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November 14, 2008

Program Manager
USDA/AMS/TM/NOP
Room 4008-So., Ag Stop 0268
1400 Independence Ave., SW
Washington, DC 20250

NOV 19 2008

Re.: NOP Petition for Eprinomectin

Dear Dr. Sir/Madam:

Merial Limited (Merial) herewith submits a petition for the inclusion of eprinomectin as a synthetic substances allowed for use in organic livestock production (§ 205.603) on the National Organic Program-National List of Substances Allowed and Prohibited in Organic Production and Handling. This petition is submitted according to the provisions set forth in 7 CFR Part 205.

Please contact me by telephone at (678) 638-3746 or e-mail at huston.howell@merial.com concerning any questions or comments about this submission.

Sincerely,

Huston Howell, Ph.D.

/enclosures

Petition for the Evaluation of Eprinomectin for the National List of Substances Allowed in Organic Production and Handling

Synthetic substances allowed for use in organic livestock production, § 205.603.

Introduction

Eprinomectin is a broad-spectrum endectocide that effectively controls many species and stages of internal and external parasites, particularly those of economic importance in the cattle industry. It is approved for use in beef and dairy cattle by national animal drug product regulatory authorities of the United States (FDA, NADA 141-079) and over fifty other countries worldwide. As approved in the United States, there is a zero-day withdrawal period for meat and a zero-day discard period for milk. Eprinomectin has a strong safety profile with respect to humans and the environment, when used as directed by the product labeling. It is classified as a semi-synthetic material, in that the starting materials are derived from fermentation of the micro-organism (*Streptomyces avermitilis*), followed by various isolation and further chemical reaction steps. It has been formulated into a weatherproof liquid solution (0.5% mg/mL) for convenient topical application under the brand name *IVOMEC® EPRINEX® Pour-On for Beef and Dairy Cattle.*

Merial Limited herewith submits this petition for the addition of eprinomectin to the National List as a Synthetic substance allowed for use in organic livestock production. This document contains the required information set forth in the Federal Register, Vol. 72, No. 11, January 18, 2007.

Submitting Petitions for § 205.606 When submitting petitions to include a non-organic agricultural substance onto § 205.606, the petitioner must state in the petition justification statement, why the substance should be permitted in the production or handling of an organic product. Specifically, the petition must include current industry information on availability of, and history of unavailability of an organic form of the substance. When providing information on commercial availability of the organic form of an agricultural product, petitioners must be aware that the global market is the universe of supply; commercial availability is not dependent upon geographic location or local market conditions.

Item A—Please indicate which section or sections the petitioned substance will be included on and/or removed from the National List.

Eprinomectin is herewith submitted for the synthetic substances allowed for use in organic livestock production, § 205.603.

Item B—Please provide concise and comprehensive responses in providing all of the following information items on the substance being petitioned:

1. The substance's chemical or material common name.

Common Name:
Eprinomectin (a mixture of two isomeric compounds)

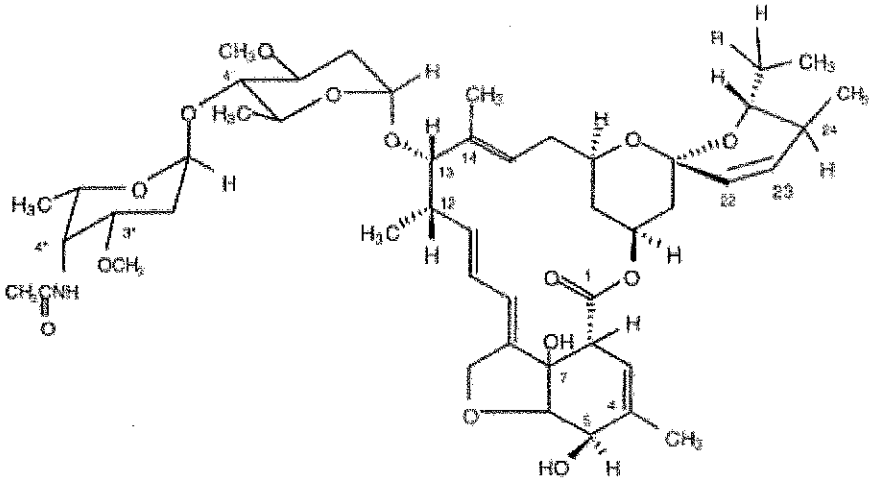
Chemical Names:
Isomer B_{1a}: (4"B)-acetylamino-5-demethyl-4"-deoxyavermectin A_{1a}
Isomer B_{1b}: (4"R)-acetylamino-5-O-demethyl-25-de(1-methylpropyl)-4"-deoxy-25-(1-methylethy1)avermectin A_{1a}

Molecular Formulas:
Isomer B_{1a}: $C_{50}H_{75}NO_{14}$
Isomer B_{1b}: $C_{49}H_{73}NO_{14}$

Molecular Weights:
Isomer B_{1a}: 914.14
Isomer B_{1b}: 914.11

Chemical Structure:

B_{1a} Component $R = C_2H_5$
B_{1b} Component $R = CH_3$



Chirality
Isomers B_{1a} and B_{1b} have 20 and 19 asymmetric centers, respectively.

2. The manufacturer's or producer's name, address and telephone number and other contact information of the manufacturer/producer of the substance listed in the petition.

Manufactured for (marketed by):
Merial Limited
3239 Satellite Blvd
Duluth, GA 30096-4640
New Animal Drug Application: 141-079
(678) 638-3000

Manufactured (produced) by:
Argenta Limited
2 Sterling Avenue
Manurewa, Auckland
New Zealand
FDA Registration No.: 3005982303

3. The intended or current use of the substance such as use as a pesticide, animal feed additive, processing aid, nonagricultural ingredient, sanitizer or disinfectant. If the substance is an agricultural ingredient, the petition must provide a list of the types of product(s) (*e.g.*, cereals, salad dressings) for which the substance will be used and a description of the substance's function in the product(s) (*e.g.*,ingredient, flavoring agent, emulsifier, processing aid).

Current Use
Eprinomectin is used worldwide for effective control of both internal and external parasites in cattle and other ruminant species (deer, goats). In the United States Eprinomectin (IVOMEC® EPRINEX® Pour-On for Beef and Dairy Cattle) is approved by the FDA for the use in beef and dairy cattle, including lactating dairy cattle.

> Indications: IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle (in the U. S.) is indicated for the treatment and control of gastrointestinal roundworms (*Haemonchus placei* (adult and L4), *Ostertagia ostertagi* (adult and L4, including inhibited L4), *Trichostrongylus axei* (adult and L4), *T. colubriformis* (adult and L4), *T. longispicularis* (adult), *Cooperia oncophora* (adult and L4), *C. punctata* (adult and L4), *C. surnabada* (adult and L4), *Nematodirus helvetianus* (adult and L4), *Bunostomum phlebotomum* (adult and L4), *Oesophagostomum radiatum* (adult and L4), *Strongyloides papillosus* (adults), *Trichuris species* (adults); lungworms (*Dictyocaulus viviparus*, adult and L4); cattle grubs (all parasitic stages of *Hypoderma lineatum*, *H. bovis*); lice (*Damalinia bovis, Linognathus vituli, Haematopinus eurysternus, Solenopotes capillatus*); mange mites (*Chorioptes bovis, Sarcoptes scabiei*); and horn flies (*Haematobia irritans*). (FDA approved labeling)
>
> Persistent Activity: IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle has been proven to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* for 21 days after treatment and *Haematobia irritans* for 7 days after treatment. (FDA approved labeling)

4. A list of the crop, livestock or handling activities for which the substance will be used. If used for crops or livestock, the substance's rate and method of application must be described. If used for handling (including processing), the substance's mode of action must be described.

Method of Application
IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle is applied topically along the midline of the back.

Product Packaging
The product is available in 250-mL, 1-liter, 2.5-liter, 5-liter, and 20-liter polyethylene containers. Each milliliter of solution contains 5 mg eprinomectin.

Dosage
The approved dosage is 500 mcg eprinomectin/kg body weight (1 mL/10 kg or 22 lb BW).

Mode of Action
Eprinomectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Antimicrobial activity
Using a standard, antimicrobial screen, eprinomectin was shown to have no significant antimicrobial effects versus 26 microbial species (including bacteria and fungi) at concentrations as high as 1,000 ppm. In all, 52 tests were performed; some species were incubated at both 25 °C and 37 °C, some species were incubated in the presence and absence of lactamases, and both normal and antibiotic-resistant strains of some species were included in the screen.

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

Eprinomectin is produced by chemical synthesis starting from the fermentation product abamectin, which is obtained by fermentation of the microorganism *Streptomyces avermitilis*. As an abamectin is a mixture of the class of compounds known as avermectins, eprinomectin is also a mixture, comprised of chiefly two isomeric (see below). These compounds are produced by chemical synthesis from the corresponding abamectin components avermectin B_{1a} and avermectin B_{1b}. Eprinomectin contains a minimum of 95% of these two components, of which at least 90% is Isomer B_{1a}.

6. A summary of any available previous reviews by State or private certification programs or other organizations of the petitioned substance. If this information is not available, the petitioner should state so in the petition.

To our knowledge, eprinomectin has not been reviewed by any State certification program

IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle is listed in the Milk and Dairy Beef Residue Prevention Protocol—2008 Producer Manual published by the Milk & Dairy Beef Quality Assurance (DQA) Center. IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle is also listed as one of the parasite treatment options required in the MERIAL SUREHEALTH® Calf Preconditioning Certification program. This program is designed to verify that calves meet the USDA requirement for Quality Systems Assessment source and age verification at the point of origin, allowing later export to QSA-requiring countries.

7. Information regarding EPA, FDA, and State regulatory authority registrations, including registration numbers. If this information does not exist, the petitioner should state so in the petition.

Eprinomectin is approved by national regulatory animal drug product authorities of the United States (FDA, NADA 141-079, IVOMEC® EPRINEX® Pour-On for Beef and Dairy Cattle) and over fifty other countries world-wide. In the United States, it is an over-the-counter product. There are no other products containing eprinomectin sold in the U. S.

The current FDA-approved package insert and the 250 mL container labels are included in **Attachment 1.** This insert is the most comprehensive, and it contains all of the information found on the other labeling components, such as bottle labels, cartons, etc. The 250 mL container labels are representative of all other container sizes, with respect to information content, format, layout, color scheme, etc.

8. The Chemical Abstract Service (CAS) number or other product numbers of the substance and labels of products that contains the petitioned substance. If the substance does not have an assigned product number, the petitioner should state so in the petition.

CAS #: 133305-88-1

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

Physico-chemical Properties

Description	White to off-white, hygroscopic, crystalline powder
Sublimation (Vapor) Pressure (23°C)	$4\pm1 \times 10^{-6}$ torr
Melting Point	163-166 ^{O}C
Water solubility (25°C.)	3.5±0.2 ppm
partition (distribution) coefficient n-octanol/water (pH 6.8 phosphate buffer)	5.4±0.3
pH (saturated aqueous solution)	7.2
Dissociation Constant (pKa)	No pK_a between 3 and 10

(a) Chemical interactions with other substances, especially substances used in organic production

Eprinomectin is formulated in a pour-on liquid solution and is applied directly to each individual animal. Thus, when used as directed, it should not come in contact with any other substance used in organic production. As noted below in Section 9 (b), eprinomectin binds tightly to soil, which substantially reduces its further dissemination in the environment.

(b) toxicity and environmental persistence

Toxicity toward *Daphnia magna*

The acute toxicity of eprinomectin to the cladoceran, *Daphnia magna*, was determined under flow-through test conditions. Based on the mortality/immobility data for 24 and 48 hours of exposure of daphnids to eprinomectin, the 48-hour EC_{50} value (95% confidence limits) was 0.45 (0.37-0.64) mcg a.i./L (ppb) while the 48-h no-mortality concentration was less than 0.37 mcg a.i./L, the lowest concentration tested.

Toxicity toward fish

The acute toxicity of eprinomectin to the rainbow trout, *Oncorhynchus mykiss*, and the bluegill sunfish, *Lepomis macrochirus*, were determined during a 96-hour exposure period under flow-through test conditions. The LD_{50} values were 1.2 and 0.37 mg a.i./L (ppm), respectively. The 96-hour no-observed effect concentrations, determined by visual examination of the mortality and observations data, were 0.37 and 0.14 mg a.i./L, respectively.

Toxicity toward avians

The acute toxicity of eprinomectin, when administered as a single oral dose in a capsule, was determined for the northern bobwhite, *Colinus virginianus*, and the mallard, *Anas platyrhynchos*. The LD_{50} values were 272 mg/kg and 24 mg/kg, respectively. With respect to sub-lethal effects, at the lowest dosage level employed in the mallard LD_{50} test (7.8 mg/kg), slight lower limb weakness and loss of coordination occurred within 3 hours after dosing and lasted through the afternoon of day two. From day 3 until the end of the test, the birds appeared normal. The subacute LC_{50} values for eprinomectin, when administered via the feed in an eight-day dietary study, 5 days on medicated feed followed by 3 days on eprinomectin-free diet, were 1,813 ppm for the northern bobwhite and 447 ppm for the mallard duck, respectively. At the lowest concentration studied (100 ppm eprinomectin) in the mallard, lethargy, reduced reaction to external stimuli, loss of coordination and lower limb weakness were observed as sub-lethal effects one day after exposure to the eprinomectin-containing diet. These effects lasted only during the on-drug phase of the study, and all birds appeared normal 24 hours following their return to the basal diet.

Earthworm toxicity

A study to determine the toxicity (LC_{50}) of eprinomectin to the earthworm, *Lumbricus terrestris,* was conducted in artificial soil for 28 days. All worms used in the test were mature with clitellum and were acclimated 14 days prior to the initiation of the test. The LC_{50} value for earthworms exposed to eprinomectin in an artificial soil was determined to be greater than 951 mg a.i./kg dry soil, the highest concentration tested. The no-mortality concentration was 295 mg a.i./kg dry soil. The no-observed-effect concentration was less than 90.8 mg a.i./kg dry soil, the lowest concentration tested, based on a treatment-related loss in body weight among worms in this treatment group.

Phytotoxicity

a) Algae

The phytotoxicity of eprinomectin to the fresh water unicellular green alga, *Selenastrum capricornutum,* was determined under static conditions for 14 days. Cell densities were determined at approximately 48-hr intervals during the 14-day study. Analyses of cell density and maximum growth rate data included the t-test and a dose-response trend test. Based on the mean log cell densities on day 14 and the maximum mean specific growth rates, the minimum inhibitory concentration (MIC) for *Selenastrum capricornutum* exposed to eprinomectin for 14 days was determined to be 15 mg a.i./L. The 14-day no-observed-adverse-effect concentration was 7.0 mg a.i./L.

b) Terrestrial Plants

The lack of phytotoxicity toward six plant species (cucumber, lettuce, soybean, perennial ryegrass, tomato, and wheat) has been demonstrated with eprinomectin in both a seed germination and root elongation study and a seedling growth study in sand. The results (NOEC values) from the studies

are presented below in "Tables 5" and "Table 6". All NOEC values were based on mean measured concentrations.

TABLE 5
RESULTS FROM THE SEED GERMINATION AND ROOT ELONGATION PHYTOTOXICITY STUDY WITH EPRINOMECTIN

SPECIES	NOEC, ppm	
	GERMINATION	ROOT ELONGATION
Cucumber	1300	95
Lettuce	1300	8.5
Soybean	1300	95
Perennial Ryegrass	1300	8.5
Tomato	1300	8.5
Wheat	1300	8.5

TABLE 6
RESULTS FROM THE SEEDLING GROWTH PHYTOTOXICITY STUDY WITH EPRINOMECTIN IN SAND

SPECIES	NOEC, ppm		
	SHOOT LENGTH	SHOOT WEIGHT	ROOT WEIGHT
Cucumber	0.47	0.47	0.47
Lettuce	6.5	6.5	6.5
Soybean	6.5	6.5	6.5
Perennial Ryegrass	0.47	0.47	0.47
Tomato	0.47	0.47	0.47
Wheat	0.47	0.47	0.47

Dung Beetles

The toxicity of eprinomectin was determined towards two species of dung beetles, *Onthophagus gazella* and *Euoniticellus intermedius*. Control feces was homogenized and divided into 5-kg aliquots. One aliquot served as a non-treated control. To the remainder, eprinomectin was added in 5 mL of dimethylformamide. Treated fecal samples contained eprinomectin B_{1a} at 0.0 (vehicle-treated control), 7.0, 24, 64.7, 166 and 590 ppb on a wet-weight basis. Fecal pats were placed on top of soil in plastic pails and three male-female pairs of *0. gazella* or *E. intermedius* beetles were placed in each of 6 pails per treatment for each species. There were no effects on adult beetles, as measured by lethality, i.e. number of live adults recovered or numbers of brood balls formed over the range of eprinomectin tested. No live progeny were recovered at the 166 or 590 ppb levels. The NOEC, based on numbers of emerged progeny relative to pooled controls (untreated and solvent controls), was 64.7 ppb for both species. An LC_{50}, based on the number of brood balls formed by the adults, could not be calculated.

RESULTS OF EFFECTS STUDIES WITH EPRINOMECTIN

Species	Study	Result	95% C.I.	No-Mortality Level	No-Effect Level
Cladoceran, *Daphnia magna*	48-h LC_{50}	0.45 ppb	0.37-0.64	<0.37 ppb	<0.37 ppb[a]
Algae, *Selenastrum capricornutum*	14-d MIC	15 ppm	---	---	7 ppm
Earthworm, *Lumbricus terrestris*	28-d LC_{50}	>951 ppm dry soil	---	295 ppm dry soil	<90.8 ppm dry soil[a]
Rainbow Trout, *Oncorhynchus mykiss*	96-h LC_{50}	1.2 ppm	0.99-1.4	0.37 ppm	0.37 ppm
Bluegill, *Lepomis macrochirus*	96-h LC_{50}	0.37 ppm	0.33-0.42	0.14 ppm	0.14 ppm
Northern bobwhite, *Colinus virginianus*	acute oral LD_{50}	272 mg/kg body wt.	203-364	125 mg/kg	<62.5 mg/kg[a]
Northern bobwhite, *Colinus virginianus*	8-day dietary LC_{50}	1813 ppm in feed	1420-2312	1000 ppm in feed	<316 ppm in feed[a]
Mallard, *Anas platyrhynchos*	acute oral LD_{50}	24 mg/kg body wt.	18-32	7.8 mg/kg	<7.8 mg/kg[a]
Mallard, *Anas platyrhynchos*	8-day dietary LC_{50}	447 ppm in feed	357-558	178 ppm in feed	<100 ppm in feed[a]

[a] Lowest Level Tested

Summary of hazard assessment in aquatic ecosystems

The MIC and NOAEC for eprinomectin towards the fresh water unicellular green alga, *Selenastrum capricornutum,* are greater than 4 times and 2 times, respectively, the aqueous solubility of eprinomectin (3.5 ppm). The concentration of eprinomectin in bodies of water adjacent to fields fertilized with manure containing eprinomectin residues or in ponds resulting from direct wash-off from cattle will be far below the LC_{50} for *Daphnia.* Although eprinomectin hydrolyzes very slowly in the dark, it photodegrades rapidly and binds tightly to soil, where it degrades aerobically. Therefore, it will neither persist nor accumulate in aquatic ecosystems.

Photodegradation

The photodegradation of the B_{1a} component of eprinomectin exposed to summer sunlight in New Jersey, U.S.A. was studied. Based on the degradation of the B_{1a} component of eprinomectin under these conditions, it was calculated that eprinomectin would photodegrade near the surface of open, flat bodies of water under clear skies in summer and winter sunlight with minimum half-lives of 0.29 and 1.10 days, respectively. This rapid photodegradation in water should effect swift elimination of eprinomectin from the aquatic environment.

Mobility in soil

The B_{1a} component of eprinomectin has K_{OC} values of 3231 to 9208 for sorption and desorption with three common soils types. Compounds possessing K_{OC} values greater than 1000 are considered tightly bound to soil organic matter, and as such can be considered to be immobile in soil. Thus, this drug has been classified as tightly bound to soil and hence immobile. Consequently, the possibility of translocation of eprinomectin through soil from one site to another in the environment is remote. When the B_{1a} component of eprinomectin was partitioned between water and loam, loam/sandy loam and clay loam soils, soil to water distributions (K_d) were 88.2, 53.1 and 133.5, respectively, averaged for sorption and desorption. Thus, in a 1:1 mixture of soil and water, ~98% of the drug would be bound, with only ~2% or less in the solution in equilibrium with the soil.

Aerobic degradation in soil

Under aerobic conditions at 22±3 °C over 64 days in three soil types (sandy loam, loam and silt loam) in triplicate, ^{14}C-eprinomectin mineralizes to $^{14}CO_2$ to an average of about 3-4%. After 64 days, the parent compound (eprinomectin) accounted for 47-50% by HPLC analysis and 51-55% by TLC analysis of the applied radioactivity, as determined by chromatography of soil extracts. Degradation products were more polar (based on reverse phase HPLC and normal phase TLC elution characteristics) than eprinomectin, but were not further identified. Thus, the half-life for aerobic biodegradation of eprinomectin in soil at ~22°C is about 64 days.

Hydrolytic Stability
The half-lives of eprinomectin at pH 4, 5, 7, and 9 were estimated to be 622, 614, 2026, and 414 days, respectively. A chemical with a half-life of greater than 1 year at 25°C is considered to be hydrolytically stable.

Environmental Fate Summary
Given the tight binding of eprinomectin to soil, which greatly reduces its effective concentration, significant transport of eprinomectin residues from fields fertilized with cattle manure to bodies of water in the vicinity is highly unlikely. Both oxidative degradation in soil under aerobic conditions and photodegradation (on soil surfaces and in water) will diminish the environmental concentration of eprinomectin. Based on the discussion of soil binding, degradation via aerobic soil metabolism and photodegradation, it can be reasonably predicted that eprinomectin present in the environment would not be expected to undergo significant movement or translocation, and would not accumulate or persist. Given its environmental fate characteristics, eprinomectin will be readily eliminated from the aquatic and terrestrial environments.

(c) environmental impacts from its use and/or manufacture

The FDA has issued this statement with respect to the environmental impact of eprinomectin:

"The Agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The Agency's finding of no significant impact (FONSI) and the evidence supporting that finding is contained in an environmental assessment which may be seen in the Dockets Management Branch (HFA-305), Park Building, (Room 1-23), 12420 Parklawn Dr., Rockville, Maryland 20857."

Ref.: FOI Summary for NADA 141-079;
http://www.fda.gov/cvm/FOI/933.htm

(d) effects on human health

Tolerances are established for residues of eprinomectin B1a (marker residue) in bovine milk of 12 parts per billion, in bovine liver (target tissue) of 4.8 parts per million, and in bovine muscle of 100 parts per billion.

Human Safety
Data supporting the human food safety of IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle are summarized in the FOI Summary for NADA 141-079 (62FR33997; June 24, 1997).

Based on a battery of toxicology tests, an Acceptable Daily Intake (ADI) of 10 mcg/kg body weight/day was calculated. A portion of the ADI (0.4 mcg/kg body weight/day) was reserved for milk and yielded a milk safe concentration of 16 ppb. The rest of the ADI (9.6 mcg/kg body weight/day) was used in the calculation of Safe Concentrations for total eprinomectin-related residues of 1.92 ppm in muscle, 5.76 ppm in liver, 11.52 ppm in kidney, and 11.52 ppm

in fat. Metabolism studies in cattle along with quantitation of the marker residue in radiolabeled milk and tissues established tolerances of 12 ppb and 4.8 ppm for the B_{1a} component of eprinomectin (the marker residue) in milk and liver (the target tissue), respectively.

Based on the milk residue data from the radiotracer studies, a zero milk discard has been established for the use of IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle. There was no pre-slaughter withdrawal time required for edible tissues from the results of marker residue depletion studies in adult cattle and preruminating calves, following a single topical application of the product at a dose rate of 500 mcg/kg animal body weight (1 mL/10 kg body weight).

As part of the approval the FDA updated the human food safety information on this product and codified an Acceptable Daily Intake (ADI) of 10 mcg/kg body weight/day, and a tolerance of 100 parts per billion (ppb) for residues of eprinomectin B_{1a} in cattle muscle.

(e) effects on soil organisms, crops, or livestock

The effects of eprinomectin on soil organisms (earthworms, dung beetles) and terrestrial plants have been presented in a preceding section, 9(d).

Animal Safety

Tolerance and toxicity studies have demonstrated the margin of safety for eprinomectin in cattle. In toxicity studies, application of 3 times the recommended dose had no adverse effects on neonatal calves, and application of up to 5 times the recommended dose 3 times at 7 day intervals had no adverse effects on 8 week old calves. In the tolerance study, one of 6 cattle treated once at 10 times the recommended dose showed clinical signs of mydriasis. Application of 3 times the recommended dose had no adverse effect on breeding performance of cows or bulls.

