsies were performed five days after treatment. Each of the five control sheep harbored all three larval stages (bors) of *O. ovis* at necropsy, whereas none of the ivermectin-treated sheep harbored any live bots. No adverse reactions occurred. Data from five other sheep given another drug are irrelevant to this summary and have been deleted.

Parasite	**% Reduction**
Oestrus ovis L1(a)	100
O. ovis L2	100
O. ovis L3	100

(a)First-, second-, and third-stage larvae (instars)

Investigators:

R. A. Roncalli, D.V.M., M.S., P.O. Box 2000 Rahway, N.J. 07065; S. Vaucher, D.V.M., and J. Solis, D.V.M., Estacao Experimental Gaucha, MSD AGVET Brazil, Uruguaiana, Rio Grande do Sol, Brazil

Trial 7257 was conducted in the United Kingdom to confirm the efficacy of ivermectin against *Nematodirus battus.* Ten sheep were artificially infected and randomly allocated to two groups of equal size. Control sheep were given vehicle, and sheep in the other group were given ivermectin in propylene glycol once orally at 200 mcg/kg. Necropsies were performed seven days after treatment and the reductions ($P<0.05$) listed below were recorded. Data from five other sheep given ivermectin at 100 mcg/kg are irrelevant to this summary and have been deleted. No adverse reactions occurred.

Nematodes	**% Reduction**
Nematodirus battus adults	100
N. battus L4	100

Investigators: J. M. Preston, M.R.C.V.S., Ph.D., and A. F. Batty, M.R.C.V.S., Merck Sharp & Dohme Ltd., Veterinary Laboratory, Highfield Farm, Goose Green, Nr. Hertford, Hertfordshire, SG13 BQJ, U.K.

Trial 7452 was conducted in Australia to compare the efficacy of ivermectin in propylene glycol or micelle formulations against immature nematodes. Twenty sheep were artificially infected and randomly allocated to four groups of equal size. Sheep in two groups received either vehicle, and sheep in the other two groups received ivermectin at 200 mcg/kg when formulated in either vehicle. Treatments were administered when the nematodes were in the fourth larval stage (L4) of development. necropsies were performed seven to nine days after treatment, and the reductions ($P<0.05$) listed below were recorded. Based on the data obtained, ivermectin given in either formulation was concluded to be equivalent. Data from another ten sheep given a third formulation are irrelevant to this summary and have been deleted. No adverse reactions occurred.

	% Reduction (mcg/kg)	
Nematodes	**Propylene glycol vehicle**	**Micelle vehicle**
Haemonchus contortus L4	100	>99
Ostertagia circumincta L4	100	100
Trichostrongylus colubriformis L4	100	100
Oesophagostomum columbianum L4	100	100

Investigators:

R.W. Butler, B.V.Sc., and B.M. Thomson,
Merck Sharp & Dohme (Australia) Pty Ltd,
Campbelltown Road, Ingleburn, N.S.W.,
Australia.

Trial 7662 was conducted in New Zealand to confirm the efficacy of ivermectin against nematodes. Fourteen sheep with natural infections as well as induced infections of *Dictyocaulus filaria* and *Haemonchus contortus* were randomly allocated to two groups of equal size. Control sheep were given vehicle, and sheep in the other group were given ivermectin in micelle solution once orally at 200 mcg/kg. necropsies were performed seven to nine days after treatment and the reductions ($p<0.05$) listed below were recorded. Data from 21 other sheep given other drugs are irrelevant to this summary and have been deleted. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus adults	100ns
H. contortus L4	100
Ostertagia spp. adults(a)	100
Ostertagia spp. L4	92
Trichostrongylus axei adults	>99
T. axei L4	97
Trichostrongylus spp. adults(b)	100
Trichostrongylus spp. L4	80ns
Cooperia curticei adults	100
C. curticei L4	89ns
Nematodirus spp. adults(c)	100
Nematodirus spp. L4	97
Oesophagostomum venulosum adults	100
Trichuris ovts adults	100
Chabertia ovina adults	100
Dictyocaulus filaria adults	>99
D. filaria L4	96

ns - Reductions were not statistically different from controls.
(a)*Ostertagta circumcincta* and *O. trifurcata*
(b)*Trichostrongylus colubriformis* and *T. vitrinus*
(c)*Nematodirus spathiger* and *N. filicollis*

Investigators:

G. C. Cairns, B.Sc., Merck Sharp & Dohme
(New Zealand) Ltd., Arahura Research Farm,
R.D.4, Masterton, New Zealand.

Trial 7683 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Twenty sheep were artificially infected and allocated to two groups. Eight sheep were untreated controls, and 12 sheep were given ivermectin in propylene glycol once orally at 200 mcg/kg when the nematodes had reached the adult stage. Necropsies were performed 14 to 16 days after treatment and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus	>99
Trichostrongylus colubriformis	>99
Nematodirus spathiger	>99
Oesophagostomum columbianum	>99
Trichuris spp.	100

Investigator:

G. E. Swan, B.V. Sc., Merck Sharp & Dohme (Pty)
Ltd., Private Bag 3, Halfway House 1685,
Transvaal, South Africa.

Trial 7685 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Twenty sheep raised worm-free except for *Trichuris* spp. were inoculated with infective nematode larvae and randomly allocated to two groups. Eight control sheep were untreated and the 12 sheep in the other group were given ivermectin in propylene glycol once orally at 200 mcg/kg when the nematodes were in the third larval stage. necropsies were performed 34 to 36 days after treatment and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Ostertagta circumcincta L3	>99
Oesophagostomum columbianum L3	96
Trichuris spp. adults	39

Investigator:

G. E. Swan, B.V. Sc., Merck Sharp & Dohme (Pry)
Lts., Private Bag 3, Halfway House 1685,
Transvaal, South Africa.

Trial 7686 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Nineteen sheep were artificially infected with *Ostertagia circumcincta* and allocated to two groups. The sheep harbored natural infections of *Trichuris ovis.* Seven sheep were untreated controls, and 12 sheep were given ivermectin in propylene glycol once orally at 200 mcg/kg when the nematodes had reached the fourth larval stage (L4) of development. Necropsies were performed 38 to 40 days after treatment and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Ostertagta circumcincta	>99
Trichuris spp.	87
Chabertia ovina	100

Investigator:

G. E. Swan, B.V. Sc., Merck Sharp & Dohme (Pry)
Ltd., Private Bag 3, Halfway House 16B5,
Transvaal, South Africa.

Trial 7687 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Nineteen sheep were artificially infected and allocated to two groups. Some sheep also harbored natural infections of *Trichuris* spp. Seven sheep were untreated controls, and 12 sheep were given ivermectin in propylene glycol once orally at 200 mcg/kg when the nematodes were in the adult stage of development. Necropsies were performed 14 to 16 days after treatment and the reductions (P<0.05) listed below were recorded. No adverse reactions occurred.

Nematodes	**% Reduction**
Ostertavia circumcincta	100
Strongyloides papillosus	>99
Chabertia ovina	100
Trichuris spp.	94
Dictyocaulus filarta	>99

Investigator:

G. E. Swan, B.V. Sc., Merck Sharp & Dohme (Pry) Ltd., Private Bag 3, Halfway House 1685, Transvaal, South Africa.

Trial 7688 was conducted in South Africa to confirm the efficacy of ivermectin against nematodes. Twenty sheep raised worm-free except of *Trichuris* spp. were inoculated with infective nematode and randomly allocated to two groups. Eight control sheep were untreated and the 12 sheep in the other group were given ivermectin in micelle solution once orally at 200 mcg/kg when the nematodes were in the parasitic third stage. Necropsies were performed 41 to 43 days after treatment and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred, except that one ivermectin-treated sheep died as a result of pharyngeal trauma inflicted while being dosed.

Nematodes	**% Reduction**
Haemonchus contortus L3	99
Nematodirus spathiger L3	>99
Strongyloides papillosus L3	93
Oesophagostomum columbianum L3	88
Trichuris spp. adults	76

Investigator:

G. E. Swan, B.V. Sc., Merck Sharp & Dohme (Pty) Ltd., Private Bag 3, Halfway House 1685, Transvaal, South Africa.

Trial 7898 was conducted in the United Kingdom to confirm the efficacy of ivermectin against nematodes. Twelve sheep with natural infections were also artificially infected with Chabertia ovina and randomly allocated to two groups of equal size. Control sheep were untreated, and the sheep in the other group were given ivermectin in micelle solution once orally at 200 mcg/kg. Necropsies were performed l4 days after treatment and the reductions ($P<0.05$) listed below were recorded. Data from 6 other sheep given a second formulation are irrelevant to this summary and have been deleted. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus	100
Ostertagia circumcincta	>99
O. circumcincta inhibited L4	99
Trichostrongylus axei	100
Nemadtodirus filicollis	100
Trichuris ovis	100
Chabertia ovina	>99

Investigator: J. Armour, Ph.D., University of Glasgow Veterinary School, Bearsden, Giasgow, United Kingdom.

Trial 8301 was conducted in the United Kingdom to confirm the efficacy of ivermectin against nematodes. Twelve sheep were artificially infected and randomiy allocated to two groups of equal size. Control sheep were untreated, and sheep in the other group were given ivermectin in micelle solution once orally at 200 mcg/kg. Necropsies were performed 14 days after treatment and the reductions ($P<0.05$) listed below were recorded. Data from 18 other sheep given other doses and other formulations are irreievant to this summary and have been deleted. No adverse reactions occurred.

Nematodes	**% Reduction**
Haemonchus contortus L4	100
Trichostrongylus axei adults	100
Nematodirus battus adults	100
Trichuris ovis adults	100
Chabertia ovina L4	100

Investigator: A.F. Batty, M.R.C.V.S., Merck Sharp & Dohme Ltd., Veterinary Laboratory, Highfieid Farm Goose Green, Nr. Hertford. Hertfordshire, SG 13 8Q3, United Kingdom.