Data supporting the animal safety of IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle are summarized in the FDA FOI Summaries for NADA 141-079 (original, April 1997 and supplemental, August 1998), and are included in **Attachment 2**.

10. Safety information about the substance including a Material Safety Data Sheet (MSDS) and a substance report from the National Institute of Environmental Health Studies. If this information does not exist, the petitioner should state so in the petition.

The material safety data sheet for IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle is included in **Attachment 3.** The FDA did not require a substance report from the National Institute of Environmental Health Studies for the registration of this product; therefore, no report has even been prepared. Extensive human and environmental health studies were conducted, as reported in Items 9(b) and 9(c) of this petition.

11. Research information about the substance which includes comprehensive substance research reviews and research bibliographies, including reviews and bibliographies which present contrasting positions to those presented by the petitioner in supporting the substance's inclusion on or removal from the National List. For petitions to include non-organic agricultural substances onto the National List, this information item should include research concerning why the substance should be permitted in the production or handling of an organic product, including the availability of organic alternatives. Commercial availability does not depend upon geographic location or local market conditions. If research information does not exist for the petitioned substance, the petitioner should state so in the petition.

A comprehensive search of publicly disseminated literature was conducted using Dialog®. There was no limitation on the date range. The search provided the twenty-seven (27) references with respect to human/animal health and the environment. The listing of these references is contained in **Attachment 4**.

12. A "Petition Justification Statement" which provides justification for any of the following actions requested in the petition:

A. Inclusion of a Synthetic on the National List, §§ 205.601, 205.603, 205.605(b)

• Explain why the synthetic substance is necessary for the production or handling of an organic product.

A recent study conducted by Iowa State University found parasite control in the cow herd has a significant impact on calf production and cost to the beef system. [Economic Analysis of Pharmaceutical Technologies in Modern Beef Production; John D. Lawrence and Maro A. Ibarburu, Iowa State University, 2006.] At the present time organic-based programs of parasite control can be effective in some cases, but it is widely recognized that exclusively organic systems have significant limitations. It is desirable to have a safe and effective alternative treatment option using a synthetic substance; moreover, intervention is sometimes necessitated from both "humanitarian" and economic considerations in order to protect the health of infected animals and herd-mates. The use of a synthetic substance, such as eprinomectin, with a well-established record of safety and efficacy among animals, man, and the environment is a rational option. Eprinomectin was developed specifically to provide very low milk and meat residues, while maintaining the excellent safety and efficacy of the avermectin class of parasiticides. FDA has approved eprinomectin (IVOMEC® EPRINEX® Pour-On for Beef and Dairy Cattle) with no pre-slaughter withdrawal period for meat and no withholding period for milk; therefore, it can provide organic producers an advantageous alternative.

• Describe any non-synthetic substances, synthetic substances on the National List or alternative cultural methods that could be used in place of the petitioned synthetic substance.

The alternatives pesticides currently available on the National List are of limited usefulness. The two currently approved parasiticide compounds, ivermectin and fenbendazole, both have meat withdrawal and milk discard periods of ninety days.

• Describe the beneficial effects to the environment, human health, or farm ecosystem from use of the synthetic substance that support its use instead of the use of a non-synthetic substance or alternative cultural methods.

Eprinomectin has an excellent safety profile for animals, man, and the environment (Section 9). Plus, it controls of more stages and species of internal and external parasites in cattle than any other known substance. Experience has shown that only 2 treatments per year (Spring and Fall) can, in most cases, provide an adequate measure parasite control. This, coupled with good management practices commonly used in organic production, can help producers raise healthier cattle and obtain a better economic return without sacrificing the quality and safety of products provided to consumers. And, importantly, eprinomectin is proven safe for the environment, when used as directed on the product label.

13. A Confidential Business Information Statement which describes the specific required information contained in the petition that is considered to be Confidential Business Information (CBI) or confidential commercial information and the basis for that determination. Petitioners should limit their submission of confidential information to that needed to address the areas for which this notice requests information. Final determination regarding whether to afford CBI treatment to submitted petitions will be made by USDA pursuant to 7 CFR 1.27(d). Instructions for submitting CBI to the National List Petition process are presented in the instructions below:

(a) Financial or commercial information the petitioner does not want disclosed for competitive reasons may be claimed as CBI. Applicants must submit a written justification to support each claim.

N/A

(b) "Trade secrets" (information relating to the production process, such as formulas, processes, quality control tests and data, and research methodology) may be claimed as CBI. This information must be (1) commercially valuable, (2) used in the applicant's business, and (3) maintained in secrecy.

N/A

(c) Each page containing CBI material must have "CBI Copy" marked in the upper right corner of the page. In the right margin, mark the CBI information with a bracket and "CBI."

N/A

(d) The CBI-deleted copy should be a facsimile of the CBI copy, except for spaces occurring in the text where CBI has been deleted. Be sure that the CBI deleted copy is paginated the same as the CBI copy (The CBI-deleted copy of the application should be made from the same copy of the application which originally contained CBI). Additional material (transitions, paraphrasing, or generic substitutions, etc.) should not be included in the CBI-deleted copy.

N/A

(e) Each page with CBI-deletions should be marked "CBI-deleted" at the upper right corner of the page. In the right margin, mark the place where the CBI material has been deleted with a bracket and "CBI-deleted."

N/A

(f) If several pages are CBI-deleted, a single page designating the numbers of deleted pages may be substituted for blank pages. (For example, "pages 7 through 10 have been CBI-deleted.")

N/A

(g) All published references that appear in the CBI copy should be included in the reference list of the CBI deleted copy. Published information cannot be claimed as confidential.

N/A

(h) Final determination regarding whether to afford CBI treatment to submitted petitions will be made by USDA pursuant to 7 CFR 1.27(d). If a determination is made to deny CBI treatment, the petitioner will be afforded an opportunity to withdraw the submission.

N/A

Attachment 1

IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle

FDA-approved Labeling

Package Insert

and

250 mL Container Labeling

NADA 141-079, Approved by the FDA

Ivomec® Eprinex®

Pour-On for Beef and Dairy Cattle (eprinomectin) Parasiticide

Contains 5 mg eprinomectin/mL

INTRODUCTION

IVOMEC EPRINEX Pour-On delivers highly effective internal and external parasite control in one application. Discovered and developed by scientists from Merck Research Laboratories, IVOMEC EPRINEX Pour-On contains eprinomectin, a unique avermectin. Its broad-spectrum efficacy in a weather-proof formulation, margin of safety, zero slaughter withdrawal and zero milk discard, make it a convenient product for parasite control in beef and dairy cattle, including lactating dairy cattle.

MODE OF ACTION

Eprinomectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells.

This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

INDICATIONS

IVOMEC EPRINEX (eprinomectin) Pour-On is indicated for the treatment and control of gastrointestinal roundworms (including inhibited *Ostertagia ostertagi*), lungworms, grubs, sucking and biting lice, chorioptic and sarcoptic mange mites, and horn flies in beef and dairy cattle of all ages, including lactating dairy cattle.

Applied at the recommended dose volume of 1 mL/10 kg (22 lb) body weight, to achieve a dose level of 500 mcg eprinomectin/kg body weight, IVOMEC EPRINEX Pour-On is indicated for the effective treatment and control of the following parasites.

Gastrointestinal Roundworms

Haemonchus placei	(adults and L4)
Ostertagia ostertagi (including inhibited L4)	(adults and L4)
Trichostrongylus axei	(adults and L4)
Trichostrongylus colubriformis	(adults and L4)
Trichostrongylus longispicularis	(adults only)
Cooperia oncophora	(adults and L4)
Cooperia punctata	(adults and L4)
Cooperia surnabada	(adults and L4)
Nematodirus helvetianus	(adults and L4)
Oesophagostomum radiatum	(adults and L4)
Bunostomum phlebotomum	(adults and L4)
Strongyloides papillosus	(adults only)
Trichuris spp.	(adults only)

Lungworms

Dictyocaulus viviparus	(adults and L4)

Cattle Grubs (all parasitic stages)

Hypoderma lineatum
Hypoderma bovis

Lice

Damalinia bovis
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites

Chorioptes bovis
Sarcoptes scabiei

Horn Flies

Haematobia irritans

Persistent Activity

IVOMEC EPRINEX (eprinomectin) Pour-On for Beef and Dairy Cattle has been proved to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* for 21 days after treatment and *Haematobia irritans* for 7 days after treatment.

Use Conditions

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

Management Considerations for Treatment of External Parasites

For best results IVOMEC EPRINEX Pour-On should be applied to all cattle in the herd. Cattle introduced to the herd later should be treated prior to introduction. Consult your veterinarian or an entomologist for the most effective timing of applications for the control of external parasites.

Chorioptic Mange: In clinical studies evaluating the efficacy of IVOMEC EPRINEX Pour-On against chorioptic mange mites, mites were not recovered from skin scrapings taken 8 weeks after treatment; however, chronic skin lesions were still present on some animals.

Horn flies: For optimal control of horn flies, as IVOMEC EPRINEX Pour-On provides 7 days of persistent activity against horn flies, the product should be used as part of an integrated control program utilizing other control methods to provide extended control.

DOSAGE

The product is formulated only for external application to beef and dairy cattle. The dose rate is 1 mL/10 kg (22 lb) of body weight. The product should be applied topically along the backline in a narrow strip extending from the withers to the tailhead.

ADMINISTRATION

Squeeze-Measure-Pour System (250 mL/8.5 fl oz Bottle with 25 mL Metering Cup)

Attach the metering cup to the bottle.

Set the dose by turning the top section of the cup to align the correct body weight with the pointer on the knurled cap. When body weight is between markings, use the higher setting.

Hold the bottle upright and squeeze it to deliver a slight excess of the required dose as indicated by the calibration lines. By releasing the pressure, the dose automatically adjusts to the correct level. The off (STOP) position will close the system between dosing. Tilt the bottle to deliver the dose.

Squeeze-Measure-Pour System (1 L/33.8 fl oz Bottle with 50 mL Metering Cup)

Attach the metering cup to the bottle.

Set the dose by turning the top section of the cup to align the correct body weight with the pointer on the knurled cap. When body weight is between markings, use the higher setting.

Hold the bottle upright and squeeze it to deliver a slight excess of the required dose as indicated by the calibration lines.

By releasing the pressure, the dose automatically adjusts to the correct level. When a 220 lb (10 mL) or 330 lb (15 mL) dose is required, turn the pointer to "STOP" before delivering the dose. The off (STOP) position will close the system between dosing. Tilt the bottle to deliver the dose.

Collapsible Pack (2.5 L/84.5 fl oz and 5 L/169 fl oz Packs)

Connect the dosing applicator and draw-off tubing to the collapsible pack as follows:

Attach the open end of the draw-off tubing to an appropriate dosing applicator. Attach draw-off tubing to the cap with the stem that is included in the pack. Replace the shipping cap with the cap having the draw-off tubing.

Gently prime the dosing applicator, checking for leaks. Follow the dosing applicator manufacturer's directions for adjusting the dose and proper use and maintenance of the dosing applicator and draw-off tubing.

20 Liter Pack (20 L/676 fl oz Pack)
Connect the dosing applicator and draw-off tubing to the container as follows:

Attach the open end of the draw-off tubing to an appropriate dosing applicator. Attach draw-off tubing to the cap with the stem. Replace the shipping cap with the cap having the draw-off tubing.

Gently prime the dosing applicator, checking for leaks. Follow the dosing applicator manufacturer's directions for adjusting the dose and proper use and maintenance of the dosing applicator and draw-off tubing.

ANIMAL SAFETY

Tolerance and toxicity studies have demonstrated the margin of safety for eprinomectin in cattle. In toxicity studies, application of 3 times the recommended dose had no adverse effects on neonatal calves, and application of up to 5 times the recommended dose 3 times at 7 day intervals had no adverse effects on 8 week old calves. In the tolerance study, one of 6 cattle treated once at 10 times the recommended dose showed clinical signs of mydriasis. Application of 3 times the recommended dose had no adverse effect on breeding performance of cows or bulls.

Residue Warning: When used according to label directions, neither a pre-slaughter drug withdrawal period nor a milk discard time is required, therefore, meat and milk from cattle treated with IVOMEC EPRINEX (eprinomectin) Pour-On may be used for human consumption at any time following treatment.

WARNING:
Keep this and all drugs out of the reach of children.
NOT FOR USE IN HUMANS.

As with any topical medication intended for treatment of animals, skin contact should be avoided. If accidental skin contact occurs, wash immediately with soap and water. If accidental eye exposure occurs, flush eyes immediately with water. The material safety data sheet (MSDS) contains more detailed occupational safety information.

To report adverse effects, obtain an MSDS or for assistance, contact Merial at 1-888-637-4251.

PRECAUTIONS

This product is for topical application only. Do not administer orally or by injection.

Do not apply to areas of the backline covered with mud or manure.

IVOMEC EPRINEX Pour-On is not recommended for use in species other than cattle. Severe adverse reactions have been reported in other species treated with products containing compounds of this class.

Restricted Drug (California) - Use only as directed.

When to Treat Cattle with Grubs
IVOMEC EPRINEX Pour-On is effective against all stages of cattle grubs. However, proper timing of treatment is important. For the most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble fly) season. While this is not peculiar to eprinomectin, destruction of *Hypoderma* larvae (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions. Killing *Hypoderma lineatum* when it is in the esophageal tissues may cause bloat; killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. Cattle should be treated either before or after these stages of grub development.

Cattle treated with IVOMEC EPRINEX Pour-On at the end of the fly season may be re-treated with IVOMEC EPRINEX Pour-On during the winter without danger of grub-related reactions. For further information and advice on a planned parasite control program, consult your veterinarian.

Environmental Safety
Studies indicate that when eprinomectin comes in contact with soil, it readily and tightly binds to the soil and becomes inactive over time. Free ivermectin/eprinomectin may adversely affect fish and certain aquatic organisms. Do not permit cattle to enter lakes, streams or ponds for at least 6 hours after treatment. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

As with other avermectins, eprinomectin is excreted in the dung of treated animals and can inhibit the reproduction and growth of pest and beneficial insects that use dung as a source of food and for reproduction. The magnitude and duration of such effects are species and life-cycle specific. When used according to label directions, the product is not expected to have an adverse impact on populations of dung-dependent insects.

ADVERSE REACTIONS

No adverse reactions were observed during clinical trials.

STORAGE CONDITIONS

Store bottle or pack in the carton to protect from light and at temperatures up to 86°F/30°C. Storage at temperatures up to 104°F/40°C is permitted for a short period of time, however, such exposure should be minimized.

HOW SUPPLIED

IVOMEC EPRINEX (eprinomectin) Pour-On for Beef and Dairy Cattle is available in a 250 mL/8.5 fl oz (67641) or 1 L/33.8 fl oz (67643) bottle with a squeeze-measure-pour system, or in a 2.5 L/84.5 fl oz (67645) or 5 L/169 fl oz (67647) collapsible pack or 20 L/676 fl oz (67648) container intended for use with appropriate automatic dosing equipment.

Made in New Zealand

Manufactured for
Merial Limited
Operational Headquarters
3239 Satellite Blvd.
Duluth, Georgia 30096-4640, U.S.A.

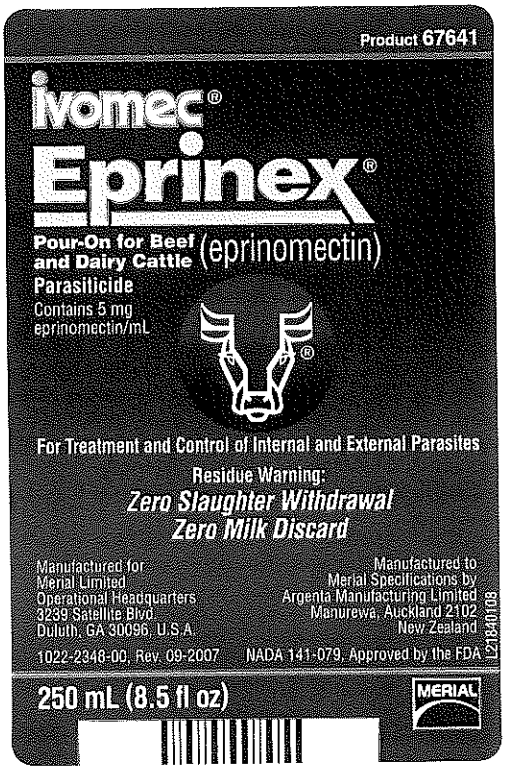
Manufactured to Merial Specifications by
Argenta Manufacturing Limited
Manurewa, Auckland 2102
New Zealand

U.S. Pat. 4427663 and 5802107

1050-2355-00
Rev. 09-2007

MERIAL

L21560108



Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

INDICATIONS

See package insert for complete indications and use directions.

Store bottle in the carton to protect from light and at temperatures up to 86°F/30°C. Storage at temperatures up to 104°F/40°C is permitted for a short period of time, however, such exposure should be minimized.

Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

Residue Warning: When used according to label directions, neither a pre-slaughter drug withdrawal period nor a milk discard time is required, therefore, meat and milk from cattle treated with IVOMEC EPRINEX (eprinomectin) Pour-On may be used for human consumption at any time following treatment.

WARNING

Keep this and all drugs out of the reach of children.

NOT FOR USE IN HUMANS.

PRECAUTIONS

This product is for topical application only. Do not administer orally or by injection.

Do not apply to areas of the backline covered with mud or manure.

IVOMEC EPRINEX Pour-On is not recommended for use in species other than cattle. Severe adverse reactions have been reported in other species treated with products containing compounds of this class.

Restricted Drug (California) - Use only as directed.

U.S. Pat 4427663 and 5602107

1022-2349-00
Rev. 09-2007

Batch No:

Expiry Date:

L21650108

C20440108

Product 67641

ivomec®
Eprinex®
Pour-On for Beef and Dairy Cattle (eprinomectin)

This topically applied formulation of IVOMEC EPRINEX Pour-On delivers effective internal and external parasite control in one application.

PRECAUTIONS:
This product is for topical application only. Do not administer orally or by injection.

Do not apply to areas of the backline covered with mud or manure.

IVOMEC EPRINEX Pour-On is not recommended for use in species other than cattle. Severe adverse reactions have been reported in other species treated with products containing compounds of this class.

Restricted Drug (California) - Use only as directed.

ENVIRONMENTAL SAFETY:
Studies indicate that when eprinomectin comes in contact with the soil it readily and tightly binds to the soil and becomes inactive over time. Free eprinomectin may adversely affect fish and certain aquatic organisms. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

STORAGE CONDITIONS:
Store bottle in the carton to protect from light and at temperatures up to 86°F/30°C. Storage at temperatures up to 104°F/40°C is permitted for a short period of time, however, such exposure should be minimized.

3 50604 67641 6

ivomec®
Eprinex®

Pour-On for Beef and Dairy Cattle (eprinomectin)

Parasiticide

Contains 5 mg eprinomectin/mL

For Treatment and Control of Internal and External Parasites

Residue Warning:
Zero Slaughter Withdrawal
Zero Milk Discard

Contains 10 Doses (550 lb)

NADA 141-079, Approved by the FDA

250 mL (8.5 fl oz)

MERIAL

ivomec®
Eprinex®
Pour-On for Beef and Dairy Cattle (eprinomectin)
Contains 5 mg eprinomectin/mL
250 mL (8.5 fl oz)
Product 67641

Product 67641

ivomec®
Eprinex®
Pour-On for Beef and Dairy Cattle (eprinomectin)

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

INDICATIONS:
IVOMEC EPRINEX Pour-On is indicated for the treatment and control of gastrointestinal roundworms (including inhibited *Ostertagia ostertagi*), lungworms (21 days of control), grubs, sucking and biting lice, chorioptic and sarcoptic mange mites, and horn flies (7 days of control) in beef and dairy cattle of all ages, including lactating dairy cattle.

See package insert for complete indications and use directions.

USE CONDITIONS:
Varying weather conditions, including rainfall, do not affect the efficacy of IVOMEC EPRINEX Pour-On.

DOSAGE:
The dose rate is 1 mL/10 kg (22 lb) of body weight. The product should be applied topically along the backline in a narrow strip extending from the withers to the tailhead.

ADMINISTRATION:
Attach the metering cup to the bottle.

Set the dose by turning the top section of the cup to align the correct body weight with the pointer on the knurled cap. When body weight is between markings, use the higher setting.

Hold the bottle upright and squeeze it to deliver a slight excess of the required dose as indicated by the calibration lines.

By releasing the pressure, the dose automatically adjusts to the correct level. The off (STOP) position will close the system between dosing. Tilt the bottle to deliver the dose.

Manufactured for
Merial Limited
Operational Headquarters
3239 Satellite Blvd.
Duluth, GA 30096, U.S.A.

Manufactured to Merial Specifications by
Argenta Manufacturing Limited
Manurewa, Auckland 2102
New Zealand

U.S. Pat. 4427663 and 5602107

Lot Number:

ivomec®
Eprinex®
Pour-On for Beef and Dairy Cattle (eprinomectin)

TAKE TIME

OBSERVE LABEL DIRECTIONS

ANIMAL SAFETY:
Tolerance and toxicity studies have demonstrated the margin of safety for eprinomectin in cattle. In toxicity studies, application of 3 times the recommended dose had no adverse effects on neonatal calves, and application of up to 5 times the recommended dose 3 times at 7 day intervals had no adverse effects on 8 week old calves. In the tolerance study, one of 6 cattle treated once at 10 times the recommended dose showed clinical signs of mydriasis. Application of 3 times the recommended dose had no adverse effect on breeding performance of cows or bulls.

Residue Warning: When *used according to label* directions, neither a pre-slaughter drug withdrawal period nor a milk discard time is required, therefore meat and milk from cattle treated with IVOMEC EPRINEX Pour-On may be used for human consumption at any time following treatment.

WARNING:
Keep this and all drugs out of the reach of children.
NOT FOR USE IN HUMANS.

As with any topical medication *intended for treatment of animals*, skin contact should be avoided. If accidental skin contact occurs, wash immediately with soap and water. If accidental eye exposure occurs, flush eyes immediately with water. The *material safety data sheet* (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Merial at 1-888-637-4251.

Attachment 2

IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle

Freedom of Information Summary

Original NADA 141-079, April 1997

and

Supplemental NADA 141-079, August 1998

Approval Date: April 16, 1997

Freedom of Information Summary
NADA 141-079

I. GENERAL INFORMATION:

NADA	141-079
Sponsor:	Merck Research Laboratories Division of Merck & Co., Inc. P. O. Box 2000 Rahway, New Jersey 07065-0914
Generic Name:	eprinomectin
Trade Name:	Ivomec® Eprinex™ Pour-On
Marketing Status:	Over the Counter (OTC)

II. INDICATIONS FOR USE

IVOMEC EPRINEX Pour-On for Beef and Dairy Cattle is indicated for treatment and control of:

Gastrointestinal nematodes (adults and fourth-stage larvae, L4)

Haemonchus placei
Ostertagia ostertagi (including inhibited L4)
Trichostrongylus axei
Trichostrongylus colubriformis
Cooperia oncophora
Cooperia punctata
Cooperia surnabada
Nematodirus helvetianus
Bunostomum phlebotomum
Oesophagostomum radiatum
Trichuris spp. (adults)

Lungworms (adults and L4)

Dictyocaulus viviparus

Cattle grubs (all parasitic stages)

Hypoderma lineatum
Hypoderma bovis

Lice

Damalinia bovis
Linognathus vituli
Haematopinus eurysternus

Solenopotes capillatus

Mange Mites

Chorioptes bovis
Sarcoptes scabiei

Flies

Haematobia irritans

IVOMEC EPRINEX (eprinomectin) Pour-On for Beef and Dairy Cattle has been proved to control infections of *Dictyocaulus viviparus* for 21 days after treatment and *Haematobia irritans* for 7 days after treatment.

III. DOSAGE

A. DOSAGE FORM	IVOMEC EPRINEX Pour-On is a clear non-aqueous solution containing 5 mg per ml of eprinomectin. The product is available in 250 ml, 1 liter, 2.5 liter and 5 liter plastic bottles.
B. ROUTE OF ADMINISTRATION	IVOMEC EPRINEX Pour-On should be applied topically along the backline from the withers to the tailhead.
C. APPROVED DOSAGES:	The recommended dose of IVOMEC EPRINEX Pour-On is 1 ml per 10 kg body weight to deliver 500 mcg per kg body weight of eprinomectin.

IV. EFFECTIVENESS

A clinical development program was conducted which supports the efficacy of eprinomectin applied topically at 500 mcg/kg bodyweight against a wide range of endo- and ectoparasites in cattle. In all clinical studies the results from the eprinomectin-treated group(s) were compared with results from an untreated or placebo-treated group. In some studies infections were induced while in others they were naturally acquired. Each claim for the control of a parasite species and stage is supported by at least two well-controlled studies. Efficacy is expressed as percentage (%) reduction compared to controls calculated as follows:

$$\%\ \text{Reduction} = \frac{AM_C - AM_T}{AM_C} \times 100$$ where

% Reduction = Percentage reduction of the parasite species
AM_C = Arithmetic mean number of parasites in control cattle
AM_T = Arithmetic mean number of parasites in treated cattle

Eprinomectin provided >= 90% reduction for each endo- and ectoparasite listed in the INDICATIONS section. Data from the development program supports the use of eprinomectin applied topically at 500 mcg/kg for treatment and control of endo- and ectoparasites in cattle.

A. Dose Determination

Dose selection studies were conducted against a wide range of important ecto- and endoparasites of cattle. There were four studies with ectoparasites and seven studies with endoparasites. Each study included an untreated control group and groups treated with three dose levels within the range of 125 to 750 mcg/kg body weight. All formulations were delivered in the commercial vehicle but the concentration of active drug varied with the dose level. Four studies examined efficacy against natural ectoparasite infestations including two studies with *Chorioptes bovis* mites and two studies with lice. Five studies examined efficacy against induced endoparasite infections including three studies in which the parasites were immature at the time of treatment and two studies where they were adults. A further two studies evaluated efficacy against natural endoparasite infections including inhibited fourth-stage *Ostertagia ostertagi* larvae.

1. Dose Selection Against *Chorioptes bovis*

a. **Type of Study**: Dose selection in cattle with infestations of *Chorioptes bovis*. There were two studies (ASR 14095 and ASR 14098).

b. **Investigator**:

Dr. D. Barth
Merck Research Laboratories
Kathrinenhof Farm
8201 Lauterbach, Germany

c. **General Design**:

i. **Purpose**: To determine the optimal dose level of eprinomectin against infestations of *C. bovis* mites.

ii. **Animals**: Forty-eight Fleckvieh and Rotbunte cows aged 3 to 10 years and weighing 447 to 766 kg. There were 24 cows in each study.

iii. **Housing**: Individual stanchions.

iv. **Infestations**: All cattle were carrying natural *C. bovis* infestations confirmed by pretreatment skin scrapings.

v. **Dosage Form**: Non-aqueous solution containing 2.5, 5 or 7.5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Doses**: 250, 500 or 750 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Control animals were untreated.

ix. **Test Duration**: Final skin scrapings were taken 56 days after treatment.

x. **Pertinent Parameters Measured:** Mite counts in skin scrapings collected from six sites on each animal at approximately weekly intervals.

d. **Results**: In ASR 14095, mite counts were reduced in all eprinomectin-treated cattle and efficacy was sustained through Day 56. The results are summarized below in Table IV.A.1.

In ASR 14098, two animals of the six treated at 250 mcg/kg had positive mite counts at each post-treatment observation and had mite counts similar to the control animals from Day 35 through Day 56. Five of six animals treated at 500 mcg/kg had zero mite counts from Day 21 onwards, and all six animals had zero mite counts from Day 35 through Day 56. The results are summarized below in Table IV.A.2.

Lesion scores were also compiled in these studies. Lesion scores, although reduced for treated cattle over controls, did not appear to be useful in distinguishing the best treatment level.

Table IV.A.1. Arithmetic mean *C. bovis* mite counts on cattle treated with eprinomectin ad topically (ASR 14095).

Count Day	0	7	14	21/22	28	35	42
Untreated Controls	444	413	343	371	344	303	270
Eprinomectin 250 mcg/kg	469	49	18	3	<1	9	<1
Percent Efficacy	-	88	95	>99	>99	97	>99
Eprinomectin 500 mcg/kg	427	33	5	3	0	0	0
Percent Efficacy	-	92	99	>99	100	100	100
Eprinomectin 750 mcg/kg	424	9	0	<1	0	0	0
Percent Efficacy	-	98	100	>99	100	100	100

Table IV. A.2. Arithmetic mean *C. bovis* mite counts on cattle treated with eprinom administered topically (ASR 14098).

Count Day	-1/0	7	14	21	28	35	42	
Untreated Controls	307	327	301	253	200	149	206	
Eprinomectin 250 mcg/kg	335	102	61	10	4	42	59	
Percent Efficacy	-	69	80	96	98	72	71	
Eprinomectin 500 mcg/kg	377	94	3	<1	<1	0	0	
Percent Efficacy	-	71	99	>99	>99	100	100	
Eprinomectin 750 mcg/kg	319	46	14	4	<1	4	0	
Percent Efficacy	-	86	96	99	>99	97	100	

e. **Adverse Reactions**: There were no adverse reactions to treatment.

2. **Dose Selection Against Lice**

a. **Type of Study**: Dose selection in cattle with infestations of lice. One study was conducted (ASR 14150).

b. **Investigator**:

Dr. L. L. Smith
Smith Research and Development
Lodi, Wisconsin 53555
USA

c. **General Design**:

i. **Purpose**: To determine the optimal dose level of eprinomectin against infestations of lice.

ii. **Animals**: Twenty-four beef crossbred calves aged 3 to 8.5 months and weighing 96 to 253 kg.

iii. **Housing**: Individual stanchions.

iv. **Infestations**: All cattle were carrying natural lice infestations confirmed by pretreatment counts in selected sites.

v. **Dosage Form**: Non-aqueous solution containing 2.5, 5 or 7.5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii.**Doses**: 250, 500 or 750 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Control animals were untreated.

ix. **Test Duration**: Final lice counts were made 56 days after treatment.

x. **Pertinent Parameters Measured:** Lice counts and identification to species in eight pre-selected sites on each animal at approximately weekly intervals.

d. **Results**: No live lice were found on any eprinomectin-treated animal after treatment. Lice numbers were maintained on control animals through Day 28 but decreased thereafter. The results are summarized in Tables IV.A.3. and IV.A.4.

Table IV. A.3. Arithmetic mean *Solenopotes capillatus* counts on cattle treated with epri administered topically (ASR 14150).

Count Day	-1	7	14	21
Untreated Controls	699	746	552	54
Eprinomectin 250 mcg/kg	854	0	0	(
Percent Efficacy	-	100	100	10(
Eprinomectin 500 mcg/kg	882	0	0	(
Percent Efficacy	-	100	100	10(
Eprinomectin 750 mcg/kg	688	0	0	(
Percent Efficacy	-	100	100	10(

Table IV. A.4. Arithmetic mean *Damalinia bovis* counts on cattle treated with eprinor administered topically (ASR 14150).

Count Day	-1	7	14	21	28
Untreated Controls	506	542	867	548	39
Eprinomectin 250 mcg/kg	370	0	0	0	
% Efficacy	-	100	100	100	10
Eprinomectin 500 mcg/kg	297	0	0	0	
% Efficacy	-	100	100	100	10
Eprinomectin 750 mcg/kg	406	0	0	0	

% Efficacy	-	100	100	100	10

e. **Adverse Reactions**: There were no adverse reactions to treatment.

3. **Dose Selection Against Endoparasites**

a. **Type of Study**: Dose selection in cattle with infections of gastrointestinal and pulmonary nematodes. Two studies are summarized (ASR 13953 and ASR 14000).

b. **Investigators**:

ASR 13953
Dr. S. R. Pitt
Merck Research Laboratories
Highfield Farm
Hertford SG 138QJ, UK

ASR 14000
Dr. J. C. Williams
Louisiana State University
Baton Rouge, LA 70803
USA

c. **General Design**:

i. **Purpose**: To determine the optimal dose level of eprinomectin against infections of gastrointestinal and pulmonary nematodes including inhibited *Ostertagia ostertagi* L4.

ii. **Animals**: Fifty-one Friesian and crossbred beef calves aged 7 to 10 months and weighing 149 to 248 kg. There were 24 calves used in ASR 13953 and 27 calves used in ASR 14000.

iii. **Housing**: Tethered in individual pens.

iv. **Infections**: In ASR 13953 the calves were helminth free as demonstrated by fecal nematode egg counts. Infective third-stage nematode larvae (L3) were administered to each calf on Day -28 and calves were assumed to be carrying adult nematode infections at the time of treatment. In ASR 14000, three calves were necropsied before treatment to confirm that the animals were carrying natural nematode infections including inhibited L4 (IL4) *O. ostertagi*.

v. **Dosage Form**: Non-aqueous solution containing 1.25, 2.5 or 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the baseline from withers to tailhead.

vii. **Doses**: 125, 250 or 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Control animals were untreated.

ix. **Test Duration**: Calves were necropsied for nematode recovery 14 to 16

days after treatment.

x. **Pertinent Parameters Measured:** Counts of nematodes recovered from the gastrointestinal and pulmonary tracts.

d. **Results**: Efficacy was >90% against *O. ostertagia* including IL4, *T. axei*, *C. oncophora*, *N. helvetianus* and *D. viviparus* at the 250 and 500 mcg per kg body weight dose levels. The results are summarized in Tables IV.A.5. and IV.A.6.

Table IV. A.5. Arithmetic mean nematode counts from cattle treated with eprinomectin ad topically (ASR 13953).

Nematode (Adult)	Control	Eprinomectin (mcg/l	
		125	250
Ostertagia ostertagi	4460	0 100%	0 100%
Trichostrongylus axei	2490	283 89%	3 >99%
Cooperia oncophora	4977	1257 75%	360 93%
Nematodirus helvetianus	1560	67 96%	0 100%
Dictyocaulus viviparus	52	0 100%	0 100%

Table IV. A.6. Arithmetic mean nematode counts from cattle treated with eprinomectin ad topically (ASR 14000).

Nematode	Control	Eprinomectin (mcg/kg	
		125	250
Ostertagia ostertagi (Adult)	18920	0 100%	18 >99%
Ostertagia ostertagi (IL_4)	60884 -	23493 61%	838 99%

e. **Adverse Reactions**: There were no adverse reactions to treatment.

4. **Additional Dose Selection Studies**

Six additional dose selection studies were conducted, five against

endoparasites, L4 and adult stages, (ASR 14018, 14134, 14145, 14165 and 14256) and one against lice (ASR 14096), with similar results to those presented above. Since the results duplicated those already presented, individual study summaries were not included.

5. **Conclusions**

Chorioptes bovis is the dose limiting parasite. Although there was high efficacy against *C. bovis* mites at the 250 mcg/kg body weight dose level, infestations recurred in some animals within the eight-week observation period of the studies. The 500 mcg/kg dose level showed optimal efficacy against *C. bovis* mites and was also effective against the other endo- and ectoparasite species examined.

B. Dose Confirmation

Each claim is supported by data from at least two studies in which cattle were treated with eprinomectin administered topically at 500 mcg per kg body weight. The commercial formulation was used in all studies.

1. **Dose Confirmation Against Mites**

a. **Type of Study**: Dose confirmation in cattle with infestations of *C. bovis* or *Sarcoptes scabiei* mites. There were four studies with *C. bovis* (ASR 14432, ASR 15067, ASR 15072 and ASR 15076) and two studies with *S. scabiei* (ASR 14115 and ASR 14608).

b. **Investigators**:

ASR 14432
Dr. J. A. Hair
Nu-Era Farms
Stillwater, OK 74074
USA

ASR 15067
Dr. R. E. Schmidt
106 Meadow Street
Lodi, WI 53555
USA

ASR 15072
Dr. K. E. Sterner
821 N. Jefferson St.
Ionia, MI 48846
USA

ASR 15076
Dr. D. Bowman
Cheri-Hill R&D
Stanwood, MI 49346
USA

ASR 14608
Dr. A. Villeneuve
University of Montreal
St-Hyacinthe, Quebec
Canada

ASR 14115
Dr. E. Kutzer
University of Vienna
A-1030 Vienna
Austria

c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against infestations of *C. bovis* or *S. scabiei* mites.

ii. **Animals**: One hundred and eight cattle. Sixteen or 20 adult Holstein cows weighing 419 to 791 kg were used in each of the studies with *C. bovis*. Sixteen or 20, Fleckvieh, Braunvieh or Holstein cattle aged from 3 months to adult and weighing 127 to 912 kg were used in each of the studies with *S. scabiei*.

iii. **Housing**: Individual stanchions, tie stalls or pens.

iv. **Infestations**: In the trials with *C. bovis* and in one trial with *S. scabiei* (ASR 14608), the cattle were carrying natural mite infestations. In the remaining trial with *S. scabiei*, infestations were induced by application of mites at selected times before treatment. All infestations were confirmed by pretreatment skin scrapings.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Topical vehicle administered at 1 ml per 10 kg body weight.

ix. **Test Duration**: Final skin scrapings were taken 28 or 56/57 days after treatment.

x. **Pertinent Parameters Measured**: Mite counts in skin scrapings collected from two, four or six sites on each animal at approximately weekly intervals.

d. **Results**: Cattle treated with eprinomectin had fewer mites than control cattle at each post-treatment observation. The results of each study are summarized in Tables IV.B.1. to IV.B.6.

Table IV. B.1. Arithmetic mean *C. bovis* mite counts on cattle treated with eprinomectin ac topically at 500 mcg/kg (ASR 14432).

Count Day	-1/0	7/8	14/15	21	28	35	42	49
Controls	198	426	237	163	191	219	60	
Eprinomectin 500 mcg/kg	191	0	0	0	0	0	0	
% Efficacy	-	100	100	100	100	100	100	1

Table IV. B.2. Arithmetic mean *C. bovis* mite counts on cattle treated with eprinomectin ac topically at 500 mcg/kg (ASR 15067).

Count Day	-1	7	14	21	28	35	42	49
Controls	296	330	375	519	310	237	290	2
Eprinomectin 500 mcg/kg	171	52	28	39	2	2	3	
% Efficacy	-	84	93	93	>99	>99	99	1

Table IV. B.3. Arithmetic mean *C. bovis* mite counts on cattle treated with eprinomectin ac topically at 500 mcg/kg (ASR 15072).

Count Day	-3	7	14	21	28	35	42	4
Controls	311	66	481	302	457	1461	1169	7
Eprinomectin 500 mcg/kg	317	0	0	0	0	0	0	
% Efficacy	-	100	100	100	100	100	100	1

Table IV. B.4. Arithmetic mean *C. bovis* mite counts on cattle treated with eprinomectin ac at 500 mcg/kg (ASR 15076).

Count Day	-2	7	14	21	28	35	42	
Controls	1056	2702	3002	3111	1674	2383	1569	1
Eprinomectin 500 mcg/kg	1353	39	8	7	<1	1	0	
% Efficacy	-	99	>99	>99	>99	>99	100	

Table IV. B.5. Arithmetic mean *S. scabiei* mite counts on cattle treated with eprinom administered topically at 500 mcg/kg (ASR 14115).

Count Day	-1	7	14	21	27/28	35	42	48/49
Controls	262	451	421	775	1008	1473	1594	316
Eprinomectin 500 mcg/kg	150	30	<1	0	0	0	0	
% Efficacy	-	93	>99	100	100	100	100	10

Table IV. B.6. Arithmetic mean *S. scabiei* mite counts on cattle treated with eprinom

administered topically at 500 mcg/kg (ASR 14608).

Count Day	-1	7	14	21
Controls	85	73	48	44
Eprinomectin 500 mcg/kg	77	<1	0	<1
% Efficacy	-	>99	100	>99

e. **Adverse Reactions**: Two control animals and two eprinomectin-treated animals died or were removed from studies for non-trial related reasons. There were no adverse reactions to treatment.

2. **Dose Confirmation Against Lice**

a. **Type of Study**: Dose confirmation in cattle with biting and/or sucking lice. There were six studies (ASR 14273, ASR 14274, ASR 14362, ASR 14366, ASR 14367 and ASR 14375).

b. **Investigators**:

ASR 14273
Dr. J. A. Hair
Nu-Era Research Farms
Stillwater, OK 74074
USA

ASR 14274
Dr. J. L. Lancaster
3076 N. Lancaster Lane
Fayetteville, AR 72703
USA

ASR 14362
Dr. J. E. Lloyd
University of Wyoming
Laramie, WY 82071
USA

ASR 14366
Dr. L. L. Smith
Smith Research and Development
Lodi, WI 53555
USA

ASR 14367 and 14375
Dr. J. E. Holste
Merck Research Laboratories
Fulton, MO 65251
USA

c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against infestations of biting and sucking lice.

ii. **Animals**: Ninety-six cattle. Sixteen Holstein or beef crossbred calves aged 5 to 12 months and weighing 113 to 338 kg were used in each study.

iii. **Housing**: Individual pens. In one trial (ASR 14273) the pens were outdoors exposed to climatic conditions.

iv. **Infestations**: All cattle were carrying natural lice infestations confirmed by

pretreatment counts in selected sites.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Topical vehicle administered at 1 ml per 10 kg body weight.

ix. **Test Duration**: Final lice counts were made 56 days after treatment.

x. **Pertinent Parameters Measured**: Lice counts and identification to species in six, seven or nine preselected sites on each animal at approximately weekly intervals.

d. **Results**: Cattle treated with eprinomectin had fewer lice than control cattle at each posttreatment observation. The results to 28 days are summarized in Tables IV.B.7. to IV.B.12. Data collected beyond 28 days was not used in the determination of efficacy against lice.

Table IV. B.7. Arithmetic mean lice counts on cattle treated with eprinomectin administere at 500 mcg/kg (ASR 14273).

Lice Species	Count Day	-1	7	14	
Linognathus vituli	Control	52	51	20	
	Eprinomectin 500 mcg/kg	40	0	0	
	% Efficacy	-	100	100	
Solenopotes capillatus	Control	679	486	492	
	Eprinomectin 500 mcg/kg	694	0	0	
	% Efficacy	-	100	100	

Table IV. B.8. Arithmetic mean lice counts on cattle treated with eprinomectin administere at 500 mcg/kg (ASR 14274).

Lice Species	Count Day	0	7	14	21
Linognathus vituli	Control	51	37	34	2
	Eprinomectin 500 mcg/kg	68	0	0	

	% Efficacy	-	100	100	1(
Damalinia bovis	Control	14	16	9	1
	Eprinomectin 500 mcg/kg	24	0	0	
	% Efficacy	-	100	100	1(

Table IV. B.9. Arithmetic mean lice counts on cattle treated with eprinomectin administere at 500 mcg/kg (ASR 14362).

Lice Species	Count Day	-1	7	14	2
Linognathus vituli	Control	49	73	74	
	Eprinomectin 500 mcg/kg	26	1	1	
	% Efficacy	-	98.5	98.8	1
Damalinia bovis	Control	34	32	28	
	Eprinomectin 500 mcg/kg	32	2	3	
	% Efficacy	-	92.9	91.1	1
Haematopinus eurysternus	Control	54	47	51	
	Eprinomectin 500 mcg/kg	33	2	1	
	% Efficacy	-	96.3	97.3	1

Table IV. B.10. Arithmetic mean lice counts on cattle treated with eprinomectin admin topically at 500 mcg/kg (ASR 14366).

Lice Species	Count Day	-1	7	14	2
Linognathus vituli	Control	46	45	49	
	Eprinomectin 500 mcg/kg	28	0	0	
	% Efficacy	-	100	100	1
	Control	70	84	55	
	Eprinomectin				

Damalinia bovis	500 mcg/kg	170	0	0	
	% Efficacy	-	100	100	1
Haematopinus eurysternus	Control	227	301	343	3
	Eprinomectin 500 mcg/kg	324	0	0	
	% Efficacy	-	100	100	1

Table IV. B.11. Arithmetic mean lice counts on cattle treated with eprinomectin admin topically at 500 mcg/kg (ASR 14367).

Lice Species	Count Day	0	7	14	21
Damalinia bovis	Control	248	127	130	14
	Eprinomectin 500 mcg/kg	183	0	0	
	% Efficacy	-	100	100	1C

Table IV. B.12. Arithmetic mean lice counts on cattle treated with eprinomectin admin topically at 500 mcg/kg (ASR 14375).

Lice Species	Count Day	0	7	14	21
Linognathus vituli	Control	136	155	116	
	Eprinomectin 500 mcg/kg	123	0	0	
	% Efficacy	-	100	100	1
Solenopotes capillatus	Control	365	631	360	1
	Eprinomectin 500 mcg/kg	539	0	0	
	% Efficacy	-	100	100	1

e. **Adverse Reactions**: There were no adverse reactions to treatment.

3. **Dose Confirmation Against Cattle Grubs**

a. **Type of Study**: Dose confirmation in cattle with infestations of *Hypoderma lineatum* and *Hypoderma bovis*. There were four studies (ASR 13976, ASR 14154, ASR 14359 and ASR 14360).

b. **Investigators**:

ASR 14154
Dr. D. D. Colwell
Agriculture Canada
Lethbridge, Alberta
Canada

ASR 14359
Dr. J. E. Holste
Merck Research Laboratories
Fulton, MO
USA

ASR 14360
Dr. J. E. Lloyd
University of Wyoming
Laramie, WY
USA

ASR 13976
Dr. N.P.M. Pinkall
Merck Research Laboratories
Highfield Farm
Hertford SG 138QJ, UK

c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against first larval stage (L1) and second/third larval stage (L2/L3) *H. lineatum* and *H. bovis*.

ii. **Animals**: One hundred and twelve calves. Thirty or 36 crossbred calves aged 7 to 9 months and weighing 126 to 274 kg were used in studies ASR 14154, 14359 and 14360. Sixteen Montbeliard calves aged 17 to 18 months and weighing 316 to 468 kg were used in study ASR 13976.

iii. **Housing**: Individual or group pens. In ASR 13976 cattle were housed in group pens throughout the study. In two trials, ASR 14154 and 14360, cattle were housed in individual pens throughout the study. In ASR 14359, cattle were housed on a group pasture from Day 56 to Day 98 and in individual pens at other times.

iv. **Infestations**: In all studies the calves were assumed to be carrying *Hypoderma* spp infestations based on a history of exposure. In two studies (ASR 13976 and ASR 14154) the calves were also tested for *Hypoderma* spp antibodies using an ELISA test.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Doses**: 500 mcg eprinomectin per kg body weight administered once on Day 0 when larvae were at the L1 stage (Treatment Group 2) or once between Days 31 and 102 when larvae were at the L2/L3 stage (Treatment Group 3). In ASR 13976 there was only one eprinomectin-treated group with treatment administered when larvae were at the L2/L3 stage.

viii. **Controls**: Control animals were untreated.

ix. **Test Duration**: Last observations were made 122 to 168 days after the first treatments were administered (Day 0), except for ASR 13976 where last

observations were made 72 days after treatment.

x. **Pertinent Parameters Measured**: Counts of *Hypoderma* spp lesions at regular intervals until all lesions had resolved. All emerging larvae were identified to the species level.

d. **Results**: Cattle treated with eprinomectin when *Hypoderma* spp were at the L1 stage had fewer larvae emerging than control animals. Efficacy against L1 was 100% in all studies. In cattle treated when *Hypoderma* spp were at the L2/L3 stage, resolution of lesions took longer in the control group compared with the eprinomectin-treated group. The results for each study are summarized in Tables IV.B.13. to IV.B.16. Studies ASR 14154, 14359 and 14360 provided pivotal data for *H. lineatum*, which was identified in at least eight control animals in each of these studies. Studies ASR 13976 and 14360 provided pivotal data for *H. bovis* which was identified in at least eight control animals in each study.

Table IV. B.13. Arithmetic mean *Hypoderma* spp. lesion counts and % efficacy on cattle t eprinomectin administered topically at 500 mcg/kg (ASR 13976).

Count Week	1	2	3	4	5	6	7	8	
Mean Trt 1 Control	16.25	16.08	12.88	10.00	7.50	6.04	4.75	3.25	C
Mean Trt 3 Eprinomectin, $L_{2/3}$/ % Efficacy	18.25/ NA	16.92/ 0.0	1.38/ 89.3	0.92/ 90.8	0/ 100	0/ 100	0/ 100	0/ 100	1

Table IV. B.14. Arithmetic mean *Hypoderma* spp. lesion counts and % efficacy on cattle t eprinomectin administered topically at 500 mcg/kg (ASR 14154).

Count Week	1	2	3	4	5	6	7	8	9	10
Mean Trt 1 Control	14.0	16.1	19.8	19.2	22.1	21.6	20.9	16.5	11.1	6.1
Mean Trt 2 Eprinomectin L_1/ % Efficacy	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100
Mean Trt 3 Eprinomectin $L_{2/3}$/ % Efficacy	14.6/ NA	7.5/ 53.1	0.8/ 96.2	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100

Table IV. B.15. Arithmetic mean *Hypoderma* spp. lesion counts and % efficacy on cattle t

eprinomectin administered topically at 500 mcg/kg (ASR 14359).