Trial 8421 was conducted in New Zealand to confirm the efficacy of ivermectin against nematodes. Fourteen sheep with natural infections were randomly allocated to two groups of equal size. Control sheep were given vehicle, and the other sheep were given ivermectin in micelle solution once orally at 200 mcglkg. Necropsies were performed seven to nine days after treatment and the reductions ($P<0.05$) listed below were recorded. No adverse reactions occurred. Data from 21 other sheep given other drugs are irrelevant to this summary and have been deleted.

Nematodes	**% Reduction**
Haemonchus contortus adults	>99
H. contortus L4	98
Ostertagia spp. adults(a)	100
Ostertagia spp. L4	98
Trichostrongylus axei adults	>99
T. axei L4	100
Trichostrongylus spp. adults(b)	100
Trichostrongylus spp. L4	93
Cooperia curticei adults	100
C. curticei L4	100
Nematodirus spp. adults(c)	100
Nematodirus spp. L4	98
Trichuris ovis adults	98
Oesophagostomum venulosum adults	100
Chabertia ovina adults	100
Dictyocaulus filaria adults	100
D. filaria L4	96

a *Ostertagia circumcincta* and *O. trifurcata*
b *Trichostronqvlus colubriformis* and *T. vitrinus*
c *Nematodirus spathiger* and *N. filicollis*

Investigator:

G.C. Cairns. B.Sc., Merck Sharp & Dohme
(New Zealand) Ltd., Arahura Research Farm,
R.D.4, Masterton, New Zealand.

Trial 8451 was conducted in the United States to compare the efficacy of ivermectin in propyiene glycol or micelle formulations against adult nematodes. Eighteen naturally infected sheep were randomly allocated to three groups of equal size. Sheep in one group were untreated controls, and sheep in the other two groups received ivermectin at 200 mcg/kg when formulated in either vehicle. Necropsies were performed seven days after treatment, and the reductions ($P<0.05$) listed below were recorded. Based on the data obtained, ivermectin given in either formulation was concluded to be equivalent. No adverse reactions occurred.

	% Reduction (mcg/kg)	
Nematodes	**Propylene glycol vehicle**	**Micelle vehicle**
Haemonchus contortus	100	100
Trichostronqylus axei	100	100
T. colubriformis	100	100
Nematodirus spp.(a)	100	100
Nematodirus spp. L4	100	100
Trichuris ovis	100	96

(a)*Nematodirus spathiger* and *N. filicollis.*

Investigator: E.S. Brokken, D.V.M., Merck Research Farm, Route 2, Box 136, Fulton, Missouri 65251.

D. Field Trial

Trial 7728 was conducted in the United States as a field evaluation of the efficacy of Ivermectin administered at use level in the commercial formulation. Eighty sheep were given ivermectin at 200 mcg/kg and 20 were used as controls. The incidence of positive nematode egg counts in fecal samples examined from ivermectin-treated sheep was reduced from 80% before treatment to 5% after treatment. No adverse reactions occurred.

Investigator: E.S. Brokken, D.V.M., Merck Research Farm, Route 2, Box 136, Fulton. Missouri 65251

III. TARGET ANIMAL SAFETY

A series of trials was conducted to demonstrate that ivermectin given in single oral administrations to sheep at 200 mcg/kg is safe and that the drug has a wide therapeutic index. These trials involved investigations of tolerance, toxic syndrome, breeding sheep safety, and other potential problems.

A. Tolerance

Trial 7524 was conducted in France as a tolerance trial. Fifty sheep (equal numbers of each sex) about three months old, were allocated to five groups of equal size. Treatments included vehicle or ivermectin in micelle solution once orally at 200 mcg/kg, 1000 mcg/kg, 2000 mcg/kg. or 4000 mcg/kg (or 1, 5, 10, or 20 times the recommended therapeutic dose level). Except for the first male replicate which was treated orally, all other treatments were given via intraesophageal intubation. Each animal was weighed and observed clinically during the 21 days after treatment. No adverse effects were observed except for coughing in the replicate treated orally.
Investigator: J. Foix, D.M.V., 10 Rue Du Mont D'Urville,
78200 Manres La Jolie, France

B. Toxic Syndrome

Trial 7000 was conducted in the United States as a toxic syndrome trial. Ten male and ten female sheep (28 to 39 kg in weight) were randomly allocated to five groups of equal size. Control sheep were given water in a quantity comparable to the average of all other treatment volumes, and other groups were given ivermectin in propylene glycol at 300 mcg/kg, 2000 mcg/kg, 4000 mcg/kg, and 8000 mcg/kg (or 1.5, 10, 20, and 40 times the use level). Two days later an additional two sheep were each given 315 m1 of propylene glycol alone. All but one of the ivermectin-treated sheep coughed during or immediately following treatment and had other signs including head shaking and labia1 licking. Sheep given ivermectin at 300 mcg/kg and 2000 mcg/kg remained clinically normal during the trial. Sheep given ivermectin at 4000 mcg/kg were mildly depressed and ataxic during the first day after treatment. At 8000 mcg/kg, ataxia and depression were observed and one sheep became comatose. Three days later, all sheep appeared normal. The two sheep given propyiene glycol had the same signs as the sheep given ivermectin at 8000 mcg/kg; one died within 24 hours of treatment and the other recovered. All the test sheep were Killed 21 to 23 days after treatment. but no gross or histologic lesions were present that could be associated with the administration of ivermectin.