Count Week	1	2	3	4	5	6	7	8	
Mean Trt 1 Control	5.7	6.7	7.1	6.2	4.8	3.9	3.9	2.5	
Mean Trt 2 Eprinomectin,L_1/ % Efficacy	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	1
Mean Trt 3 Eprinomectin, $L_{2/3}$/ % Efficacy	6.3/ NA	4.1/ 39.0	0.8/ 89.2	0.2/ 97.3	0/ 100	0/ 100	0/ 100	0/ 100	1

Table IV. B.16. Arithmetic mean *Hypoderma* spp. lesion counts and % efficacy on cattle t eprinomectin administered topically at 500 mcg/kg (ASR 14360).

Count Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean Trt 1 Control	12.5	13.8	16.0	16.2	15.8	17.0	15.7	13.0	9.9	8.4	6.1	5.2
Mean Trt 2 Eprinomectin, L_1/ % Efficacy	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100
Mean Trt 3 Eprinomectin, $L_{2/3}$/ % Efficacy	5.3/ NA	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100	0/ 100

e. **Adverse Reactions**: There were no adverse reactions to treatment.

4. **Dose Confirmation Against Hornfly**

Types of Studies: Dose confirmation in cattle with infestations of *Haematobia irritans*. There was one pen study (ASR 14276) in which animals were housed in individual pens. There were three studies (ASR 14439, ASR 14538 and ASR 14545) in which animals were housed by treatment groups at pasture.

4.1 **Pen Study**

a. **Investigator**:

Dr. R. K. Fulton
Merck Research Laboratories
Springdale, Arkansas 72766

USA

b. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against *H. irritans*.

ii. **Animals**: Twelve Holstein cattle aged 7 to 10 months and weighing 157 to 185 kg.

iii. **Housing**: Individual stanchions in individual environmentally controlled rooms during fly challenge periods (48 hours). Animals were housed in individual stalls between fly challenge periods.

iv. **Infestations**: Each animal was challenged with 200 flies before treatment and then at 7-day intervals from the day of treatment (Day 0) through Day 28.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Topical vehicle administered at 1 ml per 10 kg body weight.

ix. **Test Duration**: Last fly challenge was made 28 days after treatment.

x. **Pertinent Parameters Measured**: Counts of live flies recovered 48 hours after challenge.

c. **Results**: Cattle treated with eprinomectin had fewer *H. irritans* than control cattle from Day 0 to Day 21. Efficacy of greater than 98% was obtained through Day 14. The results are summarized in Table IV.B.17.

Table IV. B.17. Arithmetic mean *H. irritans* counts on cattle treated with eprinomectin ad topically at 500 mcg/kg (ASR 14276).

Count Day	-7	0	7	14	21
Controls	159	134	160	139	170
Eprinomectin 500 mcg/kg	167	0	<1	2	58
% Efficacy	-	100	>99	98.7	65.8

d. **Adverse Reactions**: There were no adverse reactions to treatment.

4.2 **Dose Confirmation Against Hornfly - Pasture Studies**

a. **Type of Study**: Dose confirmation in cattle with infestations of *H. irritans*. There were three studies (ASR 14439, ASR 14538 and ASR 14545) in which animals were housed by treatment groups at pasture.

b. **Investigators**:

ASR 14439
Dr. H. G. Kinzer
5065 Ocotillo
Las Cruces, NM
USA

ASR 14538
Dr. M. J. Kennedy
Symbiotica Research and Publication
Edmonton, Alberta T6J 6G8
Canada

ASR 14545
Dr. R. D. Hall
University of Missouri
Columbia, MO 65201
USA

c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against *H. irritans*.

ii. **Animals**: Sixty cattle. Twenty Holstein or crossbred cattle aged from 14 months to adult and weighing 208 to 787 kg were used in each study.

iii. **Housing**: Each treatment group was housed in a separate paddock at least 500 yards from each other and from other cattle.

iv. **Infestations**: Cattle were exposed to natural infestation with *H. irritans*.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Topical vehicle administered at 1 ml per 10 kg body weight.

ix. **Test Duration**: Last fly counts were made 21 or 27/28 days after treatment.

x. **Pertinent Parameters Measured**: Counts of *H. irritans* on each animal on Days 0, 3 or 5, 6/7, 13/14, 20/21 and 27/28.

d. **Results**: Efficacy was >90% on Day 6/7 but declined thereafter. The results are summarized in Tables IV.B.18. to IV.B.20.

Table IV. B.18. Arithmetic mean *H. irritans* counts on cattle treated with eprinomectin ad

topically at 500 mcg/kg (ASR 14439).

Count Day	0	3	6	13	20
Controls	966	1068	1503	981	485
Eprinomectin 500 mcg/kg	793	8	33	419	446
% Efficacy	-	>99	97.8	57.3	8.1

Table IV. B.19. Arithmetic mean *H. irritans* counts on cattle treated with eprinomectin ad topically at 500 mcg/kg (ASR 14538).

Count Day	0	5	7	14	21
Controls	62	17	40	42	71
Eprinomectin 500 mcg/kg	90	0	3	12	77
% Efficacy	-	100	92.7	72.4	0

Table IV. B.20. Arithmetic mean *H. irritans* counts on cattle treated with eprinomectin ad topically at 500 mcg/kg (ASR 14545).

Count Day	0	3	7	14	
Controls	253	178	734	332	
Eprinomectin 500 mcg/kg	620	<1	10	171	
% Efficacy	-	>99	98.7	48.6	

e. **Adverse Reactions**: There were no adverse reactions to treatment.

5. **Dose Confirmation Against Induced Endoparasite Infections**

a. **Type of Study**: Dose confirmation in cattle with induced endoparasite infections. There were 15 studies (ASR 14146, ASR 14153, ASR 14162, ASR 14263, ASR 14264, ASR 14356, ASR 14357, ASR 14364, ASR 14441, ASR 14549, ASR 14559, ASR 14707, ASR 14709, ASR 15078 and ASR 15186). Pivotal data were also obtained from the animals treated at the selected therapeutic dose level in three dose selection studies (ASR 14145, ASR 14165 and ASR 14256).

b. **Investigators:**

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c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against induced endoparasite infections.

ii. **Animals**: The studies included 149 cattle treated with eprinomectin at the selected therapeutic dose level and 137 control cattle. Each study used 12, 16, 18 or 20 Holstein or crossbred cattle aged 3 to 12 months and weighing 78 to 335 kg.

iii. **Housing**: In 17 of the studies, animals were housed in individual pens or stanchions. In one study (ASR 14441) animals were penned together by treatment group. Two of the studies (ASR 14364 and ASR 14441) included separate eprinomectin-treated groups housed indoors under shelter and outdoors exposed to prevailing climatic conditions.

iv. **Infections**: Infectious third-stage endoparasite larvae (L3) were administered to each animal at times before treatment selected to ensure that

the majority of parasites were at either the L4 or the adult stage at the time of treatment. *Bunostomum phlebotomum* larvae were administered topically in the ear. Larvae of all other species were administered orally. The number of larvae and days of administration for each species are summarized in Table IV.B.21.

Table IV. B.21. Approximate number of endoparasite L3 and days of administration in infection pivotal studies

Parasite	Number of Larvae	Days before Tre
		Immature
Haemonchus placei	5000-7000	5-7
Ostertagia ostertagi	3800- 20000	5-7
Trichostrongylus axei	400-20000	5-7
Trichostrongylus colubriformis	15000-30000	5-7
Cooperia oncophora	10000-20000	5-7
Cooperia punctata	15000-20000	5-7
Cooperia spp	11800-19000	5
Nematodirus helvetianus	5700-10000	7-8
Bunostomum phlebotomum	100-2000	17
Oesophagostomum radiatum	100-2000	16-17
Dictyocaulus viviparus	1000-6000	5-8

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Topical vehicle administered at 1 ml per 10 kg body weight.

ix. **Test Duration**: The animals were necropsied for nematode recovery between 14 and 28 days after treatment.

x. **Pertinent Parameters Measured**: Counts of pulmonary and gastrointestinal nematodes in 5% to 100% aliquots of material recovered at necropsy.

d. **Results**: Cattle treated with eprinomectin had fewer nematodes recovered compared with control animals. Nematode counts were reduced by >95% for each species and stage against which efficacy is claimed. The arithmetic mean

nematode counts and percentage efficacy for each nematode species in each study are summarized in Tables IV.B.22. to IV.B.39.

Table IV. B.22. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14145).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Ostertagia ostertagi	L4	**8698**	0	
Cooperia oncophora	L4	5483	0	
Cooperia punctata	L4	3909	0	
Cooperia surnabada	L4	1778	0	
Nematodirus helvetianus	L4	1190	0	
Bunostomum phlebotomum	L4	90	0	
Oesophagostomum radiatum	L4	197	0	
Dictyocaulus viviparus	L4	361	0	

Table IV. B.23. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14146).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Haemonchus placei	L4	203	0	
Ostertagia ostertagi	L4	8863	0	100
Trichostrongylus axei	L4	2698	0	100
Oesophagostomum radiatum	L4	43	0	100
Dictyocaulus viviparus	L4	131	0	100

Table IV. B.24. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14153).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	

Haemonchus placei	L4	1124	0	
Ostertagia ostertagi	L4	7355	0	
Trichostrongylus axei	L4	7657	<1	
Trichostrongylus colubriformis	L4	3155	1	
Cooperia oncophora	L4	7400	3	
Cooperia punctata	L4	16281	3	
Nematodirus helvetianus	L4	1237	1	
Oesophagostomum radiatum	L4	175	0	
Dictyocaulus viviparus	L4	34	0	

Table IV. B.25. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14162).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Ostertagia ostertagi	L4	5005	30	
Trichostrongylus axei	L4	780	0	
Cooperia oncophora	L4	2448	0	
Cooperia punctata	L4	4798	0	
Cooperia surnabada	L4	639	0	
Oesophagostomum radiatum	L4	135	0	
Dictyocaulus viviparus	L4	738	20	

Table IV. B.26. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14165).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Ostertagia ostertagi	Adult	11498	0	
Trichostrongylus axei	Adult	9600	0	

Trichostrongylus colubriformis	Adult	4692	0	
Nematodirus helvetianus	L4	1227	0	
Oesophagostomum radiatum	Adult	184	0	
Dictyocaulus viviparus	Adult	170	0	

Table IV. B.27. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14256).

Nematode	Stage	Mean Count		% I
		Control	Eprinomectin	
Haemonchus placei	L4	353	0	
Cooperia punctata	L4	17780	1	

Table IV. B.28. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14263).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Haemonchus placei	L4	886	0	
Ostertagia ostertagi	L4	11200	0	
Trichostrongylus axei	L4	1758	0	
Trichostrongylus colubriformis	L4	670	0	
Oesophagostomum radiatum	L4	249	0	
Dictyocaulus viviparus	L4	10	0	

Table IV. B.29. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14264).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Haemonchus placei	Adult	857	0	
Ostertagia ostertagi	Adult	7097	3	

Ostertagia ostertagi	L4	93	0	
Trichostrongylus axei	Adult	1593	0	
Cooperia oncophora	Adult	2748	25	
Cooperia punctata	Adult	3141	0	
Cooperia surnabada	Adult	1429	0	
Oesophagostomum radiatum	Adult	191	0	

Table IV. B.30. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14356).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Haemonchus placei	Adult	1103	0	
Ostertagia ostertagi	Adult	3775	13	
Trichostrongylus axei	Adult	625	0	
Cooperia oncophora	Adult	1902	0	
Cooperia punctata	Adult	5690	0	
Bunostomum phlebotomum	Adult	43	0	
Oesophagostomum radiatum	Adult	338	0	

Table IV. B.31. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14357).

Nematode	Stage	Mean Count		% I
		Control	Eprinomectin	
Haemonchus placei	Adult	1100	0	
Ostertagia ostertagi	Adult	4290	0	
Ostertagia ostertagi	L4	175	0	
Trichostrongylus axei	Adult	4038	0	
Cooperia oncophora	Adult	592	2	

Cooperia punctata	Adult

11012>99*Cooperia surnabada*Adult5252>99*Bunostomum phlebotomum*Adult160100*Oesophagostomum radiatum*L4100100

Table IV. B.32. Nematode count data from cattle treated with eprinomectin at 500 mcg/ separate groups housed indoors and outdoors (ASR 14364).

Nematode	Stage	Housing	Mean Count		%
			Control	Eprinomectin	
Ostertagia ostertagi	Adult	Outdoor Indoor	2247	0 0	
Ostertagia ostertagi	L4	Outdoor Indoor	63	0 0	
Trichostrongylus axei	Adult	Outdoor Indoor	1873	0 7	

Table IV. B.33. Nematode count data from cattle treated with eprinomectin at 500 mcg/ separate groups housed indoors and outdoors (ASR 14441).

Nematode	Stage	Housing	Mean Count		%
			Control	Eprinomectin	
Ostertagia ostertagi	Adult	Outdoor Indoor	1576	<1 <1	
Cooperia oncophora	Adult	Outdoor Indoor	4207	190 98	
Cooperia punctata	Adult	Outdoor Indoor	839	<1 1	
Oesophagostomum radiatum	Adult	Outdoor Indoor	27	0 0	

Table IV. B.34. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14549).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Bunostomum phlebotomum	L4	145	0	

Table IV. B.35. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14559).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Bunostomum phlebotomum	Adult	109	<1	

Table IV. B.36. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14707).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Ostertagia ostertagi	L4	1013	0	
Trichostrongylus axei	L4	60	0	
Cooperia oncophora	L4	1337	0	
Cooperia punctata	L4	976	0	
Cooperia surnabada	L4	305	0	
Nematodirus helvetianus	L4	923	0	
Oesophagostomum radiatum	L4	61	0	

Table IV. B.37. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14709).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Nematodirus helvetianus	L4	2135	3	
Dictyocaulus viviparus	L4	23	0	

Table IV. B.38. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 15078).

		Mean Count

Nematode	Stage	Control	Eprinomectin	%
Trichostrongylus colubriformis	Adult	6023	2	
Dictyocaulus viviparus	Adult	291	0	

Table IV. B.39. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 15186).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Bunostomum phlebotomum	L4	76	0	
Dictyocaulus viviparus	L4		<1	

e. **Adverse Reactions**: There were no adverse reactions to treatment.

6. **Dose Confirmation Against Natural Endoparasite Infections**

a. **Type of Study**: Dose confirmation in cattle with natural endoparasite infections. There were four studies (ASR 14281, ASR 14374, ASR 14548 and ASR 14613). Pivotal data were also obtained from the animals treated at the selected therapeutic dose level in one dose selection study (ASR 14018).

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c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against natural endoparasite infections.

ii. **Animals**: The studies included 37 cattle treated with eprinomectin at the

selected therapeutic dose level and 37 control cattle. Four studies used 12 or 16 cattle 6 to 14 months old and weighing 96 to 267 kg at treatment. In two of these studies (ASR 14018 and 14281), the cattle were beef breeds and in the other two studies (ASR 14374 and 14548) they were Holsteins. The fifth study (ASR 14613) used 14 lactating Holstein cows aged 4 to 8 years and weighing 487 to 776 kg at the time of treatment.

iii. **Housing**: Individual pens or stanchions.

iv. **Infections**: Based on grazing history all animals were expected to be carrying natural nematode infections. In four studies infections were confirmed by fecal nematode egg counts before treatment. In the fifth study (ASR 14018), two animals from the herd were necropsied to confirm the presence of inhibited *O. ostertagi* larvae (IL4). In four studies, the animals were housed under conditions that precluded further nematode infection for at least 21 days before treatment. In the fifth study (ASR 14018), they were housed under these conditions for 8 days before treatment.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: In four studies control animals were treated with topical vehicle administered at 1 ml per 10 kg body weight. In the fifth study (ASR 14018), the controls were untreated.

ix. **Test Duration**: The animals were necropsied for nematode recovery between 14 and 27 days after treatment.

x. **Pertinent Parameters Measured**: Gastrointestinal and pulmonary nematodes in 5% to 100% aliquots of material recovered at necropsy.

d. **Results**: Cattle treated with eprinomectin had fewer nematodes recovered compared with control animals. Nematode counts were reduced by >98% for each species and stage against which efficacy is claimed. The arithmetic mean nematode counts and percentage efficacy for each nematode species in each study are summarized in Tables IV.B.40. to IV.B.44.

Table IV. B.40. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14018).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Haemonchus placei	Adult	504	0	

Ostertagia ostertagi	Adult	4760	0	
Ostertagia ostertagi	IL4	13630	0	
Trichostrongylus axei	Adult	6127	0	
Cooperia oncophora	Adult	2173	0	
Cooperia punctata	Adult	1693	0	
Oesophagostomum radiatum	Adult	25	0	

Table IV. B.41. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14281).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Ostertagia ostertagi	Adult	5970	18	
Ostertagia ostertagi	IL4	51	0	
Trichostrongylus axei	Adult	362	0	
Cooperia oncophora	Adult	2994	29	
Cooperia punctata	Adult	3530	1	
Cooperia surnabada	Adult	424	3	
Nematodirus helvetianus	Adult	3914	8	
Nematodirus helvetianus	L4	375	0	
Oesophagostomum radiatum	Adult	86	0	
Trichuris spp	Adult	73	1	

Table IV. B.42. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14374).

Nematode	Stage	Mean Count		% I
		Control	Eprinomectin	
Ostertagia ostertagi	Adult	2795	0	
Cooperia oncophora	Adult	832	13	

Trichuris spp	Adult	105	<1	

Table IV. B.43. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14548).

Nematode	Stage	Mean Count		%
		Control	Eprinomectin	
Ostertagia ostertagi	Adult	33	0	
Cooperia oncophora	Adult	297	0	
Cooperia punctata	Adult	734	0	
Cooperia surnabada	Adult	55	0	
Nematodirus helvetianus	Adult	168	0	
Dictyocaulus viviparus	Adult	64	0	

Table IV. B.44. Nematode count data from cattle treated with eprinomectin at 500 mcg/l 14613)

Nematode	Stage	Mean Count		% I
		Control	Eprinomectin	
Ostertagia ostertagi	Adult	1303	0	
Ostertagia ostertagi	L4	744	0	
Trichostrongylus axei	Adult	93	0	

e. **Adverse Reactions**: There were no adverse reactions to treatment.

7. **Dose Confirmation of Persistent Efficacy Against *Dictyocaulus viviparus***

a. **Type of Study**: Dose confirmation to demonstrate control against *Dictyocaulus viviparus* for 21 days following treatment. There were two studies (ASR 14701 and ASR 15074).

b. **Investigators**:

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ASR 15074
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c. **General Design**: i. **Purpose**: To confirm the persistent efficacy of eprinomectin administered topically at 500 mcg/kg against *D. viviparus*.

ii. **Animals**: The studies included 28 cattle treated with eprinomectin and 28 control cattle. In one study the cattle were Holsteins and in the other they were beef crossbred. The cattle were less than 6 months of age and weighed 51 to 104 kg at the time of treatment.

iii. **Housing**: The animals were housed in individual outdoor pens exposed to prevailing climatic conditions.

iv. **Infections**: Forty or 50 *D. viviparus* infectious L3 were administered to each animal once daily for 14 or 21 days after treatment.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: Control animals were untreated in one trial (ASR 14701) and were treated with topical vehicle administered at 1 ml per 10 kg body weight in the other trial (ASR 15074).

ix. **Test Duration**: The animals were necropsied for nematode recovery 28 days after the last administration of larvae, that is, 42 or 49 days after treatment.

x. **Pertinent Parameters Measured**: Number of *D. viviparus* recovered at necropsy.

d. **Results**: Cattle treated with eprinomectin had fewer *D. viviparus* recovered than control cattle. *D. viviparus* counts were reduced by >94% in cattle challenged with infectious larvae for 14 days or for 21 days after treatment. The arithmetic mean *D. viviparus* counts and percentage efficacy from each study are summarized in Table IV.B.45.

Table IV. B.45. Nematode count data for cattle treated with eprinomectin at 500 mcg/ challenged with *D. viviparus* L3 after treatment.

Trial	Challenge Interval (Days)	Mean *D. viviparus* Count		% Ef
		Control	Eprinomectin	
14701	21	112	5	

15074	14 21	122 156	1 9

e. **Adverse Reactions**: There were no adverse reactions to treatment.

8. Effect of Weather

a. **Type of Study**: Confirmation of efficacy against internal parasites in cattle exposed to prevailing weather conditions or to simulated rainfall before or after treatment. There were six dose confirmation studies. Four of the studies provided pivotal data confirming therapeutic (ASR 14364 and ASR 14441) or persistent (ASR 14701 and ASR 15074) efficacy. These studies are summarized in Sections IV.B.5 and IV.B.7, respectively. Additional data are provided by two corroborative studies (ASR 14384 [simulated rainfall] and 14385).

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ASR 15074
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c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against induced endoparasite infections in cattle exposed to prevailing weather conditions or to simulated rainfall.

ii. **Animals**: The studies included 120 cattle treated with eprinomectin at the selected therapeutic dose level and 78 control cattle. Each study used between 18 and 60 Holstein or beef crossbred cattle aged 3 to 10 months and weighing 51 to 335 kg.

iii. **Housing**: In five of the studies, animals were housed in individual pens. In one study (ASR 14441) animals were penned together by treatment group. Three of the studies (ASR 14364, 14385 and ASR 14441) included separate eprinomectin-treated groups housed inside under shelter and outside exposed to prevailing climatic conditions. In two of the studies (ASR 14701 and ASR

15074), all animals were housed outside. One study (ASR 14384) included groups exposed to simulated rainfall before treatment or at various intervals after treatment.

iv. **Infections**: Infectious third-stage endoparasite larvae (L3) were administered orally to each animal at selected times before or after treatment.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 500 mcg eprinomectin per kg body weight administered once on Day 0.

viii. **Controls**: In five studies topical vehicle was administered at 1 ml per 10 kg body weight. In one study (ASR 14701) the controls were untreated.

ix. **Test Duration**: The animals were necropsied for nematode recovery between 14 and 28 days after treatment in the therapeutic efficacy studies and 42, 49 or 56 days after treatment in the persistent efficacy studies.

x. **Pertinent Parameters Measured**: Counts of pulmonary and gastrointestinal nematodes in 5% to 100% aliquots of material recovered at necropsy.

d. **Results**: Cattle treated with eprinomectin had fewer nematodes recovered compared with control animals. Nematode counts were reduced by >90% for each species and stage against which efficacy is claimed. The results of the pivotal studies are summarized in Tables IV.B.32, IV.B.33 and IV.B.45. The arithmetic mean nematode counts and percentage efficacy for each nematode species in corroborative studies, ASR 14384 and ASR 14385, are summarized in Tables IV.B.46. to IV.B.47.

Table IV. B.46. Arithmetic mean nematode counts on cattle exposed to simulated rain bef treatment with eprinomectin administered topically at 500 mcg/kg (ASR 14384).

Nematode Species	Control	No Rain	Rain -1 hour	Rain +1 hour	Rain +3 hours
Osertagia ostertagi	3342	0	0	17	8
Percent Efficacy		100	100	>99	>99
Trichostrongylus axei	1496	0	0	0	0
% Efficacy		100	100	100	100

Table IV. B.47. Nematode count data from cattle treated with eprinomectin at 500 mcg/

separate groups housed indoors and outdoors (ASR 14385).

Nematode	Stage	Housing	Mean Count Control	Mean Count Eprinomectin	%
Ostertagia ostertagi	Adult	Outdoor Indoor	7088	0 8	
Ostertagia ostertagi	L4	Outdoor Indoor	458	4 0	
Trichostrongylus axei	Adult	Outdoor Indoor	5000	25 0	
Cooperia pectinata	Adult	Outdoor Indoor	10017	17 0	

9. Conclusions: Eprinomectin administered topically at 500 mcg/kg is effective against the following endo- and ectoparasites.

Gastrointestinal nematodes (adults and fourth-stage larvae, L4)

Haemonchus placei
Ostertagia ostertagi (including inhibited L4)
Trichostrongylus axei
Trichostrongylus colubriformis
Cooperia oncophora
Cooperia punctata
Cooperia surnabada
Nematodirus helvetianus
Bunostomum phlebotomum
Oesophagostomum radiatum
Trichuris spp. (adults)

Lungworms (adults and L4)

Dictyocaulus viviparus

Cattle grubs (all parasitic stages)

Hypoderma lineatum
Hypoderma bovis

Lice

Damalinia bovis
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites

Chorioptes bovis
Sarcoptes scabiei

Flies

Haematobia irritans

IVOMEC EPRINEX (eprinomectin) Pour-On for Beef and Dairy Cattle has been proved to control infections of *Dictyocaulus viviparus* for 21 days after treatment and *Haematobia irritans* for 7 days after treatment.

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

C. Field Trials

1. **Endoparasites**

a. **Type of Study**: Field trials in cattle with natural endoparasite infections. There were six trials (ASR 14327, ASR 14329, ASR 14618, ASR 14694, ASR 14810 and ASR 15068).

b. **Investigators**:

ASR 14327
Dr. J. A. Stuedemann
USDA
Watkinsville, GA 30677
USA

ASR 14329
Dr. C. H. Courtney
University of Florida
Gainesville, FL 32611
USA

ASR 14618
Dr. D. D. Bowman
Cheri-Hill R&D
Stanwood, MI 49346
USA

ASR 14694
Dr. R. Young
Young Veterinary Research
Modesto, CA 95356
USA

ASR 14810
Dr. G. Myers
Dr. Gil Myers, Inc.
Magnolia, KY 42757
USA

ASR 15068
Dr. R. L. Sifferman
Bradford Park Veterinary Hospital
Springfield, MO 65804
USA

c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against endoparasites under field conditions.

ii. **Animals**: The studies included 388 cattle treated with eprinomectin and 97 control cattle. Sixty of the eprinomectin-treated cattle were lactating cows. Details of the trial animals are summarized in Table IV.C.1.

Table IV. C.1. Details of cattle used in field trials with eprinomectin administered topica mcg/kg.

Trial Number	Location	Number of Cattle	Breed	Age	Lactating	Bod
14327	GA	125	Angus, Angus cross	14-16 mo	No	1
14329	FL	100	Angus cross, Brahman, Holstein	4-16 mo	No	2
14618	MI	55	Holstein, Jersey	6 mo-Adult	No/Yes[b]	1
14694	CA	35	Holstein	Adult	Yes	
14810	KY	80	Beef Cross	8-15 mo	No	1
15068	MO	90	Beef Cross, Holstein	9 mo	No	

a Actual or estimated
b 40 adult females were lactating

iii. **Housing**: In five of the trials the animals were housed in group pastures or dry lots. In the sixth trial (ASR 14618), the animals were housed in stanchions, group pens or group pastures. Animals from the control and eprinomectin-treated groups were always housed separately.

iv. **Infections**: All animals were carrying natural nematode infections confirmed by fecal nematode egg counts before treatment.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead.

vii. **Dose**: 1 ml per 10 kg body weight to provide 500 mcg eprinomectin per kg body weight. The dose was calculated and applied by a non-Company operator such as the investigator, the animals' owner or a herdsman.

viii. **Controls**: Control animals were untreated.

ix. **Test Duration**: The post-treatment fecal samples were collected 14/15 days after treatment.

x. **Pertinent Parameters Measured**: Fecal nematode egg per gram (epg) counts from samples collected before and after treatment.

d. **Results**: There was >99% reduction in strongylid eggs in all studies. The arithmetic mean epg counts and percentage efficacy for each study are summarized in Table IV.C.2.

Table IV. C.2. Mean strongylid epg counts and percentage efficacy for cattle treated eprinomectin in field trials.

Trial Number	Treatment	Number of Cattle	EPG Counts[a]		
			Before	After	I
14327	Control Eprinomectin	25 100	91 86	95 <1	 >99
14329[b]	Control Eprinomectin	14 56	56 86	24 <1	 >99
	Control Eprinomectin	6 24	78 115	218 <1	 >99
14618[c]	Control Eprinomectin	11 44	5 6	7 <1	 >99
14694[c]	Control Eprinomectin	7 28	4 3	3 <1	 >99
14810[b]	Control Eprinomectin	3 12	150 167	60 <1	 >99
	Control Eprinomectin	13 52	107 98	119 <1	 >99
15068	Control Eprinomectin	18 72	118 122	99 <1	 >99

a Samples collected Days -5 to 0 and Days 14/15
b Study conducted at two different sites; data from each site summarized separately
c Studies were conducted with mature lactating dairy cows, which generally carry lower bu internal parasites

e. **Adverse Reactions**: There were no adverse reactions to treatment.

2. Ectoparasites

a. **Type of Study**: Field trials in cattle with natural ectoparasite infestations. There was one pivotal study (ASR 14496) and one supportive study (ASR 14567).

b. **Investigators**:

Pivotal Study:

Dr. A. Villeneuve

University of Montreal
St. Hyacinthe, Quebec
Canada

Supportive Study:

Dr. L. L. Smith
Smith Research and Development
Lodi, WI 53555
USA

c. **General Design**:

i. **Purpose**: To confirm the efficacy of eprinomectin administered topically at 500 mcg/kg against ectoparasites under field conditions.

ii. **Animals**: The pivotal study included 20 cattle treated with eprinomectin and five control cattle. The cattle were Holsteins aged approximately 4 months and weighing 78 to 150 kg at the time of treatment. The supportive study included 28 cattle treated with eprinomectin and seven control cattle. The cattle were of mixed dairy breeds aged 8 months to adult and weighing 148 to 705 kg at the time of treatment. Ten of the eprinomectin-treated cows were lactating.

iii. **Housing**: In the pivotal study the animals were housed in group pens. The supportive study included animals at two locations. At one of these locations the animals were housed in group pens. At the second location the animals were housed in stanchions. Animals from the control and eprinomectin-treated groups were always housed separately.

iv. **Infestations**: In the pivotal study, animals were carrying natural *L. vituli* infestations. At one location in the supportive study, animals were carrying natural *D. bovis* infestations. At the second location in the supportive study, animals were carrying natural *C. bovis* infestations.

v. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

vi. **Route of Administration**: Topical application along the backline from withers to tailhead using commercial application equipment.

vii. **Dose**: 1 ml per 10 kg body weight to provide 500 mcg eprinomectin per kg body weight. The dose for each animal was calculated and applied by a non-Company operator such as the investigator or the animals' owner.

viii. **Controls**: Control animals were untreated.

ix. **Test Duration**: The last observation was made 28 days after treatment in the pivotal study and 56 days after treatment in the supportive study.

x. **Pertinent Parameters Measured**: Lice counts in seven or 12 preselected sites on each animal at approximately weekly intervals. Mite counts in skin

scrapings collected from one to four sites on each animal at approximately weekly intervals.

d. **Results**: In the pivotal study, no *L. vituli* were counted on the eprinomectin-treated animals from Day 7 through Day 21. At the final count on Day 28, one eprinomectin-treated animal had *L. vituli* found within the count sites and another four animals were positive on body search.

In the supportive study, no *D. bovis* or *C. bovis* were counted on the eprinomectin-treated animals after treatment.

The results are summarized for the pivotal study (Table IV.C.3.) and the supportive study (Tables IV.C.4. and IV.C.5.).

Table IV. C.3. Arithmetic mean *L. vituli* counts and percentage efficacy for cattle treat eprinomectin in a pivotal field trial (ASR 14496).

Days after Treatment	Mean Counts	Percent Efficacy	Control
Eprinomectin	-16454-	75701001424010021240100281	4<194.1

Table IV. C.4. Arithmetic mean *D. bovis* counts and percentage efficacy for cattle treat eprinomectin in a supportive field trial (ASR 14567).

Days after Treatment	Mean Counts	Percent Efficacy	Control
Eprinomectin	-215152-	72030100142390100212270100281900100352000100422190100491540100569701	00

Table IV. C.5. Arithmetic mean *C. bovis* counts and percentage efficacy for cattle treat eprinomectin in a supportive field trial (ASR 14567).

Days after Treatment	Mean Counts	Percent Efficacy	Control
Eprinomectin	-1129154-	72290100142780100214300100283680100355070100423970100493680100563370100	

e. **Adverse Reactions**: There were no adverse reactions to treatment.

3. **Conclusions**: Eprinomectin administered topically at 500 mcg/kg under commercial field conditions is safe and effective against endo- and ectoparasites.

V. TARGET ANIMAL SAFETY

The clinical effects of eprinomectin administered topically at 1X to 10X the recommended therapeutic level of 500 mcg/kg were assessed. In the tolerance study, dairy and beef calves were treated with eprinomectin at 10X the therapeutic dose (5000 mcg/kg) administered once. In the toxicity study, dairy calves were treated with eprinomectin at 1X, 3X or 5X the therapeutic dose level (500, 1500 or 2500 mcg/kg) administered three times at 7-day intervals. Studies were also conducted to examine the safety of eprinomectin at 3X the therapeutic dose (1500 mcg/kg) in breeding bulls and cows.

A. Target Animal Safety Studies

1. Tolerance Study

a. **Type of Study**: Evaluation of the safety of eprinomectin administered to cattle once at an elevated dose level ten times the recommended dose.

b. **Investigator**:

Dr. R. P. Gogolewski
Merck Research Laboratories
Ingleburn, NSW
Australia

c. **General Design**:

i. **Purpose**: To investigate the toxicity of eprinomectin in cattle.

ii. **Animals**: Twelve cattle aged approximately 12 months and weighing 159 to 268 kg at the time of treatment. There were four male and two female Holsteins and two male and four female beef cattle.

iii. **Housing**: Individual pens each measuring approximately 5 square meters.

iv. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

v. **Route of Administration**: Topical application along the backline from withers to tailhead through a flat-fan spray nozzle.

vi. **Dose**: 5000 mcg eprinomectin per kg body weight administered once on Day 0.

vii. **Controls**: Topical vehicle administered once at 10 ml per 10 kg.

viii. **Test Duration**: The cattle were necropsied 21 to 23 days after treatment.

ix. **Pertinent Parameters Measured**: Clinical examinations were conducted daily from Day -7 to Day 21. Additional examinations for specific toxic signs (depression, ataxia, mydriasis, salivation) were made 4 and 8 hours after treatment and then twice daily to Day 7. Blood samples were collected at regular intervals for hematology and blood chemistry examination. Daily feed and water consumption was measured from Day -7 to Day 20. Weights were measured weekly from Day -14 through Day 21. Animals were necropsied for gross and histopathological examination on Days 21 to 23.

d. **Results**: One of six calves treated with eprinomectin at 10X the recommended therapeutic dose showed clinical signs of mydriasis on Days 4 to 7 after treatment. There were no other treatment-related clinical signs and no remarkable gross or histopathological changes seen at necropsy.

Some clinical pathology variables had significant ($p<0.10$) interactions of treatment and sampling day or significant ($p<0.10$) differences between the treatment groups but all these parameters, with the exception of plasma iron levels, were within the range of accepted normal variation seen among individuals. The iron levels were particularly low in two eprinomectin-treated animals on Day 14. The abnormality was attributed to inflammation associated with hepatic abscessation. Significant ($p<0.10$) differences were detected in phosphate, glucose, and alkaline phosphate levels between control and eprinomectin treatment groups; however, values were within the range of normal variation seen among individuals.

There were differences detected in total feed intake from Day 0 to 20 and in weight gain from Day 0 to 21. The data are shown in Table V.A.1.

Table V.A.1.

Variable	Vehicle Control* (n=6)	eprinomectin 5000 mcg/kg (n=
Body weight (kg) Day 0 Day 21 Weight Gain Day 0-21 (kg)	207.00±11.07 239.83±10.52 32.83±2.23	233.92±11.07 257.50±10.52 23.75
Daily Feed Intake (kg) Week -1 Day 0 to 20	7.89±.48 9.30±.55	8.62±.48 8.89±.55
Total Feed Intake Day -7 to -1 Day 0 to 20	53.90±3.56 195.55±3.90	60.34±3.56 181.18±3.90
*Least square means and standard errors		

e. **Conclusions**: The only significant clinical adverse effect observed after treatment at 10X the recommended dose was mydriasis on Days 4 to 7 in one of six cattle.

2. Toxicity Study

a. **Type of Study**: Evaluation of the safety of eprinomectin administered to cattle repeatedly at elevated dose levels.

b. **Investigator**:

Dr. S. R. Pitt
Merck Research Laboratories

Hertford, SG 138QJ UK

c. **General Design**:

i. **Purpose**: To determine the safety of eprinomectin in cattle.

ii. **Animals**: Twelve male and 12 female Holstein calves aged 8 weeks and weighing 74 to 102 kg at the time of first treatment.

iii. **Housing**: Individual pens each measuring approximately 4 square meters.

iv. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

v. **Route of Administration**: Topical application along the backline from withers to tailhead. The 1X dose was applied with a glass syringe. The 3X and 5X doses were applied through a flat-fan spray nozzle.

vi. **Doses**: 500, 1500 or 2500 mcg eprinomectin per kg body weight administered three times at 7-day intervals beginning on Day 0.

vii. **Controls**: Topical vehicle administered at 5 ml per 10 kg three times at 7-day intervals.

viii. **Test Duration**: The calves were necropsied 22 to 24 days after the first treatment.

ix. **Pertinent Parameters Measured**: Clinical examinations were conducted daily from Day -7 to Day 21. Additional examinations for specific toxic signs (depression, ataxia, mydriasis, salivation) were made 4 and 8 hours after treatment and then twice daily to Day 21. Blood samples were collected at regular intervals for hematology and blood chemistry examination. Daily feed and water consumption was measured from Day -7 to Day 21. Calves were weighed weekly starting on Day -14 through Day 21. Animals were necropsied for gross examination on Days 22 to 24. Tissues from the control and 5X treatment groups were subjected to histopathological examination.

d. **Results**: Some clinical pathology variables had significant ($p<0.10$) interactions of treatment and sampling day or significant ($p<0.10$) differences between the treatment groups. Examination of the data suggests that the differences are due to normal variation and are not of biological significance. For all the clinical pathology variables, group means were within the normal range of values supplied by the assay laboratory.

All gross pathology lesions observed at necropsy were minor and considered unrelated to administration of the test compound.

Mydriasis could not be scientifically evaluated due to a problem in the evaluation technique used. Feed intake and weight gain could not be scientifically evaluated because of the use of limit feeding of the test animals. The investigator deemed limit feeding necessary to prevent digestive disorders

(bloat, diarrhea, etc). Other clinical evaluations were normal at most time points and no trends were noted for adverse effects in either group.

e. **Statistical Analysis**: Weight change, feed intake and water intake were analyzed by analysis of variance or covariance. Analyses of clinical pathology variables were performed using analysis of variance or covariance for a repeated measures design, including the factors treatment, sampling day and interaction of treatment and day as fixed effects, and replicate and its interactions with treatment and day as random effects.

f. **Conclusions**: Topical administration of eprinomectin at up to 5X the recommended therapeutic dose level repeated 3X at weekly intervals had no observable adverse effects on treated cattle.

3. Safety in Breeding Bulls

a. **Type of Study**: The study was designed to evaluate the safety of eprinomectin administered at an elevated dose level (3X the recommended dose) to breeding bulls.

b. **Investigator**:

Dr. C. J. Bierschwal
1607 Ross
Columbia, MO 65201
USA

c. **General Design**:

i. **Purpose**: Evaluation of the safety of eprinomectin administered to bulls at an elevated dose level throughout spermatogenesis.

ii. **Animals**: Ten Holstein and 10 Angus bulls aged 18 to 32 months and weighing 480 to 667 kg at the time of treatment. One hundred and twenty beef crossbred cows between 4 and 10 years of age and weighing 399 to 619 kg.

iii. **Housing**: Four group pastures until Day 64. Bulls were assigned to pasture based on breed and treatment group. After Day 64 each bull was pastured separately with six cows.

iv. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

v. **Route of Administration**: Topical application along the backline from withers to tailhead through a flat-fan spray nozzle.

vi. **Dose**: 1500 mcg eprinomectin per kg body weight. One bull was treated on each of Days 0, 1, 14, 15, 28, 29, 42, 43, 56 or 57.

vii. **Controls**: Topical vehicle administered at 3 ml per 10 kg body weight. One bull was treated on each of Days 0, 1, 14, 15, 28, 29, 42, 43, 56 or 57.

viii. **Test Duration**: 178 days after the first treatment was administered (Day 0).

ix. **Pertinent Parameters Measured**: Each bull was examined for breeding soundness, including semen evaluation, 13 or 14 days before the first animal was treated, 7 days before starting on trial, on its start date, 7 days later and at weekly intervals through Day 63 or 64. On Day 64, each bull was placed in a paddock with six untreated cows for evaluation of breeding ability.

The cows were checked for pregnancy on Day 178 which was 51 days after the end of the breeding period.

d. **Results**: There was no significant ($p>0.10$) overall treatment effect or treatment x day interaction for primary sperm abnormalities, secondary sperm abnormalities, total sperm abnormalities, any individual sperm abnormality, proportion of motile sperm, total sperm volume, weekly sperm production, or breeding soundness score. There was no significant ($p>0.10$) difference in proportion of pregnant cows; 57 of 60 cows mated to controls and 56 of 60 cows mated to eprinomectin-treated bulls became pregnant during the 63-day mating period. There were no significant ($p>0.10$) treatment differences for bull weights or average daily gain. There was a significant ($p<0.10$) treatment x day interaction for scrotal circumference. This interaction was likely due to normal variation in such a small population. All the bulls fall within the range expected for their breed and age. (Coulter *et al*, 1975. J. An. Sci. 41: 1383-1389, Elmore *et al*, 1976. Theriogen. 6:485-494, Coulter and Foote, 1977. J. An. Sci. 44:1076-1079). No adverse reactions attributable to treatment were detected in any animals during the study.

e. **Statistical Analysis**: Breeding soundness variables (primary sperm abnormalities, secondary sperm abnormalities, proportion motile sperm and total sperm volume) and scrotal circumference were analyzed using mixed model repeated measures analysis of covariance, assuming a first order autoregressive (AR(1)) covariance structure. Fixed effects included treatment, day, and treatment x day interaction. The random effects were replicate, replicate x treatment interaction, replicate x day interaction, and residual error.

f. **Conclusions**: Eprinomectin administered topically at 3X the recommended therapeutic dose throughout the spermatogenic cycle had no observable adverse effects on the performance of breeding bulls.

4. Safety in Breeding Cows

a. **Type of Study**: Evaluation of the safety of eprinomectin administered at an elevated dose level to breeding cows.

b. **Investigator**:

Dr. A. A. Bridi[1]
Merck Research Laboratories
Uruguaiana, RS

Brazil

c. **General Design**

i. Purpose: To evaluate the safety of eprinomectin administered to cows at an elevated dose level throughout the reproductive cycle.

ii. **Animals**: Sixty-four Brangus and 64 Hereford cows aged 4 to 8 years and weighing 333 to 523 kg. Four Hereford and five Angus bulls.

iii. **Housing**: Two sets of eight paddocks measuring 4.7 to 4.9 hectares were used alternately. Cows were housed together by replicate within breed.

iv. **Dosage Form**: Non-aqueous solution containing 5 mg eprinomectin per ml.

v. **Route of Administration**: Topical application along the backline from withers to tailhead as a single line.

vi. **Doses**: 1500 mcg eprinomectin per kg body weight. There were three eprinomectin treatment groups: treatment during the 28 days before mating (Group 2), during the 56 days of mating (Group 3) or from after mating through parturition (Group 4). Each cow in Group 2 was treated once, on Day 0, 7, 14 or 21. The mating period was from Day 28 to Day 83. Each cow in Group 3 was treated three times starting on Days 29, 35, 42 or 50 and thereafter at 27/28 day intervals. Each cow in Group 4 received its first treatment on Days 84, 112, 140 or 168, and was treated at 112-day intervals until calving; each of these cows received two or three treatments.

vii. **Controls**: Controls were untreated.

viii. **Test Duration**: 405 days after the first treatment was administered (Day 0).

ix. **Pertinent Parameters Measured**: Conception rates, calving rates, abortion rates (as observed), dystocias, live calves at birth and at 30 days were all measured to assess any drug effects on the breeding cow throughout the prebreeding/breeding/conception cycle. Cows were weighed at allocation, within 30 days before any treatment, within 7 days after calving and when the calf was approximately 30 days old. Cows that did not calve were weighed on Day 405. Each calf was weighed and examined within 24 hours after birth. Surviving calves were weighed again approximately 30 days after birth.

d. **Results**:

Table V.A.2. Results of cow breeding and calving data (ASR 13639).

Variable	Group 1 Control	Group 2 Before Mating	Group 3 During Mating	G Afte

Cows	32	32	32	
Brangus	16	16	16	
Hereford	16	16	16	
Cows pregnant	29	30[a]	26	
Brangus	14	14[a]	13[b]	
Hereford	15[b]	16	13	
Cows calving[c]	29	29	26	
Brangus	14	15	13	
Hereford	15	15[c]	13	
Perinatal Deaths[d]	0	1	2	
Brangus	0	1	1	
Hereford	0	0	1	
Assisted births	1	0	1	
Brangus	0	0	0	
Hereford	1	0	1	
Calves alive at 30 days	29	29	25	
Brangus	14	14	13	
Hereford	15	15	12	

a One cow was dropped from the study when it was discovered she was pregnant at the tim initiation.
b Does not include 1 cow that was initially diagnosed pregnant, but determined to be open date.
c One cow aborted
d Includes one still birth
e One calf died 6 days after birth and is not included in perinatal deaths (see text).

Table V.A.3. Calf average daily gains and birth weights (ASR 13639).

Variable	Control	Treatment before mating	Treatment during mating	T af
Calf birth weight	32.1	32.7	32.4	

Brangus	29.8	29.9	29.2	
Hereford	34.3	35.5	35.6	
Calf avg. daily gain- birth to 30 days	1.07	1.15	1.13	
Brangus	1.14	1.21	1.13	
Hereford	1.00	1.09	1.12	

There were no significant ($p>0.10$) differences between the control group and any of the eprinomectin-treated groups for cow average daily weight gain from allocation to calving, from calving to 30 days after calving, or from allocation to final weighing, or for birth weight or calf average daily gain from birth to final weighing.

There were no significant ($p>0.10$) differences between the control group and any of the eprinomectin-treated groups for number of cows pregnant, number calving, perinatal deaths and assisted births. There was a significant ($0.1>p>0.05$) difference between the control group and the group treated with eprinomectin after mating (Group 4) for the number of calves alive at the final examination (30 day examination).

There were seven calf deaths, six of which occurred during parturition or on the day of birth. Four of these six calves, three from Group 4 and one from Group 3, resulted from assisted calvings. Two of the calves were abnormally presented at parturition and in the other two, the investigator noted that the cows had a narrow pelvic canal. No abnormalities were found in the calves except those attributable to parturition trauma and/or anoxia. The fifth calf (Group 2), weighed only 18.5 kg at birth and died without nursing. The sixth calf (Group 3), was one of twins. Its forelegs were not fully extended and it died within 8 hours of birth. The other twin survived to trial termination. The seventh calf (Group 4), died 6 days after birth from an eviscerated umbilical hernia. The calf had no abnormalities reported when examined soon after birth and the herniation with subsequent evisceration was presumed to have resulted from trauma.

e. **Statistical Analysis**: For the dichotomous variables (*i.e.*, pregnant vs non-pregnant), the control group was compared to each eprinomectin-treated group. The comparisons were made using Fisher's Exact Test. All cows were included for the analysis of number of cows pregnant. Only pregnant cows were used in the subsequent analyses: number calving, perinatal deaths, assisted births and calves alive at the final examination.

The continuous variables (weight and average daily gain) were analyzed using analysis of variance for a mixed-model design, with the factors of breed, paddock within breed, replicate within breed and paddock, treatment, and interactions of treatment with breed and treatment with paddock within breed. Single degree of freedom contrasts were done comparing the controls to each eprinomectin-treated group.

f. **Conclusions**: Eprinomectin administered topically at 3X the recommended therapeutic dose had no attributable adverse effect on cows at all stages of breeding and pregnancy or on their calves.

B. Overall Conclusions

The following paragraph summarizes the Target Animal Safety studies and is found on the label under the ANIMAL SAFETY section.

The safety of eprinomectin was tested in cattle 8 weeks of age and older. Tolerance and toxicity studies have demonstrated the margin of safety for eprinomectin in cattle. In the toxicity study, 8-week-old calves showed no adverse effects after treatment with eprinomectin administered at up to 5 times the recommended dose three times at 7 day intervals. In the tolerance study, one of 6 cattle treated once at 10 times the recommended dose showed clinical signs of mydriasis. Application of three times the recommended dose had no adverse effects on the breeding performance of cows or bulls.

VI. HUMAN SAFETY

A. Toxicity Tests

1. Microbial Mutagen Tests With and Without Rat Liver Enzyme (S-9) Activation

a. **Report Number:** TT #90-8004.

b. **Study Dates:** Started 16JAN90, ended 18JAN90.

c. **Principal Investigators:** J. Sina and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648) as a solution in DMSO. Positive control mutagens were used as follows: 2-aminoanthracene (2-10 µg/plate with and without metabolic activation with all *Salmonella* strains and *Escherichia coli* strains WP2 uvrA and WP2 uvrA pKM101 and hydrazine sulfate (500 and 1000 µg/plate) with metabolic activation for *E coli* strain WP2.

f. **Species and Strain:** *Salmonella typhimurium* (TA1535, TA97a, TA98, and TA100) with and without rat liver S-9 microsomal activation system. *Escherichia coli* (WP2, WP2 uvrA, WP2 uvrA pKM101).

g. **Dose Levels Tested:** 100, 300, 1000, 3000, and 10,000 µg/plate. Positive control mutagens with S-9 and without S-9 gave the expected response.

h. **Results:** No two-fold increases in revertants, relative to the vehicle controls in any of the tester strains.