In conclusion. the adverse effects observed in the sheep given ivermectin formulated in propylene glyco1 seemed to be more attributable to the vehicle than to ivermectin.

Investigator: F.V. Hashko, D.V.M., Ph.D. Merck Sharp and Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065.

C. *Breedinq Animal Safety*

Trial 6455 was conducted in New Zealand to determine whether ivermectin has any teratogenic effects in ewes. There were 364 ewes allocated to seven groups of equal size. Treatments were given to ewes once during the first, second, or third week of pregnancy; and again during the fourth, fifth, or sixth week of pregnancy. Three replicates were given ivermectin once orally at 400 mcg/kg, three replicates were given vehicle in a comparable volume, and one replicate was untreated. There was a range of seven days in ages of embryos exposed to treatment within each regimen, and hence there were ewes treated on each of the first 43 days of pregnancy. No marked differences in rates or return to estrus after matings were recorded among the ewes. All lambs born alive were examined shortly after birth, and those born dead were necropsied. No adverse effects attributable to treatment with ivermectin were detected either in the ewes or in their lambs.

Investigator: P.G. Scott, B.V.Sc., Merck Sharp & Dohme (New Zealand) Ltd., Arahura Research Farm, R.D. 4, Masterton, New Zealand.

Trial 6660 was conducted in Australia to determine whether ivermectin has any effects in ewes on pregnancy. Thirty-six ewes were allocated to two groups of equal size. Ewes in one group were given ivermectin orally at 400 mcg/kg (twice the use level) at 14-day intervaIs starting before the 51st day of pregnancy and ending when their ewes were weaned at 56 days of age. The second group of ewes was given comparable volumes of vehicle on the same schedule. No significant differences were found between groups in the numbers of lambs born, birth weight of lambs, or the weaning weights. No stillbirths occurred in either group and no deformities were found in any lambs. Ivermectin was concluded to have had no effect on these pregnant ewes or their lambs.

Investigator: R.H. Butler, B.V.Sc., Merck Sharp & Dohme (Australia> Pry. Ltd., Campbelltown Road, Ingleburn, N.S.N., Australia

Trial 6729 was conducted in South Africa to determine whether Ivermectin has any effects in the reproductive performance of rams. Twenty breeding rams were allocated to two groups of equal size. Rams in one group were untreated controls whereas the other group of rams was given ivermectin once orally at 400 mcg/kg (twice the use level). Semen samples were collected from each ram by electro-ejaculation three times before and twice after each treatment, and no important differences were found between the groups. Further, each ram was hemicastrated six days after the last observation; histologica1 examination revealed no differences between the groups. Ivermectin was concluded to have had no effect on the breeding performance of the rams studied.

Investigator: 3. Schroder, B.V. Sc., and G.E. Swan, B.V. Sc., Merck Sharp and Dohme (Pty) Ltd., Private Bag 3. Hailway House 1685, Transvaal, South Africa.

D. Field Trials

There were 124 field trials conducted to assess safety of ivermectin use under field conditions. A dose of 200 mcg/kg was utilized in one United States tria1 and in another in New Zealand. All the other trials utilized a dose of 400 mcg/kg. propyiene glycol was used as vehicle in 95 trials whereas micelle vehicle was used in the other 29, including the U.S. trial.

These trials involved 10,730 sheep given ivermectin at 400 mcg/kg, of which 1782 were given ivermectin in micelle vehicle at 400 mcg/kg and 80 given ivermectin in micelle solution at 200 mcg/kg. No adverse reactions occured in these trials. However, the amount of coughing in sheep given the propylene glyco1 vehicle was sufficient to result in a formulation change to the micelle solution.

E. Investigators

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- R. Restani, D.V.M., Instituto di Malattie Infertive, Profilassi & Polizia Veterinaria, via S. Giacomo 9/2, I-40126, Bologna, Italy
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- P. Tassi, D.V.M., Merck Sharp & Dohme (Italia) S.p.A., Via del Caravaggio 105. 00147 Rome, Italy

F. Efficacy Trials

During the efficacy trials, no adverse reactions attributable to ivermectin occured. There was, as already stated, sufficient coughing among sheep given the propylene glycol formulation to result in the selection of a micelle vehicle for commercial use. Three deaths occured in the trials, including an illness existing prior to treatment.

Pharyngeal trauma occuring during dosing, and enterotoxemia. None of these deaths was caused by ivermectin.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests

Not relevant to FDA requirements.

1. Acute Oral Toxicity Study in Dogs

Report Number and Starting Date: IT #79-2869 started 6/27/79.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and strain of Test Animal: Beagle Dogs. Number of Animals of Each Sex/Group: 2/sex/group. Dose Levels: 2.5, 5.0, 10.0 mg/kg.

Route of Drug Administration: Oral.

Toxicity Observed: There was no mortality. Mydriasis was noted following dosing of dogs at 2.5 or l0 mg/kg/day. Tremors were seen in dogs given 5 and l0 mg/kg/day, and one dog at 10 mg/kg/day was comatose on the morning following dosing. This dog recovered within 48 hours of dosing but was ataxic and had occasional tremors until 72 hours post-dosing.

2. Microbial Mutagen Test with and without Rat Liver

Report Numbers and Starting Date: TT started l2/l5/77; TT #78-8l05 started ll/2l/78; TT #79-8033 started 6/14/79.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933; L-638,109 (22,23-dihydroavermectin Bla) L-639,222 (22,23-dihydroavermectin Blb).

Species and Strain: Salmonella typhimurium (TA1535, TA1537, TA98, TA100) with and without an 5-9 metabolic activation system prepared from rat liver.

Dose Levels Tested: MK-933 - 400. l000 and 2000 mcg/plate;

L-638,709 - 100, 500 and l000 mcg/plate;

L-639,622 - 20, 200 and 2000 mcg/plate.

Results: None of the test compounds studied produced significant increases in reversion to histidine prototrophy under any of the test conditions.

3. Cytotoxicity Tests and Mutagen Assays in Mouse

Report Number and Starting Date:

TT #79-8034 started 6/20/79;
TT #79-8035 started 6/26/79;
TT #79-8043 started 7/02/79;
TT #79-8044 started 7/09/79;
TT #79-8047 started 8/06/79.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point. PA.

Substance and Dosage Form Tested: MK-933 as a solution in DMSO.

Species and Strain Used: Mouse lymphoma cell line (L5178Y).

Dosage Levels: 20.40 and 60 mcg/m1 with S-9 metabolic activation system; 5, 10 and 20 mcg/ml w/o an S-9 activation system.

Results: MK-933 did not produce any significant increases in mutation frequency when compared with the negative controls.

4. Unscheduled DNA Synthesis in Human IMR-90 Fibroblasts

Report Number and Starting Date: #80-8205 started I/I2/80-

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in DMSO.

Species and Strain: Human Fibroblast cell line (IMR-90).

Dosage Levels Used: 10 to l000 mcg/ml with and w/o an S-9 metabolic activation system.

Results: MK-933 did not induce unscheduled DNA synthesis in human cells at any dose level.

5. Oral Reproduction Study in Rats

Report Number and Starting Date: started 4/l7/78.

Laboratory: Merck Sharp & Dohme Research Laboratories. West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: Charles River (CD) rats.

Number of Animals/Sex/Group: 15 females/group

Dose Levels: 0.4, 0.8 and 1.6 mg/kg/day from 15 days before mating throughout gestation and lactation until Day 20 postpartum.

Route of Drug Administration: Oral by gavage.

Parameters Examined: Daily clinical appearance, body weight gain and F0 females and offspring, survival and physical development of offspring.

Toxicity Observed: Increased mortality among offspring in the l.6 mg/kg/day dosage level group. The purpose of this study was to provide offspring which had been exposed to MK-933 in utero and throughout the lactation period for use in a subsequent three-month oral toxicity study in rats (TT #78-037-0).

No Observed Effect Level: 0.8 mg/kg/day.

6. 14-Week Oral Toxicity Study in Rats Following In Utero Exposure

Report Number and Starting Date: TT #78-037-0 started 6/19/78.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: Charles River rats born of F0 females which had been administered MK-933 throughout gestation and lactation in a study previously described (TT #78-7l0-0).

Number of Animals/Sex/Group: 20

Dose Levels: 0.4, 0.8 and l.6 mg/kg/day daily for 14 weeks.

Route of Drug Administration: Oral.

Parameters Examined: Daily clinical appearance, body weight gain, opthalmologic, hematologic and serum biochemical studies in Drug Weeks 4, 8 and 13. All rats were necropsied, detailed microscopic examination of tissues from all control and high dose rats; liver, kidney, spleen and bone marrow from all rats were also examined microscopically.

Toxicity Observed: Splenomegaly, extramedullary hematopoiesis, and iron positive pigment in the renal tubular epithelium in three rats from the 1.6 mg/kg/day group and one from the 0.6 mg/kg/day group. These changes suggest possible drug-related intravascular hemolysis. There were no other ante- or postmortem changes related to drug administration.

No Observed Effect Level: 0.4 mg/kg/day.

7. 14-Week Oral Toxicity Study in Dogs

Report Number and Starting Date: TT #78-038-0 started 6/26/78.

Laboratory: Merck Sharp & Dohme Research Laboratories, West. Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: Beagle dogs.

Number of Animals/Sex/Group: 4/sex/group

Dose Levels: 0.5, 1.0 and 2.0 mg/kg/day for 94 to 95 days.

Route of Drug Administration: Oral by gavage.

Parameters Examined: Daily clinical appearance, body weight, hematologic and serum biochemical studies and urinalyses in Drug Weeks 4.8 and 12. Opthalmologic examinations in Drug Weeks 3, 7 and 12. Electrocardiograms in Drug Weeks 5, 9 and 13. All animals were necropsied in Drug Week 14. Histomorphologic examination was conducted on tissues of all dogs.

Toxicity Observed: Mydriasis and slight body weight loss at doses of l and 2 mg/kg/day. Four dogs in the 2 mg/kg/day group developed tremors, ataxia. anorexia and dehydration and were sacrificed prior to scheduled necropsy. Treatment-related postmortem changes were limited to small areas of agonal gastrointestinal congestion and/or hemorrhage in 2 of the 4 dogs that were sacrificed in poor physical condition.