2. *In Vitro* Alkaline Elution/Rat Hepatocyte Assay

2.1 First Assay:

a. **Report Number:** TT #90-8305.

b. **Study Dates:** Started 10JAN90, ended 10JAN90.

c. **Principal Investigators:** R. Storer and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X012) as a solution in DMSO.

f. **Species and Strain:** Crl:CD®(SD) BR rat hepatocytes.

g. **Dosage Levels Tested:** 3, 10, 30, 100, 300, and 500 uM

h. **Results:** Relative viability ranged from 105 to 30 percent of controls over the dose range of 3 to 500 µM. Concentrations of 100 µM and above resulted in excessive cytotoxicity for assessment of DNA damage in subsequent studies in the alkaline elution/rat hepatocyte assay.

2.2 Second Assay:

a. **Report Number:** TT #90-8309.

b. **Study Dates:** Started 13FEB90, ended 15FEB90.

c. **Principal Investigators:** R. Storer and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X012) as a solution in DMSO.

f. **Species and Strain:** Crl:CD® (SD)BR rat hepatocytes.

g. **Dosage Levels Tested:** 10, 15, 23, 34, and 51 µM. Aflatoxin B1 at a concentration of 1 µM was used as the positive control.

h. **Results:** MK-0397 did not give an induced elution slope of 0.034 or greater (criteria for a positive response) at any non-cytotoxic concentration. The positive control produced an induced elution slope of 0.087 with 98% relative cell viability. Therefore, MK-0397 is considered negative in this assay.

2.3 Third Assay:

a. **Report Number:** TT #90-8314.

b. **Study Dates:** Started 28FEB90, ended 02MAR90.

c. **Principal Investigators:** R. Storer and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X012) as a solution in DMSO.

f. **Species and Strain:** Crl:CD® (SD)BR rat hepatocytes.

g. **Dosage Levels Tested:** 10, 15, 22, 29, and 35 µM. Aflatoxin B1 at a concentration of 1 µM was used as the positive control.

h. **Results:** MK-0397 did not give an induced elution slope of 0.034 or greater (criteria for a positive response) at any non-cytotoxic concentration. The positive control produced an induced elution slope of 0.087 with 98% relative cell viability. Therefore, MK-0397 is considered negative in this assay.

3. *In Vitro* V-79 Mammalian Cell Mutagenesis Assay With and Without Rat Liver Enzyme (S-9) Activation

3.1 First Assay:

a. **Report Number:** TT #91-8502.

b. **Study Dates:** Started 26APR91, ended 02MAY91.

c. **Principal Investigators:** J. DeLuca and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X014) as a solution in DMSO.

f. **Species and Strain:** V-79 Chinese hamster lung cell line.

g. **Dosage Levels Tested:** 10, 20, 30, 40, 50, 60, 70, and 80 µM with and without rat liver S-9 metabolic activation.

h. **Results:** Plating efficiency ranged from 79 to 14 percent of controls over a dose range of 10 to 40 µM with S-9 and from 43 to 11 percent over the same dose range without S-9. At concentrations above 40 µM relative plating efficiency was <0.3 percent.

3.2 Second Assay:

a. **Report Number:** TT #91-8510.

b. **Study Dates:** started 10MAY91, ended 17MAY91.

c. **Principal Investigators:** J. DeLuca and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X014) as a solution in DMSO.

f. **Species and Strain:** V-79 Chinese hamster lung cell line.

g. **Dosage Levels Tested:** 5, 10, 30, and 40 µM with S-9 and 1, 3, 7, 10, 30, and 40 µM without rat liver S-9 metabolic activation.

h. **Results:** Plating efficiency ranged from 95 to 18 percent of controls over a dose range of 5 to 40 µM with S-9 and from 80 to 12 percent over a dose range of 1 to 40 µM without S-9.

3.3 Third Assay:

a. **Report Number:** TT #91-8503.

b. **Study Dates:** Started 04JUN91, ended 27JUN91.

c. **Principal Investigators:** J. Deluca and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X014) as solution in DMSO.

f. **Species and Strain:** V-79 Chinese hamster lung cell line.

g. **Dosage Levels Tested:** 0.01, 0.02, 0.03, and 0.04 µM with S-9 metabolic activation and 0.001, 0.005, 0.02, and 0.04 µM without S-9. Positive controls used were methylnitrosourea without S-9 and 3-methylcholanthrene with S-9.
h. **Results:** Statistical analyses of the mutation frequencies with MK-0397 with and without S-9 did not result in any significant increases relative to the solvent controls. All mutation frequencies with MK-0397 were within the laboratory's 95% confidence limit for historical controls. The positive control mutagens resulted in highly significant increases in mutation frequency ($P < 0.001$) compared to the solvent control. Therefore, MK- 0397 is considered negative for induction of mutations in V-79 mammalian cells *in vitro*.

4. *In Vitro* Assay for Chromosomal Aberrations With and Without Rat Liver Enzyme Activation (S-9) in Chinese Hamster Ovary Cells

4.1 First Assay:

a. **Report Number:** TT #90-8611.

b. **Study Dates:** Started 06FEB90, ended 07FEB90.

c. **Principal Investigators:** S. Galloway and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X012) as a solution in DMSO. Cyclophosphamide at a concentration of 5 μM with S-9 and mitomycin C at a concentration of 0.5 μM without S-9 were used as positive controls.

f. **Species and Strain:** Chinese hamster ovary (CHO) cells, Clone WBL.

g. **Dosage Levels Tested:** 0.08, 0.16, 0.31, 0.63, 1.3, 2.5, 5.0, 10.0 and 20.0 μM with and without S-9 metabolic activation.

h. **Results:** Cell counts 85 to 1 percent of negative controls were found at 5 and 10 μM with S-9 with no significant effect on cell survival at concentrations < or = 2.5 μM. Without S-9 cell counts ranged from 76 to 13 percent of negative controls at concentrations of 10 and 20 μM. No effects on survival were found at concentrations < or = 5.0 μM without S-9. The positive controls, cyclophosphamide and mitomycin C, produced cell counts of 68 and 75 percent of the negative controls, respectively, as expected.

4.2 Second Assay

a. **Report Number:** TT #90-8614.

b. **Study Dates:** Started 13MAR90, ended 30APR90.

c. **Principal Investigators:** S. Galloway and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X012) as a solution in DMSO.

f. **Species and Strain:** Chinese hamster ovary (CHO) cells, Clone WBL.

g. **Dosage Levels Tested:** 5, 6, and 7 μM with S-9 and 8, 10, and 12 μM without S-9 activation. Mitomycin C at concentrations of 0.25, 0.35, 0.5, and 0.75 μM without S-9 and Cyclophosphamide at 2.5 and 5.0 μM with S-9 were included as positive controls.

h. **Results:** Cytotoxicity of 63% cell survival was produced at concentrations of 12 μM without S-9 with 68% survival at a concentration of 7 μM with S-9. No significant increases in percentages of cells with chromosome aberrations were found in the treated groups relative to the solvent or untreated controls. The positive control mutagens produced statistically significant increases ($P < 0.05$) in the number of cells with aberrations relative to the solvent control. Therefore, MK-0397 is considered negative for production of chromosomal aberrations *in vitro* in CHO cells.

5. *In Vivo* Assay for Micronucleus Induction in Mouse Bone Marrow

a. **Report Number:** TT #93-8719.

b. **Study Dates:** started 07DEC93, ended 18APR94.

c. **Principal Investigators:** S. Galloway and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X021) as a suspension in 0.5% aqueous methylcellulose administered at a dose volume of 0.1 ml/10 g body weight.

f. **Species and Strain:** Mouse, Crl:CD-1®(ICR)BR strain.
g. **Dosage Levels Tested:** 0, 10, 20, and 40 mg/kg administered to 10 mice/sex/group. The negative control received the vehicle only while the positive controls (5 mice/sex) received 0.35 and 2.0 mg/kg of Mitomycin C. Five mice/sex/group were sacrificed at 24 and 48 hours after dosing for harvesting bone marrow for examination except for the positive control groups which were sacrificed only at 24 hours after Mitomycin C treatment. Approximately 2000 cells per animal were examined.

h. **Results:** Clinical signs of toxicity including ptosis, decreased activity, bradypnea, ataxia, tremors, and spastic movements were observed within 4 hours after dosing with MK-0397 in all animals at 40 mg/kg. Most animals were normal by 24 hours after treatment. Similar signs were observed in 2 of 10 males treated with 20 mg/kg of MK-0397. All animals survived until scheduled necropsy. No dose group treated with MK-0397 at either sacrifice time had a significant ($P < \text{or} = 0.05$) increase in micronucleated polychromatophilic erythrocytes compared to the concurrent control by pairwise comparison. There were highly significant increases ($P < 0.001$) in micronucleated polychromatophilic erythrocytes in the positive control groups. Therefore, MK-0397 is negative for induction of micronucleated polychromatophilic erythrocytes in mouse bone marrow *in vivo*.

6. Fourteen-Week Oral Toxicity Study in Rats

a. **Report Number:** TT #90-037-0.

b. **Study Dates:** Started 28MAR90, ended 28JUN90 (Males) and started 30MAR90, ended 29JUN90 (Females).

c. **Principal Investigators:** H. Allen, J. Coleman, and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X012).

f. **Species and Strain:** Rat/Sprague-Dawley (Crl:CD®(SD)BR).

g. **Number of Animals/Sex/Group:** 20 rats/sex/group.

h. **Dosage Levels Tested:** 0, 1, 5, and 30/20 mg/kg/day.

i. **Route of Administration:** Oral via diet.

j. **Parameters Examined:** Physical signs daily, body weights and food consumption weekly, ophthalmic exams on all control and high dose group animals in weeks 4, 7, and 12 for males and 3, 7, and 12 for females, hematology and serum biochemistry in weeks 4, 8, and 12, urinalysis in weeks 8 and 12 on all animals. Complete necropsies and organ weights recorded for all animals. Histology conducted on all control and high dose group animals and gross lesions and target organs examined for all animals in all groups.

k. **Toxicity Observed:** Whole body tremors and decreased food consumption and body weight gain were found in the high dose group males and females, necessitating lowering the high dose level from 30 to 20 mg/kg/day in week 4 (females) and week 5 (males). The high dose females had decreased lymphocyte counts relative to controls throughout the study while both sexes in the high dose group had slight elevations in blood urea nitrogen and increased urinary specific gravity. Also, there was evidence of hemoconcentration in the high dose group based on increases in the erythron and serum protein concentrations. Postmortem examination revealed a variety of organ weight changes which were statistically significant ($P < \text{or} = 0.05$) compared to controls in the high dose group only. Treatment-related histologic changes were limited to sciatic nerve degeneration in the high dose group only.

l. **No-Observed-Effect Level:** 5 mg/kg/day.

7. Fifty-Three-Week Oral Toxicity Study in Dogs

a. **Report Number:** TT #92-116-0.

b. **Study Dates:** Started 10DEC92, ended 17DEC93.

c. **Principal Investigators:** W. Bagdon, L. Gordon, and M. Kloss

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X021) as a suspension in 0.5% aqueous methylcellulose administered at a dose volume of 5 ml/kg body weight.

f. **Species and Strain:** Dogs, Beagle.

g. **Number of Animals/Sex/Group:** 4/sex/group.

h. **Dosage Levels Tested:** 0, 0.5, 1.0, and 2.0 mg/kg/day.

i. **Route of Administration:** Oral via gavage.

j. **Parameters Examined:** Physical signs daily, body weights weekly, food consumption daily 2-5 times each week, ophthalmic exams pretest and in weeks 13, 28, 39, and 53, hematology and serum biochemistry in weeks 4, 12, 25, 39, and 51, urinalysis in weeks 12, 25, 39, and 51 for all dogs. Electrocardiograms were recorded pretest and in weeks 12, 26, 38, and 52 for all dogs. Complete necropsies and organ weights were recorded for all animals. Histology was conducted on all control and high dose group animals and gross lesions and target organs examined for all animals in all groups.

k. **Toxicity Observed:** Mydriasis was observed in the high dosage group dogs throughout the study. In addition, one high dose group animal became progressively less active, with salivation, weight loss, ataxia and recumbency. This animal was sacrificed in week 13. There were no treatment-related postmortem findings in this animal. Treatment-related postmortem findings were limited to very slight focal neuronal degeneration in the cerebellum in 3 of 8 high dose group dogs.

l. **No-Observed-Effect Level:** 1.0 mg/kg/day.

8. Oral Developmental Toxicity Study in Rats

a. **Report Number:** TT #90-718-0.

b. **Study Dates:** Started 09JUL90, ended 03AUG90.

c. **Principal Investigators:** M. Cukierski and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X014) as a suspension in 0.5% aqueous methylcellulose at a dose volume of 5 ml/kg body weight.

f. **Species and Strain:** Rat/Sprague-Dawley (Crl:CD[[dieresis]](SD)BR).

g. **Number of Animals/Sex/Group:** 25 females/group.

h. **Dosage Levels Tested:** 0, 0.5, 1.0, 3.0, and 12.0 mg/kg/day administered on gestation days 6-17.

i. **Route of Administration:** Oral via gavage on days 6 through 17 of gestation.

j. **Parameters Examined:** Physical signs daily, food consumption measured over three-day interval from days 3-20 of gestation, maternal body weights recorded on days 0, 6, 8, 10, 12, 14, 16, 18, and 20 of gestation. Reproductive parameters examined included the numbers of corpora lutea, implants, resorptions, live and dead fetuses, fetal weights, and external, visceral, and skeletal examination of fetuses. In addition, a gross necropsy was performed on all sacrificed dams.

k. **Toxicity Observed:** During the treatment period, increased body weight gains were found in the 3 and 12 mg/kg/day groups. However, following treatment on gestation days 18 to 20, there were significant ($P < or = 0.05$) treatment-related decreases in body weight gain in the 3 and 12 mg/kg/day groups compared to controls. Treatment-related increases in food consumption paralleled the increased body weight gains during the treatment period in these same groups. There was no evidence of developmental toxicity in any of the treated groups based on postimplantation survival, fetal weights, or external, visceral, or skeletal fetal examinations.

l. **No-Observed-Effect Level:** 1.0 mg/kg/day for maternal toxicity and > 12 mg/kg/day (highest dose tested) for developmental toxicity.

9. Oral Developmental Toxicity Study in Rabbits

a. **Report Number:** TT #90-719-0.

b. **Study Dates:** Started 02OCT90, ended 02NOV90.

c. **Principal Investigators:** L. D. Wise and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA

e. **Substance and Dosage Form Tested:** MK-0397 (L 653,648-000X014) as a suspension in 0.5% aqueous methylcellulose.

f. **Species and Strain:** Rabbits, New Zealand White.

g. **Number of Animals/Sex/Group:** 18 females/group.

h. **Dosage Levels Tested:** 0, 0.5, 2.0, and 8.0 mg/kg/day.

i. **Route of Administration:** Oral via gavage on gestation days 6-18.

j. **Parameters Examined:** Physical signs and food consumption daily, maternal body weights, numbers of corpora lutea, implants, resorptions, live and dead fetuses, fetal weights, and external, visceral, and skeletal examination of fetuses.

k. **Toxicity Observed:** Slowed pupillary reflex was observed in dams in the 2 and 8 mg/kg/day groups. Slight decreases in maternal body weight gain of about 10% compared to controls were found in the high dose group only. There were statistically significant ($P < or = 0.05$) decreases in the numbers of implants/pregnant female and live fetuses/pregnant female in the high dose group only compared to controls. Although not statistically significant ($P > 0.05$) in the mid dose group, these parameters were also decreased relative to controls in this group as well. No other evidence of developmental toxicity was found in this study.

l. **No-Observed-Effect Level:** 0.5 mg/kg/day for both maternal and

developmental toxicity.

10. Oral Embryo/Fetal Viability Study in Rabbits

a. **Report Number:** TT #94-707-0.

b. **Study Dates:** Started 21JAN94, ended 23 MAY94.

c. **Principal Investigators:** M. Cukierski and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA

e. **Substance and Dosage Form Tested:** MK-0397 (L 653,648-000X021) as a suspension in 0.5% aqueous methylcellulose.

f. **Species and Strain:** Rabbits, New Zealand White.

g. **Number of Animals/Sex/Group:** 24 females/group.

h. **Dosage Levels Tested:** 0, 1.2, 2.0, and 8.0 mg/kg/day.

i. **Route of Administration:** Oral via gavage.

j. **Parameters Examined:** Physical signs daily, maternal body weights, numbers of corpora lutea, implants, resorptions, and live and dead fetuses.

k. **Toxicity Observed:** Maternal toxicity was limited to the 8 mg/kg/day group and consisted of slowed pupillary reflex and decreased body weight gain during days 6-18 of gestation. There were no effects on preimplantation loss, corpora lutea/pregnant female, implants/pregnant female, percent resorptions plus dead fetuses/implant, or live fetuses per pregnant female.

l. **No-Observed-Effect Level:** 2 mg/kg/day for maternal toxicity and > 8 mg/kg/day for embryo/fetal viability.

11. Multigeneration Study in Rats

a. **Report Number:** TT #90-9010.

b. **Study Dates:** Started 22JUN90, ended 20JUN91.

c. **Principal Investigators:** A. Brooker, D. Myers, C. Parker.

d. **Laboratory:** Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.

e. **Substance and Dosage Form Tested:** MK-0397 (L-653,648-000X014)

f. **Species and Strain:** Rat/Sprague-Dawley (Crl:CD"(SD)BR).

g. **Number of Animals/Sex/Group:** 32/sex/group for F0 generation; 28/sex/group and 24/sex/group for F1 and F2 generations, respectively.

h. **Dosage Levels Tested:** 0, 6, 18, and 54 ppm (equivalent to approximately 0.5, 1.5, and 4.5 mg/kg/day).

i. **Route of Administration:** Oral via diet.

j. **Parameters Examined:** Physical signs, food consumption and body weights were recorded weekly. Water consumption was measured daily over the initial and final two weeks of pre-mating for each generation. Reproductive parameters assessed included mating performance, fertility index, numbers of pups/litter, pup weights and sexual maturation of pups. Histologic examination of the reproductive tract was conducted for the F_0 and F_1 high dose and control group males and females and target organs and gross lesions from all animals.

k. **Toxicity Observed:** Increases in body weight gain and food and water consumption were found in the high dose group F_0 animals. Decreased mating performance was also evident in the high dose group. Neonatal toxicity characterized by increased pup mortality, tremors, and decreased pup weights were found in the high dose F_1 and F_2 pups, while toxicity in the mid dose F_1 pups was limited to tremors in a few pups. Due to marked increases in food consumption during lactation resulting in increases in drug intake in the F_0 and F_1 animals, the F_1 animals were re-mated and the diet concentrations of drug reduced by a factor of 2 to maintain more constant drug intake values. As a result, drug intake values were approximately 0.4, 1.3, and 3.3 mg/kg/day during lactation of the F_{2b} offspring, compared to values of 1.0, 3.0, and 6.5 mg/kg/day for the F_{2a} offspring. In the F_{2b} offspring tremors were again noted in the high dose group pups. However, no toxicity was found in the mid and low dose group pups

l. **No-Observed-Effect Level:** 1.0 to 1.5 mg/kg/day.

B. Safe Concentrations of Total Residues

The most appropriate toxicity study for determining the safe concentrations for eprinomectin-related residues in milk and edible tissues is the 53-week oral toxicity study in dogs. The no-observed-effect level (NOEL) for this study is 1.0 mg/kg/day. The Acceptable Daily Intake (ADI) based on a NOEL of 1.0 mg/kg/day and a safety factor of 100 is 10 mcg/kg/day, calculated as follows:

```
ADI  =  1.0 mg/kg/day  ÷  100 safety factor  =  10 mcg/kg/day
        (600 mcg/day/60 kg person)
```

The portion of the ADI set aside for milk is 4%. Consequently, the ADI for cattle is allocated in the following manner:

```
ADI (milk)  =  0.4 mcg/kg/day (24 mcg/day/60 kg person)
```

```
ADI (tissues)    =   9.6 mcg/kg/day (576 mcg/day/60 kg person)
```

Safe Concentrations (SC's) for Cattle Tissues and Milk:

```
SC (milk)        =   0.4 mcg/kg x 60 kg/1.5L
                 =   16 mcg/L or 16 ppb

SC (muscle)      =   9.6 mcg/kg x 60 kg/0.3 kg
                 =   1920 mcg/kg = 1920 ppb or 1.92 ppm

SC (liver)       =   9.6 mcg/kg x 60 kg/0.1 kg
                 =   5760 mcg/kg = 5760 ppb or 5.76 ppm

SC (kidney)      =   9.6 mcg/kg x 60 kg/0.05 kg
                 =   11,520 mcg/kg = 11,520 ppb or 11.52 ppm

SC (fat)         =   9.6 mcg/kg x 60 kg/0.05 kg
                     11,520 mcg/kg = 11,520 ppb or 11.52 ppm
```

C. Total Residue Depletion and Metabolism Studies 1. Total Residue Depletion in Milk.

1.1 Stability of Tritium Labeled L-653,648 in Lactating Dairy Cows Treated Topically with a Single Dose of L-653,648 Labeled with Tritium and Carbon-14 (CA-365).

a. **Name and Address of Investigator:**

Narayana I. Narasimhan
Merck Research Laboratories
Box 2000
Rahway, NJ 07065

b. **Test Animals:** Four lactating Holstein dairy cows in the second lactation and in either the first or the third trimester of milk production were treated in this study.

c. **Route of Drug Administration and Time and Duration of Dosing:** Test animals were administered a single dose of eprinomectin (L-653,648; MK-0397) topically at 750 mcg/kg body weight (1.5 x the use level).

d. **Radiotracers:** Two cows were dosed with a dosing solution containing 5-^{3}H-L-653,648 and ^{14}C-N-acetyl-L-653,648. The other two cows were dosed with a second dosing solution containing 4a-methyl-^{3}H-L-653,648 and ^{14}C-N-acetyl-L-653,648. The radiochemical purity of L-653,648 (both tritium and C-14 labels) was in the range of 98.8-99.2% by high performance liquid chromatography. The two dosing solutions used in this study were the same as the formulation to be marketed for use on cattle.

e. **Milk Sample Collection:** Milk samples were collected at twelve hours predosing, immediately prior to dosing and every twelve hours thereafter until 21 days post-dose.

1.2 Milk, Plasma, and Tissue Radioresidues in Lactating Dairy Cows Treated Topically with a Single Dose of Radiolabeled L-653,648 (Trial CA-367).

a. **Name and Address of Investigator:**

Narayana I. Narasimhan
Merck Research Laboratories
P. O. Box 2000
Rahway, NJ 07065

b. **Test Animals:** Four lactating Holstein dairy cows in either the third or the fourth lactation cycle and in either the first or the third trimester of milk production were treated in this study.

c. **Route of Drug Administration and Time and Duration of Dosing:** Test animals were administered a single dose of eprinomectin topically at 750 mcg/kg body weight (1.5 x the use level).

d. **Radiotracer:** Four cows were dosed with a dosing solution containing 5-^{3}H-L-653,648. The radiochemical purity of the drug substance was 99.1% by high performance liquid chromatography. The topical solution used in this study was the same as the formulation to be marketed for use on cattle.

e. **Milk Sample Collection:** Milk samples were collected at twelve hours predosing, immediately prior to dosing and every twelve hours thereafter until 21 days post-dose.

1.3 Depletion of Total Eprinomectin-Related Residues from Milk.

The milk samples collected during the course of both studies CA-365 and CA-367 were assayed for total radioresidues directly using a liquid scintillation counter. Peak levels of total radioresidues ranged from 3.08 to 25.84 ng/mL (ppb) and occurred during the period of 1.5 - 8.0 days post-dose. Since the total radioresidue levels included the contribution from tritiated water, a by-product of a low level of tritium label loss, the tritiated water levels were subtracted from the total radioresidue levels. The corrected eprinomectin-related peak residue levels were in the range of 2.53 - 24.68 ng/mL.