No Observed Effect Level: 0.5 mg/kg/day.

8. Oral Teratogenic Study in the Mouse

Report Number and Starting Date: TT #79-7l4-0 started 8/2/79.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: Mice (CF1).

Number of Animals/Sex/Group: 25 mated females/group

Dose Levels and Duration of Treatment: 0.1, 0.2, 0.4 and 0.8 mg/kg/day from Days 6 through 15 of gestation.

Route of Drug Administration: Oral by gavage.

Parameters Examined: Clinical appearance, maternal body weight, numbers of implants, resorptions, live and dead fetuses at cesarean section; external, visceral and skeletal examination of letuses.

Toxicity Observed: There were treatment-related deaths of 1, 1 and 3 females in the 0.2, 0.4 and 0.8 mg/kg/day dosage groups. respectively. In most of these mice intermittent whole body muscular tremors were observed 1 to 2 days prior to death or sacrifice. Teratogenicity was evident at external examination of fetuses in the 0.8 and 0.4 mg/kg/day dosage level groups as an increased incidence of cleft palate.

No Observed Effect Level: Maternotoxicity - 0.1 mg/kg/day; teratogenicity - 0.2 mg/kg/day.

9. Oral Teratogenic Study in Rats

Report Number and Starting Date: TT #79-709-0 started 6/25/79.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: 14K-933 as a solution in sesame oil.

Species and Strain: Rats (Charles River CD).

Number of Animals/Sex/Group: 25 mated females/group

Dose Levels and Duration of Treatment: 2.5, 5.0 and 10.0 mg/kg/day from Days 6 through 17 of gestation.

Route of Drug Administration: Oral by gavage.

Parameters Examined: Clinical appearance. maternal body weight. numbers of implants, resorptions, live and dead fetuses per litter, fetal weight; external visceral and skeletal examination of fetuses.

Toxicity Observed: In the 10 mg/kg/day dosage level, group 3 females were sacrificed in poor condition. Treatment-related clinical signs of toxicity in this dosage group included sedation and focal alopecia. Teratogenicity, as evidenced by cleft palate was observed at a dose of lO mg/kg/day.

Observed Effect Level: Maternotoxicity - 5 mg/kg/day; teratogenicity - 5 mg/kg/day.

10. Oral Teratogenic Study in Rabbits

Report Number and Starting Date: TT #79-713-0 started 1/30/19.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: New Zealand albino rabbits.

Number of Animals/Sex/Group: 16 inseminated females/group.

Dose Levels and Duration of Treatment: 1.5, 3.0 and 6.0 mg/kg/day from Days 6-18 of gestation.

Route of Drug Administration: Oral by gavage.

Parameters Examined: Clinical appearance, maternal body,weight, numbers of implants, resorptions, live and dead fetuses, fatal weight; external visceral and skeletal examination of fetuses.

Toxicity Observed: Slight to marked sedation. significant decrease in mean body weight gain, and an increased number of abortions occurred in females from the 6 mg/kg/day group. Fetotoxicity was evident in the mg/kg/day group as a significant increase in fetal deaths and a decrease in mean live fatal weight, Decrease in mean live fetal weight was also apparent in fatuses from the mg/kg/day group. Teratogenicity was evident as a dose-related incidence of cleft palate and clubbed forepaws among letuses from the 3 and 6 mg/kg/day dosage groups.

No Observed Effect Level: Maternotoxicity 3.0 mg/kg/day; teratogenicity and fetotoxicity l.5 mg/kg/day.

11. Multigeneration Study in Rats

Report Number and Starting Date: 4f78-713-0/-1/-2 started 6/5/78.

Laboratory: Merck Sharp & Dohme Research Laboratories. West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: Charles River CD rats.

Number of Animals/Sex/Group: 20 female/TO male/group.

Dose Levels and Duration of Treatment: 0.4, 1.2 and 3.6 mg/kg/day; the study was designed so that dosing of F0, F1b and F2b weanling male and female rats would be continuous for 70 days and throughout the production of two litters in each of three generations. The study was terminated prior to mating of the F1b generation for production of an F2b litter when it became apparent that toxicity observed in F1a, F1b and F2a offspring would preclude the establishment of a no-effect level.

Route of Drug Administration: Oral by gavage.

Parameters Examined: Clinical appearance, body weight, postpartum survival, physical and reflex development of offspring, reproductive performance.

Toxicity Observed: There was a decrease in survival of F1a offspring in the 3.6 mg/kg/day groups. and in F1b offspring from the 1.2 and 0.4 mg/kg/day dosage levels. Surviving pups in all treatment groups showed decreased weight gain during the lactation period.

No Observed Effect Level: Less than 0.4 mg/kg/day

12. Multigeneration Study in Rats

Report Number and Starting Date: started 5/14/19.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-933 as a solution in sesame oil.

Species and Strain: Charles River CD rats.

Number of Animals/Sex/Group: 20 female/10 male/group.