Since milk is pooled in the dairy industry before being marketed, daily averages of the total residue levels were computed in order to simulate the drug residue levels in the marketed milk. The pooled daily average of the total radioresidues (eprinomectin and structurally related metabolites) peaked at 7.02 ng/mL at 3.0 days post-dose

From the results of studies CA-365 and CA-367, where eight lactating dairy cows were treated topically with eprinomectin at a level of approximately 1.5 times the market dose, all daily averages of the total eprinomectin-related residues in milk samples were below the milk safe concentration of 16 ng/mL.

2. Total Residue Levels in Tissues.

2.1 Depletion of Radioresidues in Tissues of Cattle Dosed Topically with a Single Dose of Radiolabeled MK-0397 (Trial CA-368).

a. **Name and Address of Investigator:**

Narayana I. Narasimhan
Merck Research Laboratories
P.O. Box 2000
Rahway, NJ 07065

b. **Test Animals:** Six heifers and six steers, consisting of Angus and Hereford breeds and eight to ten months of age, were dosed in this study. The twelve cattle were divided into four treatment groups with three animals in each group.

c. **Route of Drug Administration and Time and Duration of Dosing:** Test animals were administered a single dose of eprinomectin topically at 500 mcg/kg body weight. The animals were sacrificed by groups at 7, 14, 21 and 28 days after dose administration.

d. **Radiotracer:** The cattle were dosed with a dosing solution containing 5-^{3}H-MK-0397. The radiochemical purity of the drug substance was greater than 98% by high performance liquid chromatography. The topical solution used in this study was the same as the formulation to be marketed for use on cattle.

e. **Total Residue Concentration:** The following tissues were collected in this study: liver, kidney, fat, dose-site muscle, and muscle. Tissue samples were combusted and subjected to radioactivity analysis in a liquid scintillation counter. Mean concentrations of total radioresidues are shown in Table VI.C.1.

Table VI.C.1. Mean Concentration (ng/g orppb) of Total Residue in Tissues of Cattle Fol
Topical Dose of 5-^{3}H-Eprinomectin at 500 mcg/kg bw

Tissue	Post Dosing Interval to Sampling (Days)			
	7	14	21	
Liver	977 ± 136	751 ± 240	465 ± 238	1
Kidney	181 + 62	121 ± 39	70 ± 30	
Fat	34 ± 15	22 ± 6	14 ± 8	
Dose site muscle	24 ± 5	10 ± 4	19 ± 9	
Muscle	8 ± 3	6 ± 2	4 ± 2	

Limit of detection varied from about 0.15 ppb to 0.16 ppb and limit of quantitation varied from about 0.27 ppb to 2.24 ppb. The total radioresidue concentrations in all edible tissues were already below their respective tissue-

safe concentrations by 7 days post-treatment.

2.2 Residues in Tissues of One-Day Old Calves from Cows Dosed 7 - 14 Days Prior to Parturition with a Single Topical Application of Formulated ^{3}H-MK-0397 (Trial CA-372, Protocol Number 4042).

a. **Name and Address of Investigator:**

Narayana I. Narasimhan
Merck Research Laboratories
P. O. Box 2000
Rahway, NJ 07065

b. **Test Animals:** Six near-term pregnant Holstein dairy cows were treated in this study.

c. **Route of Drug Administration and Time and Duration of Dosing:** Test animals were administered a single dose of eprinomectin topically at 750 mcg/kg body weight (1.5 x the use level) 7 to 14 days prior to parturition. The calves born to the dosed cows were sacrificed 12 to 24 hours after birth.

d. **Radiotracer:** The cows were dosed with a dosing solution containing 5-^{3}H-MK-0397. The radiochemical purity of the drug substance was greater than 98% by high performance liquid chromatography. The topical solution used in this study was the same as the formulation to be marketed for use on cattle.

e. **Milk and Tissue Sample Collection:** Milk samples were collected at least once during the first 24 hours after parturition and every twelve hours from approximately 1.5 days through 7 days post parturition. Liver, kidney, fat, and muscle were collected from the calves. Milk and combusted tissue samples were subjected to radioactivity analysis using liquid scintillation spectrometry.

f. **Total Residue Concentration:** In colostrum and milk, peak radioresidue levels were in the range of 7.14 - 13.18 ng/mL (lower than the safe concentration of 16 ng/mL allowed in milk). The total residue levels observed in milk in study CA-372 were similar to or lower than the total milk residue levels observed in studies CA-365 and CA-367 described above. Total residue levels in fat and muscle of the calves were below the limit of quantitation (3.9 ppb for fat and 1.1 ppb for muscle). The total residue levels in kidneys were all equal to or below 2.0 ppb. The total residue levels in livers ranged from 5.8 ppb to 55.0 ppb and averaged 21.4 ppb.

3. Metabolism of Eprinomectin in Cattle.

Metabolite profiles in milk (Studies CA-365 and CA-367) and tissues and feces (metabolism study ADMES-3, samples from study CA-368) were determined. The radioresidues derived from eprinomectin and structurally similar metabolites were all essentially extractable into organic solvents. These solvent extracts were analyzed by reversed phase HPLC. Eprinomectin was not metabolized to a significant extent in lactating and beef cattle. The total amount

of all the metabolites in the edible tissues or milk was 10% or less of the total radioresidues in any particular matrix. Also none of the metabolites was greater than 10% of the total radioresidues or was present in amounts greater than 0.1 ppm. Therefore, metabolites were not structurally identified. In general, the metabolite profile in a given matrix (tissues, plasma, or excreta) did not change with time post-dose in either dairy or beef cattle. Also, in beef cattle, the metabolite profiles in all matrices were independent of the sex of the animal. The metabolism of eprinomectin in all the biological matrices is nearly identical qualitatively and quantitatively.

Eprinomectin is not metabolized extensively in cattle and the B1a component is the major residue in all matrices. For example, in milk, liver, kidney, fat, dose-site muscle, and muscle, the percent contribution from the B1a component was 85.6, 86.4, 86.2, 86.7, 83.3, and 82.0, respectively. The percent contribution from eprinomectin and metabolite residues to the overall metabolite profile in milk, liver, fat, and feces are shown in Table VI.C.2.

Table VI.C.2. Percent Contribution of Eprinomectin and Metabolites to the Overall Metabc in Milk and Tissues

Matrix	Eprinomectin			Metabolites
	B_{1b}	B_{1a}	Total	
Milk	7.9	85.6	93.5	two metabolites > 1.0%
Liver	9.3	86.4	95.7	one metabolite 1.1%
Fat	7.2	86.7	93.9	one metabolite 1.0%
Feces	8.3	78.3	86.6	one metabolite 7.4%, one metabolite 1.6%

D. Comparative Metabolism of Eprinomectin in Rats

1. The Distribution, Excretion, and Metabolism of MK-0397 (L-653,648) in Rats (ADMES-1).

a. **Name and Address of Investigator:**

Bruce A. Halley
Merck Research Laboratories
Box 2000
Rahway, NJ 07065

b. **Test Animals:** Sprague-Dawley (CRL-CD-SD BR) VAF rats (fourteen males and fourteen females), approximately seven weeks of age, were used in this study. The same strain of rats was treated in the fourteen-week and multigeneration oral toxicity studies and an oral developmental toxicity study.

c. **Route of Drug Administration and Time and Duration of Dosing:**

Twelve animals of each sex were administered seven consecutive daily oral gavage doses of eprinomectin at approximately 6.0 mg/kg body weight. Two animals of each sex (controls) received approximately the same volume of unmedicated vehicle.

d. **Radiotracer:** The dosing solution contained 5-^{3}H-L-653,648. The radiochemical purity of the drug substance was 98% by high performance liquid chromatography.

e. **Samples Collected:** Three male and three female rats were sacrificed at approximately 7 hours, 1, 2, and 5 days after the seventh dose. Liver, kidney, fat, muscle, and GI tract were collected. In addition, urine and feces were collected daily from each rat.

f. **Results:** Through day 5 after the last dose, 90% of the administered dose was excreted in feces and less than 1% in urine. Based on chromatographic retention times, the metabolite profiles in rat tissues and feces were shown to be qualitatively similar to the profiles in cattle milk, plasma, tissues, and feces. Although in most of the rat tissues, especially at later times, the percent contribution from one metabolite (M5, identified as the N-desacetyl MK-0397) was greater than 10%, metabolism of eprinomectin to M5 does not occur to any significant degree as a whole in the rat. This was based on the fact that in rat feces, where 90% of the dose was accounted for, M5 constituted only 1.5% and 6.2% of the total residues in males and females, respectively. All the metabolites that were observed in cattle tissues and milk were also observed in several rat tissues. Whereas the metabolism of eprinomectin was independent of sex in cattle, the metabolism of eprinomectin to M5 was sex-dependent in rats, i.e., the female rats produced more of M5. From this comparative metabolism study, it was evident that the rat, a laboratory toxicity test species, was exposed to the major drug residue components which were present in cattle tissues.

E. Selection of a Target Tissue, Marker Residue, and Determination of a Tolerance

Since the residue levels in liver were higher than those in other tissues and the total residue levels and the marker residue levels deplete in parallel in liver, liver was considered as the target tissue. Total residue levels in liver also depleted in parallel to total residue levels in other tissues.

Metabolite profiles of milk and other edible tissues indicated that the B1a component of eprinomectin was the major residue. The levels of the B1a component depleted in parallel to the total residues in all edible tissues, and was selected as the marker residue. Marker residue levels in milk and edible tissues were determined using the validated high pressure liquid chromatography-fluorescence detection method.

In studies CA-365 and CA-367, the peak levels of the marker residue in milk were in the range of 2.15 - 21.10 ng/mL. The ratios of marker residue levels to total eprinomectin-related residues (corrected for the contribution from tritiated

water) at every milking interval were calculated and averaged to be 0.77. Hence, the tolerance of 12 ng/mL for the eprinomectin B1a component marker residue in milk was obtained by multiplying this ratio with the milk safe concentration of 16 ng/mL.

In study CA-368, the marker residue levels were determined in various edible tissues and are presented in Table VI.E.1.

Table VI.E.1. Marker Residue Levels (ng/g or ppb) in Edible Tissues of Cattle following Dose of 5-^{3}H-Eprinomectin at 500 mcg/kg bw

Tissue	Post-Dosing Sample Interval (Days)			
	7	14	21	
Liver	807 ± 168	546 ± 185	369 ± 194	1
Kidney	161 ± 55	113 ± 35	54 ± 23	
Fat	30 ± 11	19 ± 6	14 ± 8	
Dose-site muscle	17 ± 4	8 ± 4	14 ± 6	
Muscle	6 ± 3	4 ± 0.7	3 ± 1	

The ratio of marker residue concentration to the total residue concentration in each animal tissue was calculated and averaged for each tissue type. The average ratios in liver, kidney, fat, dose-site muscle, and muscle were 0.83, 0.85, 0.92, 0.71, and 0.69, respectively. The marker residue (eprinomectin B1a component) tolerance in the liver (target tissue) was calculated by multiplying the safe concentration in liver by the average ratio of marker to total residues in liver. Therefore, the tolerance in liver was 5760 ppb x 0.83, or 4800 ppb after rounding.

In study CA-372, marker residue levels in livers of one-day old calves were also determined. The marker residue levels in livers were averaged to be 19.3 ppb with a marker to total residue ratio of 0.90.

F. Studies to Establish a Withdrawal Time

1. Zero Milk Discard:

A zero milk discard has been established for IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle using 24 mcg of the total ADI for a person weighing 60 kg as the portion assigned to milk. This was based on the milk residue data from the radiotracer studies CA-365 and CA-367 as described in parts VI. C and VI. E of this summary.

2. Zero Tissue Withdrawal Period:

Three studies using the commercial pour-on formulation were conducted to

demonstrate that no withdrawal period is required for edible tissues.

2.1 Eprinomectin (MK-0397): A Study in Cattle to Determine the MK-0397 Marker Residue for Establishing a Withdrawal Period (Study 94031, CA-371).

a. **Name and Address of Investigator:**

Study Director:

Lori D. Payne, Ph.D.
Merck Research Laboratories
Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065

Principal Biologist:

Terry D. Faidley, Ph.D.
Merck Research Laboratories
Merck & Co., Inc.
Somerville, NJ 08876

b. **Test Animals:** Seventeen male castrates and seventeen heifers, Hereford x Holstein, beef cattle weighing 436 to 656 kg and ranging in age from approximately 17 to 20 months were used in this study.

c. **Route of Drug Administration:** Thirty cattle were dosed by topical administration at 500 mcg/kg body weight (1 mL/10 kg body weight) with a solution containing 5 mg eprinomectin per mL of formulation (0.5%). The topical solution used in this study was the same as the formulation to be marketed for use on cattle. For calculation of the volume dosed, the animal's body weight was rounded up to the nearest 50 kg.

d. **Time and Duration of Dosing:** The cattle were treated once at Day 0. Five treated animals were sacrificed at each of six times post-dose: 10, 17, 24, 34, 44, and 55 days. Four animals served as unmedicated controls.

e. **Results**: Marker residue assays were conducted on the liver samples (the target tissue) and dose-site muscle using a validated high pressure liquid chromatography-fluorescence detection method. The average marker residue concentrations found are presented in Table VI.F.1.

Table VI.F.1. Average Marker Residue Concentrations (ng/g or ppb) in Liver and Dose-Si of Cattle Dosed Topically with Eprinomectin at 500 mcg/kg bw

	Post-Dose Sampling Interval (Days)						
	10	17	24	34	44	55	

ng/g (Liver)	748	237	56	26	4	<1	
Std. dev.	78	125	28	24	3	---	
ng/g (Dose-site muscle)	8	3	<2	<1	<1	NA	
Std. dev.	2	2	---	---	---	---	
NA = not assayed							

The analytical method used to determine the marker residue has a lower limit of reliable measurement of 2 ng/g and a limit of detection of 1 ng/g. The marker residue tolerance for eprinomectin-treated cattle has been established to be 4800 ng/g for liver. The average marker residue concentrations in liver from study CA-371 were at least six times lower than the liver tolerance.

2.2 Eprinomectin Topical: A Study in Cattle to Determine Eprinomectin (MK-0397) Marker Residue in Edible Tissue at 0.5, 1, 3, 5, and 7 Days After Treatment (Study 94458, ASR 14741).

a. **Name and Address of Investigator**:

Study Director:

Lori D. Payne, Ph.D.
Merck Research Laboratories
Merck & Co., Inc.
P. O. Box 2000
Rahway, NJ 07065

Principal Biologist:

Ron Gogolewski, Ph.D.
Merck Research Laboratories
Merck Sharp & Dohme Pty Ltd
P. O. Box 135
Ingleburn NSW 2565
Australia

b. **Test Animals:** Beef cattle (fourteen male castrates and thirteen heifers), of either Angus or Hereford breed, weighing 227 to 389 kg, and ranging in age from approximately 12 to 19 months were used in this study. The in-life phase was conducted in New South Wales, Australia.

c. **Route of Drug Administration:** Twenty-five cattle were dosed by topical administration at 500 mcg/kg body weight (1 mL/10 kg body weight) with a solution containing 5 mg eprinomectin per mL of formulation (0.5%). The topical solution used in this study was the same as the formulation to be marketed for use on cattle. For calculation of the volume dosed, the animal's body weight was rounded up to the nearest 50 kg.

d. **Time and Duration of Dosing:** The cattle were treated once at Day 0. Five animals were slaughtered at each of five times post-dose, 0.5, 1, 3, 5, and 7 days. Two animals served as unmedicated controls.

e. **Results:** Liver and dose-site muscle samples were assayed by the validated high pressure liquid chromatography-fluorescence detection method for marker residue. The average marker residue concentrations found are presented in Table VI.F.2.

Table VI.F.2. Average Marker Residue Concentrations (ng/g or ppb) in Liver and Dose-Si of Cattle Dosed Topically with Eprinomectin at 500 mcg/kg bw

	Post-Dose Sampling Interval (Days)					
	0.5	**1**	**3**	**5**	**7**	
ng/g (Liver)	278	551	710	376	323	
Std. dev.	71	148	177	134	83	
ng/g (Dose-site muscle)	<2	3	4	2	<2	
Std. dev.	---	1	1	---	---	
NA = not assayed						

The criteria for a zero-withdrawal time were that the average marker residue concentration at each slaughter time in liver had to be no greater than one-half the liver marker residue tolerance of 4800 ppb. The criteria were met with this study, thus establishing a zero-withdrawal time for cattle. The average marker residue concentrations in dose-site muscle at all slaughter times were lower than 1/450 of the muscle safe concentration of 1920 ppb.

2.3 Eprinomectin (MK-0397): A Study in Non-ruminating Calves to Determine Eprinomectin Marker Residue Concentrations in Edible Tissues at 1, 3, 7, and 14 Days after Treatment (Study 94633, ASR 14645).

a. **Name and Address of Investigator:**

Study Director:

Lori D. Payne, Ph.D.
Merck Research Laboratories
Merck & Co., Inc.
Box 2000
Rahway, NJ 07065

Principal Biologist:

Terry D. Faidley, Ph.D.
Merck Research Laboratories
Merck & Co., Inc.

Somerville, NJ 08876

b. **Test Animals:** Fourteen preruminating male Holstein calves, weighing 90.4 to 103 kg and to be less than 16 weeks old at slaughter, were used in this study.

c. **Route of Drug Administration:** Twelve calves were dosed by topical administration at 500 mcg/kg body weight (1 mL/10 kg body weight) with a solution containing 5 mg eprinomectin per mL of formulation (0.5%). The topical solution used in this study was the same as the formulation to be marketed for use on cattle. For calculation of the volume dosed, the animal's body weight was rounded up to the nearest 10 kg.

d. **Time and Duration of Dosing:** The cattle were treated once at Day 0. Three treated calves were sacrificed at each of four times post-dose: 1, 3, 7, and 14 days. Two calves served as unmedicated controls.

e. **Results:** Marker residue assays were conducted on the liver samples (the target tissue), kidney, and dose-site muscle using a validated high pressure liquid chromatography-fluorescence detection method. The average marker residue concentrations found are presented in Table VI.F.3.

Table VI.F.3. Average Marker Residue Concentrations (ng/g or ppb) in Liver, Kidney, and Muscle of Calves Dosed Topically with Eprinomectin at 500 mcg/kg bw

	Post-Dose Sampling Interval (Days)				
	1	**3**	**7**	**14**	**C**
ng/g (Liver)	618	832	1220	803	
Std. dev.	377	130	386	46	
ng/g (Kidney)	119	166	237	120	
Std. dev.	113	48	14	55	
ng/g (Dose-site muscle)	9	26	57	23	
Std. dev.	11	12	8	5	

The criteria for a zero-withdrawal time were that the average marker residue concentration at each slaughter time in liver had to be no greater than one-half the liver marker residue tolerance of 4800 ppb. The criteria were met with this study, thus establishing a zero-withdrawal time for preruminating cattle. The average marker residue concentrations in kidney and dose-site muscle at all slaughter times were lower than 1/45 of the kidney safe concentration of 11520 ppb and 1/30 of the muscle safe concentration of 1920 ppb, respectively.

G. Regulatory Methods

Because no withdrawal time applies to this product for either milk or edible tissues, no regulatory method is required. However, a determinative method

using a high pressure liquid chromatography assay for the B1a component of eprinomectin has been validated in a sponsor-monitored method trial meeting CVM requirements. In addition, a validated research method for the B1a component of eprinomectin in milk has been made available by the sponsor.

H. User Safety

1. Acute Oral Toxicity Study in Mice

a. **Report Number:** TT #93-2733.

b. **Study Dates:** Started 21SEP93, ended 04OCT93.

c. **Principal Investigators:** W. Bagdon and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 Cattle Topical Formulation (L-653,648-127C).

f. **Species and Strain:** Mouse, Crl:CD-1®(ICR)BR.

g. **Number of Animals/Sex/Group:** 10/sex.

h. **Dosage Levels Tested:** 5000 mg/kg (5.45 ml of formulation/kg body weight).

i. **Route of Administration:** Oral via gavage.

j. **Parameters Examined:** Physical signs of toxicity were recorded daily and body weights were recorded pretest and days 7 and 14.

k. **Toxicity Observed:** No mortality or treatment-related physical signs were observed in any mouse throughout the study.

l. **No-Observed-Effect Level:** > 5000 mg/kg (highest dose tested).

2. Ocular Irritation Study in Rabbits

a. **Report Number:** TT #93-2732.

b. **Study Dates:** Started 04OCT93, ended 18OCT93.

c. **Principal Investigators:** W. Bagdon and M. Kloss.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 Cattle Topical Formulation (L-653,648-127C).

f. **Species and Strain:** Rabbits, New Zealand White.

g. **Number of Animals/Sex/Group:** 2 males and 2 females per group.

h. **Dosage Levels Tested:** 0.1 ml of the formulation.

i. **Route of Administration:** Intraocular.

j. **Parameters Examined:** Daily examinations were conducted for systemic toxicity. Ocular examinations for signs of irritation were conducted for all animals 15 minutes and 2 hours after treatment on most days until study termination on day 15. One group received only the MK-0397 formulation while the other group received the formulation followed by rinsing the treated eye with approximately 20 ml of warm tap water 20 seconds following intraocular administration.

k. **Toxicity Observed:** Slight conjunctival redness was found in 1 of 4 rabbits in the unwashed group. This effect was completely reversible by 2 hours post-treatment. No other rabbits in this group or the group which received the water rinse showed any signs of irritation throughout the study.

3. Guinea Pig Dermal Sensitization Study

a. **Report Number:** TT #93-643-0.

b. **Study Dates:** Started 04OCT93, ended 03FEB94.

c. **Principal Investigators:** G. Durand-Cavagna.

d. **Laboratory:** Merck Research Laboratories, Chibret, France.

e. **Substance and Dosage Form Tested:** MK-0397 Cattle Topical Formulation (L-653,648-127C).

f. **Species and Strain:** Hartley albino guinea pigs.

g. **Number of Animals/Sex/Group:** 10 females in the negative control group, 11 females in each of the vehicle control and MK-0397-treated groups.

h. **Dosage Levels Tested:** 0.4 ml/treatment for induction, challenge, and re-challenge.

i. **Route of Administration:** Dermal.

j. **Parameters Examined:** Daily examinations for physical signs of toxicity and dermal irritation.

k. **Toxicity Observed:** Slight dermal irritation was found in the vehicle control and MK-0397-treated groups. However, the MK-0397 formulation is considered negative for dermal sensitization since on re-challenge, dermal signs

were less than upon primary challenge and were similar in the vehicle and MK-0397 groups. The observed effects are considered due to the slight irritation produced by the formulation vehicle.

4. Thirty-Day Dermal Toxicity and Irritation Study

a. **Report Number:** TT #93-128-0.

b. **Study Dates:** Started 30SEP93, ended 07APR94.

c. **Principal Investigators:** M. Kloss, M. Hubert, and J. Majka.

d. **Laboratory:** Merck Research Laboratories, West Point, PA.

e. **Substance and Dosage Form Tested:** MK-0397 Cattle Topical Formulation (L-653,648-127C).

f. **Species and Strain:** Hanford mini-swine.

g. **Number of Animals/Sex/Group:** 4/sex/group.

h. **Dosage Levels Tested:** 5ml/animal/day for each of the saline control, vehicle control, and MK-0397 formulation groups.

i. **Route of Administration:** Dermal.

j. **Parameters Examined:** All animals were observed daily for physical signs and evidence of dermal irritation. In addition, all animals were weighed pretest and once weekly and food consumption was estimated twice daily. Complete necropsies were performed on all animals and the dermal application sites, brain, cervical spinal cord, and sciatic nerves as well as all gross changes from all animals were examined histopathologically.

k. **Toxicity Observed:** No treatment-related mortality, clinical signs, body weight or food consumption changes were found during the study. The only treatment-related finding was a slight increase in the incidence and severity of focal cellular infiltration noted histologically in the vehicle control and MK-0397-treated groups compared to the saline control. This finding is indicative of a mild degree of irritancy related to the formulation vehicle, since the presence of MK-0397 did not affect the incidence or severity of the response.

l. **No-Observed-Effect Level:** <5mL/dermal application site

5. Handler Safety Evaluation

The MK-0397 cattle topical formulation is not acutely toxic in mice as no toxicity was observed at 5000 mg/kg, the highest dose tested. The formulation was practically non-irritating to the eyes in the rabbit ocular irritation study. Irrigation of the eyes prevented the mild irritation that was observed. The formulation was not a dermal sensitizer in guinea pigs and did not produce any

systemic toxicity when tested dermally in mini-swine. In one field trial, the person applying the drug did report a mild skin irritation on one hand which was directly exposed to the drug and was not immediately washed, however, this individual has a history of multiple hypersensitivities. The following direction is on the product:

As with any topical medication intended for treatment of animals, skin contact should be avoided. If accidental skin contact occurs, wash immediately with soap and water. If accidental eye exposure occurs, flush eyes immediately with water.