Dose Levels and Duration of Treatment: 0.05, 0.1, 0.2 and 0.4 mg/kg/day; dosing of F0 male and female rats was continuous for 71 days and continued throughout the production of two litters in each of three successive generations.

Route of Drug Administration: Oral by gavage.

Parameters examined: Clinical appearance, body weight, postpartum survival of offspring, physical and reflex development of offspring, opthalmologic examinations of F0, F1b and F2b rats, reproductive perfomance.

Toxicity Observed: Slight increase in pup mortality at 0.2 and 0.4 mg/kg/day and slight decrease in body weight gain in F1b weanling rats at the 0.4 mg/kg/day dosage level.

No Observed Effect Level: 0.1 mg/kg/day.

13. Metabolism Study in Rats

Report Number and Starting Date: TT #79-7ll-0 started 6/14/19.

Laboratory: Merck Sharp & Dohme Research Laboratories, West Point, PA.

Substance and Dosage Form Tested: MK-932 (22,23-dihydroavermectin B1a), tritium-labeled.

Species and Strain: Charles River CD rats.

Number of Animals/Sex/Group: 6 females/group.

Dose Levels and Duration of Treatment: 2.5 mg/kg/day; one group received tritium-labeled MK-932 as a solution in sesame oil for days, then throughout mating, gestation and lactation until Day 9 postpartum. A second group received tritium-labeled MK-932 at the same dosage level from Days 1 to 9 postpartum.

Route of Drug Administration: Oral.

Parameters Examined: Maternal plasma, milk, as well as samples of blood, brain, liver and carcass from mother and offspring were analyzed for drug residues.

Results: Steady state plasma drug levels were reached in the maternal animal within 10 days of dosing. Maternal drug plasma levels increased three- to four-fold on Day l postpartum, possibly indicating a mobilization of depot fat during the latter stages of gestation. Concentrations of MK-932 in the milk were three to four times higher than revels in the plasma. based on estimates of milk intake by neonatal rats, the quantity of MK-932 secreted in the milk reached levels as high as 50% of the LD50 for infant rats. Neonatal blood/brain ratios indicated that the blood/brain barrier was formed in the rat between Day 6 and Day lO postpartum. The results of this study indicated that the high concentrations of MK-932 in the milk of 1aerating dams chronically administered the drug may explain the toxicity observed among offspring in MK-933 multigeneration studies during the lactation period.

No Observed Effect Level: Not applicable.

B. Safe Concentration of Residues

The lowest no-observable-effect-levels (NOEL) in the battery of toxicity studies described in Section A above were determined in the multigeneration study in rats (0.1 mg/kg/day) and in the oral teratogenic study in the mouse (0.1 mg/kg/day for maternotoxicity and 0.2 mg/kg/ day for teratogenicity). The minimum safety margins required for the effects observed in these studies are 100x for the multigeneration study and for the maternotoxicity in the mouse teratological study and 1000x for the teratological effects also seen in the latter study. Due to the significance of the terata (cleft palate) seen in the teratology study the 1000x safety factor was used for determining an acceptable daily intake of up to two tenths micrograms (0.2) per kg 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 swine 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:

safe concentration in muscle = ***(60 kg) (0.2 mcg/kg)*** = 24 ppb.

500

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 5 (food factor) = 125 ppb
- Kidney: 25 ppb x 5 (food factor) = 125 ppb
- Fat: 25 ppb x 5 (food factor) = 125 ppb

The H2B1a component of the unaltered drug has been selected as the marker substance for ivermectin, since it is the major component in liver at all slaughter periods and has the appropriate depletion characteristics in that tissue. An Rm value of 30 ppb has been established for liver (the target tissue). since H2Bla represents 25% of the residue in liver when the total residue in the tissue is at the safe concentration of 125 ppb.

C. Metabolism and Total Residue Depletion Studies

Total radioactive residue (averaged value from three animals) from two separate experiments in edible tissues of sheep dosed intraruminally with 3H-labeled MK-933 at levels of 0.3 mg/kg body weight is shown in the table below:

Total Residue (ppb)

	Days Post Dose						
Tissue	**1**	**3**	**5**	**7**	**14**	**21**	**28**
	212	105	23	44	-	-	-
Liver	-	-	-	11	5	1	2
	245	153	63	73	-	-	-
Fat	-	-	-	32	24	13	10
	62	37	8	13	-	-	-
Kidney	-	-	-	4	2	0	2
	43	37	7	10	-	-	-
Muscle	-	-	-	0	0	0	0

Although both liver and fat were candidate target tissues. liver has been chosen as the target tissue because of the integrity of that tissue as one organ and the difficulty in extracting and isolating residues of the drug from fat. The H2B1a component of the unaltered drug has been selected as the marker substance for ivermectin, since it is the major component in liver at all slaughter periods and has the appropriate depletion characteristics in that tissue. An Rm of 30 ppb has been established for liver (the target tissue).

That value represents the average 1eve1 of the H2B1a marker in liver tissue as measured by the regulatory assay when the average total residue in fat (the tissue in which residues persist longest) depletes to the safe concentration of 125 ppb.

The radioactive residue in the edible tissues is essentially all extractable in organic solvents indicating that there is very little, if any, intractable covalently bound residues in these tissues. The unaltered drug (H2B1a and H2B1b) accounts for about 78% of the total radioactive residue in liver at 3 days and about 65% at 5 days after

dosing. In fat, the unaltered drug accounts for about 56% of the total residue 3 days after dosing and 33% at 5 days after dosing.

The major polar metabolite in the sheep liver is identified to be 24-hydroxymethyl-H2B1a. Other polar metabolites are identified as the monosaccharide of 24-hydroxymethyl-H2B1a and the 24-hydroxymethyl-H2Blb. The total residue identified as unaltered drug or known metabolites is 68% in the liver at 5 days after dosing. In fat, the major metabolites are nonpolar. Chemical and enzymatic hydrolysis studies suggest that these metabolites exist in the fat as an acy1 esters of the 24-hydroxymethylated metabolite. None of the unidentified metabolites in tissues represented more than 10% of the total residue.

Since the unaltered drug is the major component in the liver at all slaughter periods, the unaltered drug (i.e., H2B1a component) should be a satisfactory marker substance.

Comparative metabolism studies indicate a striking similarity in metabolism of ivermectin in sheep and rat, the test species. The analyses for unaltered drug in various tissues, the HPLC profile of the radioactive residue in the liver, and the in vitro liver microsomal metabolism are all comparable in sheep and rats. Thus, the test species is exposed to the major drug residue components (i.e., unaltered drugs and known metabolites) known to be present in sheep tissues.

D. Studies Demonstrating a Withdrawal Time

Ivermectin (MK-933): Tissue Residue in Sheep Dosed Orally at 0.3 mg/kg with Micellar Formulation (Study SH-238).

A study was performed to determine residues in sheep tissues resulting from dosing the animals with ivermectin orally with a micellar formulation at 0.3 mg/kg. The vehicle contained 0.8 mg of ivermectin/ml in an aqueous vehicle containing 20% propylene glycol and B% surfacant. Three wethers and two ewes were sacrificed at each withdrawal time. The withdrawal times involved being 1, 3, 5, 7, 10, and 14 days. An additional set of five animals served as controls.

Liquid chromatographic-fluorescence determinative tissue residue assays were run on all Livers (the target tissue) from this study. Average residues found were as follows:

Day Post Dose	**1**	**3**	**5**	**7**	**10**	**14**	**Control**
ppb found	72	12	11	8	0	0	0

The analytical method used to make the determination quoted easily has a lower limit of reliable measurement of 10 ppb. The 1imit of detection is 1-2 ppb. The Rm value for sheep derived from toxicity and metabolism data has been determined to be 30 ppb. Statistical analysis of the depletion data using the upper tolerance limit containing 99 percentile of the population with confidence yields a withdrawal period of 11 days.

E. Regulatory Methods

Ivermectin Determinative Assay Scheme

The determinative assay measures the marker substance, 22,23-dihydroavermectin B1a, by liquid chromatography of a fluorescent derivative. The marker substance is extracted into isooctane from an aqueous acetone homogenate of the 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 10-88% and Lm is estimated to be 10 ppb with a limit of detection of 1-2 ppb.

Ivermectin Confirmatory 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 15 sulfuric acid in isopropanol to form the monosaccharide or removing both saccharide groups with 15 sulfuric acid in methanol to form the aglycone of 22,23-dihydroavermectin B1a. 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 B1a.

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 fluorescing 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 iso-butyl aicohol 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.

F. Validation

The determinative and confirmatory methods were 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).

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA ccmply with the requirements of Section 512 of the Act and demonstrate that Ivomec (Ivermectin) Sheep Drench, 0.08% Solution when used under its proposed conditions of use is safe and effective.

The requirements under 21 CFR 514.1(b)(3) have been met. The firm has described practicable methods for determining the quantity of the drug and any substance formed in food because of its use. Both determinative and confirmatory methods were validated by FDA and USDA laboratories.

The drug and its metabolites were accounted for by appropriate metabolism and total residue depletion studies utilizing an acceptable radiotracer. These studies included comparative metabolism studies in the target (sheep) and test (rat) species.

A tolerance (Rm of 30 ppb) has been established for the marker residue (22,23-dihydroavermecrin B1a) in the target tissue (liver) and a withdrawal period (11 days) has been determined experimentally using the 99% statistical tolerance limit with 95% confidence under field conditions to assure that the prescribed use of the subject drug will be safe and that residues of ivermectin in sheep will be safe for human consumption.

Based on the provisions in the Threshold Assessment guideline, the agency initially placed ivermectin in toxicity category "C". Following an evaluation of data from a battery of three short-term geno-toxicity tests and from 90-day rat studies in the rat and dog which raised no suspicion of carcincgenicity, the agency assigned ivermectin to category "A". Additional toxicity data provided by the sponsor were adequate to satisfy the agency's general food safety requirements for NADA approval.

The Agency concludes that adequate directions for use by the lay persons have been written for the proposed over-the-counter use of this anthelmintic and endoparasitic drug which is indicated for the treatment of endoparasites commonly occuring in sheep.

VI. ATTACHMENTS

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.