In addition, a toll-free telephone number will be available on the label to inform users of where to obtain additional information concerning user safety relative to the MSDS and to report adverse events involving the target species or human exposure.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that IVOMEC® EPRINEXTM Pour-On for Beef and Dairy Cattle is safe and effective for the treatment and control of gastrointestinal roundworms, lungworms, grubs, horn flies, lice and mange mites in cattle when administered topically as a single dose of 500 mcg eprinomectin per kilogram body weight. IVOMEC® EPRINEXTM Pour-On for Beef and Dairy Cattle has also been proven to protect cattle against infection or reinfection with *Dictyocaulus viviparus* for 21 days when administered at the recommended dose.

Based on a battery of toxicology tests, an acceptable daily intake (ADI) of 10 mcg/kg body weight/day was calculated. A portion of the ADI (0.4 mcg/kg body weight/day) was reserved for milk and yielded a milk safe concentration of 16 ppb. The rest of the ADI (9.6 mcg/kg body weight/day) was used in the calculation of safe concentrations for total eprinomectin-related residues of 1.92 ppm in muscle, 5.76 ppm in liver, 11.52 ppm in kidney, and 11.52 ppm in fat. Metabolism studies in cattle along with quantitation of a marker residue in radiolabeled milk and tissues established tolerances of 12 ppb and 4.8 ppm for the B1a component of eprinomectin (the marker residue) in milk and liver (the target tissue), respectively.

Based on the milk residue data from the radiotracer studies, a zero milk discard has been established for the use of IVOMEC® EPRINEX™ (eprinomectin) Pour-On product. There was no pre-slaughter withdrawal time required for edible tissues from the results of marker residue depletion studies in adult cattle and preruminating calves, following a single topical application of IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle at a dose rate of 500 mcg/kg animal body weight (1 mL/10 kg body weight).

The data submitted for IVOMEC® EPRINEXTM Pour-On for Beef and Dairy Cattle support the marketing of the product as an over-the-counter new animal

drug. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall have over-the-counter marketing status.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The Agency's finding of no significant impact (FONSI) and the evidence supporting that finding is contained in an environmental assessment which may be seen in the Dockets Management Branch (HFA-305), Park Building, (Room 1-23), 12420 Parklawn Dr., Rockville, Maryland 20857.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) of the drug has been approved in any other application. IVOMEC® EPRINEXTM Pour-On for Beef and Dairy Cattle is under patent number 4,427,663, which expires on March 16, 2002 and patent number 5,602,107, which expires on May 10, 2013.

VII. APPROVED PRODUCT LABELING

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

Approval Date: August 9, 1998

Freedom of Information Summary
NADA 141-079

I. GENERAL INFORMATION:

NADA	141-079
Sponsor:	Merial Ltd. 2100 Ronson Rd. Iselin, New Jersey 08830-3077
Generic Name:	Eprinomectin
Trade Name:	Ivomec® Eprinex™ Pour-On for Beef and Dairy Cattle
Marketing Status:	Over the Counter (OTC)
Effect of Supplement:	This supplemental application adds indications for the treatment and control of adult *Strongyloides papillosus* and adult *Trichostrongylus longispicularis* and removes the age restriction for use in cattle under 8 weeks of age

Previously registered indications are discussed in the FOI Summary for NADA 141-079, approved April 16, 1997, and in the Federal Register (62 FR 33997; June 24, 1997).

II. INDICATIONS FOR USE

For the treatment and control of the following parasites:

Gastrointestinal Roundworms:

Haemonchus placei	(adults and L4)
Ostertagia ostertagi	(adults and L4, including inhibited L4)
Trichostrongylus axei	(adults and L4)
Trichostrongylus colubriformis	(adults and L4)
Trichostrongylus longispicularis	(adults only)
Cooperia oncophora	(adults and L4)
Cooperia punctata	(adults and L4)
Cooperia surnabada	(adults and L4)
Nematodirus helvetianus	(adults and L4)
Oesophagostomum radiutum	(adults and L4)
Bunostomum phlebotomum	(adults and L4)
Strongyloides papillosus	(adults only)
Trichuris spp	(adults only)

Lungworms:

Dictyocaulus viviparus (adults and L4)

Cattle Grubs (all parasitic stages):

Hypoderma lineatum
Hypoderma bovis

Lice:

Damalinia bovis
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites:

Chorioptes bovis
Sarcoptes scabiei

Horn Flies:

Haematobia irritans

Persistent Activity: IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle has been proved to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* for 21 days after treatment and *Haematobia irritans* for 7 days after treatment.

III. DOSAGE

A. DOSAGE FORM	IVOMEC®EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle is available in 250-mL, 1-liter, 2.5-liter, and 5-liter polyethylene containers. Each milliliter contains 5 mg eprinomectrin.
B. ROUTE OF ADMINISTRATION	IVOMEC®EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle should be administered topically to the skin along the midline of the back.
C. APPROVED DOSAGES:	500 mcg eprinomectrin/kg body weight (1 mL/10 kg or 22 lb BW).

IV. EFFECTIVENESS

Data supporting the effectiveness of previously approved indications are summarized in the FOI Summary for NADA 141-079 (62 FR 33997; June 24, 1997).

A. Type of Study: Three dose confirmation studies in cattle with natural nematode infections were conducted by the following investigators:

Dr. T. A. Yazwinski
University of Arkansas
Fayetteville, AR 72701

Dr. R. E. Plue
Merck Research Laboratories
Fulton, MO 65251

Dr. E. G. Johnson
Johnson Research
Parma, ID 83660

B. General Design

1. Purpose: To confirm the efficacy of eprinomectin administered topically at 500mcg/kg against natural endoparasite infections.

2. Animals and Housing: Each study had 10 eprinomectin-treated and 10 vehicle-treated cattle. All animals were 4 to 12 months of age, 102 to 305 kg body weight, and individually housed. Both beef and dairy breeds were used.

3. Infections: Animals were naturally infected by grazing contaminated pasture as confirmed by fecal egg counts. In the 14 days prior to treatment, housing conditions were designed to preclude further nematode exposure.

4. Dosage Form, Dose, and Route of Administration: On Day 0, a single dose of a non-aqueous solution of 5 mg eprinomectin per mL was applied to each animal's back (withers to tailhead) at a rate of 500 mcg eprinomectin per kg body weight. Control animals were treated similarly with 1 mL vehicle per 10 kg body weight.

5. Parameters Measured: Cattle were necropsied at Day 14 or 15 and gastrointestinal contents (5% minimum) were inspected for nematode presence.

C. Results: Results are summarized below in Table 4.1.

Table 4.1.

Nematode count data for cattle treated with eprinomectin at 500 mcg/kg.

		Arithmetic Mean Count		
Study Number	Nematode	Control	Eprinomectin	% Efficacy
ASR 15112	*Trichostrongylus*	100	0	100

	longispicularis			
ASR 15199	*Strongyloides papillosus*	14	0	100
ASR 15201	*Strongyloides papillosus*	46	0	100

D. Adverse Reactions: There were no adverse reactions to treatment.

E. Conclusions: The data demonstrate that IVOMEC® EPRINEX™ (eprinomectrin) Pour-On for Beef and Dairy Cattle is safe and effective for the control of infections of adult *Strongyloides papillosus* and adult *Trichostrongylus longispicularis* 500 mcg eprinomectrin/kg body weight.

V. ANIMAL SAFETY

Data supporting the target animal safety of IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle are summarized in the FOI Summary for NADA 141-079 (62FR 33997; June 24, 1997).

A. Type of Study: The safety of a single administration of eprinomectin at 500 mcg/kg (recommended dose) or 1500 mcg/kg was evaluated in neonatal calves by:

Dr. B. N. Kunkle
Merck Research Laboratories
Fulton, MO 65251

B. General Design

1. Purpose: To investigate the toxicity of eprinomectin in neonatal calves.
2. Animals and Housing: Twenty-one male and female crossbred beef calves, aged 24 to 48 hours and weighing 19.2 to 46.0 kg on the day of treatment, were housed individually.
3. Dosage Form, Dose, and Route of Administration: On Day 0, animals received a single dose of a non-aqueous solution of 5 mg eprinomectin per mL along the back (withers to tailhead).at a dose rate of either 500 mcg/kg or 1500mcg/kg. Control animals were treated similarly with vehicle at 3 mL per 10kg.
4. Parameters Measured: Clinical examinations were conducted daily from Day 0 (pretreatment) to Day 10. Blood samples were collected for hematology and blood chemistry on Days 0 (pretreatment), 1, 4, and 10.

C. Results: Certain clinical pathology variables had significant ($p<0.10$) interactions of treatment and sampling day or significant ($p<0.10$) differences between treatment groups; however, all values approximated those reported for untreated neonatal calves

under the same conditions as the trial animals. Abnormal physical findings such as diarrhea, swollen umbilicus, and lacrimal secretion were not considered unusual in neonatal calves and were not attributable to use of eprinomectin.

D. Conclusions: Topical administration of eprinomectin at 500 mcg/kg BW is safe when used in neonatal calves under the approved conditions of use specified in the labeling.

VI. HUMAN SAFETY

Data supporting the human food safety of IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle are summarized in the FOI Summary for NADA 141-079 (62FR33997; June 24, 1997).

Based on a battery of toxicology tests, an Acceptable Daily Intake (ADI) of 10 mcg/kg body weight/day was calculated. A portion of the ADI (0.4 mcg/kg body weight/day) was reserved for milk and yielded a milk safe concentration of 16 ppb. The rest of the ADI (9.6 mcg/kg body weight/day) was used in the calculation of Safe Concentrations for total eprinomectin-related residues of 1.92 ppm in muscle, 5.76 ppm in liver, 11.52 ppm in kidney, and 11.52 ppm in fat. Metabolism studies in cattle along with quantitation of a marker residue in radiolabeled milk and tissues established tolerances of 12 ppb and 4.8ppm for the B_{1a} component of eprinomectin (the marker residue) in milk and liver (the target tissue), respectively.

Based on the milk residue data from the radiotracer studies, a zero milk discard has been established for the use of IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle. There was no pre-slaughter withdrawal time required for edible tissues from the results of marker residue depletion studies in adult cattle and preruminating calves, following a single topical application of the product at a dose rate of 500 mcg/kg animal body weight (1 mL/10 kg body weight).

As part of the approval of this supplement, the Agency has taken the opportunity to update the human food safety information on this product and to codify an Acceptable Daily Intake (ADI) of 10mcg/kg body weight/day, and a tolerance of 100 parts per billion (ppb) for residues of eprinomectin B_1a in cattle muscle. This value is consistent with the data for residues found in muscle under the conditions of use for the pour-on product and will not jeopardize the approval of the established withdrawal time for the pour-on product. The 100 ppb value also harmonizes the tolerance for meat with internationally accepted Maximum Residue Level (MRL) values.

VII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that IVOMEC® EPRINEX™ (eprinomectrin) Pour-On for Beef and Dairy Cattle is safe and effective for the treatment and control of infections of adult *Strongyloides papillosus* and adult *Trichostrongylus longispicularis*, and that the current age restriction may be removed.

As described in Section VI, a tolerance of 100 parts per billion (ppb) for residues of eprinomectin B_1a in cattle muscle is established and the ADI is codified at 10mcg/kgbodyweight/day.

Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall retain over-the-counter marketing status.

In accordance with 21 CFR 514.106(b)(2)(v) & (ix), this is a Category II change that did not require a reevaluation of the safety or effectiveness data in the parent application.

In accordance with 21 CFR 25.33(a)(1) & (7), this action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for three years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new indications for which the supplemental application was approved.

IVOMEC® EPRINEX™ (eprinomectin) Pour-On for Beef and Dairy Cattle is under U.S. patent numbers 4,427,663 and 5,602,107 which expire on March 16, 2002, and May10,2013, respectively.

VIII. LABELING (Attached)

Facsimile labeling components are provided for the package outsert, bottle, and carton for each of the 250-mL, 1-liter, 2.5-liter,

and 5-liter pack sizes.

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

Attachment 3

Material Safety Data Sheet

IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle

NOV 19 2008

Material Safety Data Sheet
ISO/DIS 11014 / 29 CFR 1910.1200 / ANSI Z400.1

Printing date 10/25/2007 Reviewed on 10/25/2007

1 Identification of substance

· **Product details**

· **Trade name:** Eprinomectin
EPRINEX Pour-On for Cattle

· **Item number:** 30250-30253

· **Manufacturer/Supplier:**
Merial Limited
3239 Satellite Blvd.
Duluth, Ga. 30096-4640
1-888-MERIAL 1 (1-888-637-4251)

· **Emergency information:**
Spill Information:
CHEMTREC® 1-800-424-9300
CHEMTREC® International 1+703-527-3887
International calls 011+703-527-3887
Reverse charges.

2 Composition/Data on components

· **Chemical characterization**

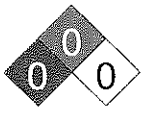
· **Components:**

	Non hazardous inert ingredients		99.5 %
133305-88-1	Eprinomectin	T, N; R 25-48-50	0.5%

· **Additional information:** Used for the treatment of cattle.

3 Hazards identification

· **Hazard description:** Not applicable.
· **Classification system:**
The classification was made according to the latest editions of international substances lists, and from company and regulatory data.
· **NFPA ratings (scale 0 - 4)**



Health = 0
Fire = 0
Reactivity = 0

· **HMIS-ratings (scale 0 - 4)**

Health = 0
Fire = 0
Reactivity = 0

4 First aid measures

· **General information:** No special measures required.

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ISO/DIS 11014 / 29 CFR 1910.1200 / ANSI Z400.1

Printing date 10/25/2007 Reviewed on 10/25/2007

Trade name: Eprinomectin
EPRINEX Pour-On for Cattle

· **After inhalation:** If breathing is difficult, give oxygen. If not breathing, give artificial respiration.
· **After skin contact:** Immediately wash with water and soap and rinse thoroughly.
· **After eye contact:**
Rinse opened eye for a minimum of 15 minutes under running water. Get medical attention immediately.
· **After swallowing:** If symptoms occur consult doctor.

5 Fire fighting measures

· **Suitable extinguishing agents:** Use appropriate media for underlying fire.
· **Protective equipment:**
Fire fighters should wear self-contained breathing apparatus and full protective equipment.
Self-contained breathing apparatus and full protective equipment.

6 Accidental release measures

· **Measures for environmental protection:** Do not allow product to reach sewage system or any water course.
· **Measures for cleaning/collecting:** Dispose of contaminated material as waste according to section XIII.

7 Handling and storage

· **Handling:**
· **Information for safe handling:** No special measures required.
· **Information about protection against explosions and fires:** No special measures required.

· **Storage:**
· **Requirements to be met by storerooms and receptacles:** Store only in the original container.
· **Information about storage in one common storage facility:** Not required.
· **Further information about storage conditions:**
· **Recommended storage temperature:** <40°C

8 Exposure controls and personal protection

· **Components with limit values that require monitoring at the workplace:**
The product does not contain any relevant quantities of materials with critical values that have to be monitored at the workplace.

· **Personal protective equipment:**
· **General protective and hygienic measures:**
Wash hands before breaks and at the end of work.
Avoid contact with the eyes.
Do not eat, drink, smoke or inhale.
Do not store food in the working area.
· **Breathing equipment:** If in particulate form, MSHA-NIOSH approved respirator for dust.
· **Protection of hands:**

Rubber or other impervious gloves

· **Penetration time of glove material**
The exact break through time has to be found out by the manufacturer of the protective gloves and has to be observed.

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Trade name: Eprinomectin
EPRINEX Pour-On for Cattle

· **Eye protection:**

Safety goggles.

· **Body protection:** Not required under normal conditions of use.

9 Physical and chemical properties

· **General Information**	
Form:	Liquid
Color:	Colorless to Yellow
Odor:	Odorless
· **Change in condition**	
Melting point/Melting range:	Undetermined.
Boiling point/Boiling range:	Undetermined.
· **Flash point:**	220°C (428°F)
· **Auto igniting:**	Product is not self-igniting.
· **Danger of explosion:**	Product does not present an explosion hazard.
· **Specific gravity:**	Not determined.
· **Solubility in / Miscibility with**	water soluble
· **Solvent content:**	0 %
· **Organic solvents:**	0.0 %
· **Solids content:**	0.5 %

10 Stability and reactivity

· **Thermal decomposition / conditions to be avoided:** No decomposition if used according to specifications.
· **Dangerous reactions** No dangerous reactions known.
· **Dangerous products of decomposition:** No dangerous decomposition products known.

11 Toxicological information

· **Acute toxicity:**

· **LD/LC50 values that are relevant for classification:**		
133305-88-1 Eprinomectin		
Oral	LD50	70 mg/kg (mouse) 55 mg/kg (rat)

· **Primary irritant effect:**
· **on the skin:** No irritating effect known.
· **Sensitization:** No sensitizing effects known.

Material Safety Data Sheet
ISO/DIS 11014 / 29 CFR 1910.1200 / ANSI Z400.1

Printing date 10/25/2007 Reviewed on 10/25/2007

Trade name: Eprinomectin
EPRINEX Pour-On for Cattle

· **Additional toxicological information:**
The product is not subject to classification according to internally approved calculation methods for preparations.
When used and handled according to specifications, the product does not have any harmful effects according to our experience and the information provided to us.

12 Ecological information

· **Ecotoxological effects:**

· **Aquatic toxicity:**

133305-88-1 Eprinomectin	
LC50 / 48 hrs	0.45 ppb (Daphnia magna)
LC50 / 96hrs	1.2 ppb (Rainbow Trout)

· **General notes:** The material is harmful to the environment.

13 Disposal considerations

· **Product:**
· **Recommendation:** Disposal must be made according to official regulations.

· **Uncleaned packagings:**
· **Recommendation:** Disposal must be made according to official regulations.

14 Transport information

· **DOT regulations:**
· **Proper shipping name (technical name):** Not Regulated

· **Land transport ADR/RID (cross-border):**
· **UN-Number:** 3082
· **Packaging group:** III
· **Proper shipping name:** Enviromentally Hazardous Substance, liquid, n.o.s. (eprinomectin),

· **Maritime transport IMDG:**
· **Proper shipping name:** Not Regulated

· **Air transport ICAO-TI and IATA-DGR:**
· **Proper shipping name:** Not Regulated

15 Regulations

· **SARA**

· **Section 355 (extremely hazardous substances):**
None of the ingredients are listed.

· **Section 313 (Specific toxic chemical listings):**
None of the ingredients are listed.

· **TSCA (Toxic Substances Control Act):**
None of the ingredients are listed.

Material Safety Data Sheet
ISO/DIS 11014 / 29 CFR 1910.1200 / ANSI Z400.1

Printing date 10/25/2007 Reviewed on 10/25/2007

Trade name: Eprinomectin
EPRINEX Pour-On for Cattle

· **CA Proposition 65**

· **Chemicals known to cause cancer:**
None of the ingredients are listed.

· **Chemicals known to cause reproductive toxicity for females:**
None of the ingredients is listed.

· **Chemicals known to cause reproductive toxicity for males:**
None of the ingredients is listed.

· **Chemicals known to cause developmental toxicity:**
None of the ingredients is listed.

· **Carcinogenesis potential categories**

· **EPA (Environmental Protection Agency)**
None of the ingredients is listed.

· **IARC (International Agency for Research on Cancer)**
None of the ingredients is listed.

· **NTP (National Toxicology Program)**
None of the ingredients is listed.

· **TLV (Threshold Limit Value established by ACGIH)**
None of the ingredients is listed.

· **MAK (German Maximum Workplace Concentration)**
None of the ingredients is listed.

· **NIOSH-Ca (National Institute for Occupational Safety and Health)**
None of the ingredients is listed.

· **OSHA-Ca (Occupational Safety & Health Administration)**
None of the ingredients is listed.

· **Product related hazard informations:** Observe the general safety regulations when handling chemicals.

· **Hazard-determining components of labelling:**
Eprinomectin

· **Safety phrases:**
29/56 Do not empty into drains, dispose of this material and its container at hazardous or special waste collection point

· **Water hazard class:** Generally not hazardous for water.

16 Other information

This information is based on our present knowledge. However, this shall not constitute a guarantee for any specific product features and shall not establish a legally valid contractual relationship.

· **Contact:** MSDS Coordinator, msds@merial.com

Attachment 4

Literature References for eprinomectin relevant to human/animal health and the environment.

Human and Animal Health

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3. Role of the p-glycoprotein in the cellular efflux of macrocyclic lactones: Influence of interfering agents; Lespine A; Roulet A; Dupuy J; Pineau T; Alvinerie M Journal of Veterinary Pharmacology and Therapeutics, 26 (Suppl. 1): 161-162 August 2003.

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8. Efficacy of eprinomectin against Hypoderma spp in cattle; Holste, JE; Colwell, DD; Kumar, R; Lloyd, JE; Pinkall, NPM; Sierra, MA ; Waggoner, JW; Langholff, WK; Barrick, RA; Eagleson, JS; American Journal of Veterinary Research, v 59, n 1 , p 56-58 , January 1998.

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10. Evaluation of certain veterinary drug residues in food; Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series (888): 1999 World Health Organization, Geneva, Switzerland.

11. Toxicological evaluation of certain veterinary drug residues in food: 50th meeting of JECFA, Rome, February 1998; World Health Organization; Food and Agriculture Organization; Joint Expert Committee on Food Additives, WHO Food Additive Series No.41, WHO, Geneva.

12. Efficacy of eprinomectin against Toxacara canis in dogs; Kozan E.; Sevimli F.K.; Birdane F.M.; AdanIr R.; Parasitology Research (Germany), 102(3), pp. 397-400, February 1, 2008.

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May 14, 2009

Program Manager
USDA/AMS/TM/NOP
Room 4008-So., Ag Stop 0268
1400 Independence Ave., SW
Washington, DC 20250

Re.: Supplement to NOP Petition for Eprinomectin

Dear Dr. Sir/Madam:

Merial Limited herewith submits a supplement to the petition dated 14 November 2008 for the inclusion of eprinomectin as a synthetic substances allowed for use in organic livestock production (§ 205.603) on the National Organic Program-National List of Substances Allowed and Prohibited in Organic Production and Handling pursuant to 7 CFR Part 205.

This supplement contains additional information requested in a letter from Shannon Nally dated 05 January 2009. Specifically, the following requested information has been included:

- A new paragraph for the Frequency of Application (of the labeled 500 mcg dose) has been added to Section 4.
- A detailed description of the manufacturing procedures has been included in Section 5. The information presents the step-wise chemical reaction scheme for the synthesis of eprinomectin beginning with the commercially available starting material. Due to the proprietary nature of the information, this section has been designated "Confidential Business Information" in accordance with the criteria in Section 13.

In addition to the aforementioned revisions, Section 13 has been revised to reflect the addition of Confidential Business Information presented in Section 5. Accordingly, "CBI Copy" and "CBI Deleted" versions of this supplement are enclosed. All other sections of the original supplement remain unchanged.

Please contact me by telephone at (678) 638-3746 or e-mail at huston.howell@merial.com concerning any questions or comments about this submission.

Sincerely,

Huston Howell, Ph.D.

/enclosures

www.merial.com

MERIAL

Supplement to NOP Petition for Eprinomectin

CBI Deleted Version

www.merial.com

4. A list of the crop, livestock or handling activities for which the substance will be used. If used for crops or livestock, the substance's rate and method of application must be described. If used for handling (including processing), the substance's mode of action must be described.

Method of Application
IVOMEC® EPRINEX® (eprinomectin) Pour-On for Beef and Dairy Cattle is applied topically along the midline of the back.

Product Packaging
The product is available in 250-mL, 1-liter, 2.5-liter, 5-liter, and 20-liter polyethylene containers. Each milliliter of solution contains 5 mg eprinomectin.

Dosage
The approved dosage is 500 mcg eprinomectin/kg body weight (1 mL/10 kg or 22 lb BW).

Frequency of Application
Parasite burdens can vary according to regional and environmental conditions. The user should consult with a veterinarian for the diagnosis, control, and treatment of parasites, including the most effective timing and repetition of applications.

Mode of Action
Eprinomectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Antimicrobial activity
Using a standard, antimicrobial screen, eprinomectin was shown to have no significant antimicrobial effects versus 26 microbial species (including bacteria and fungi) at concentrations as high as 1,000 ppm. In all, 52 tests were performed; some species were incubated at both 25 °C and 37 °C, some species were incubated in the presence and absence of lactamases, and both normal and antibiotic-resistant strains of some species were included in the screen.

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

CBI

CBI

13. A Confidential Business Information Statement which describes the specific required information contained in the petition that is considered to be Confidential Business Information (CBI) or confidential commercial information and the basis for that determination. Petitioners should limit their submission of confidential information to that needed to address the areas for which this notice requests information. Final determination regarding whether to afford CBI treatment to submitted petitions will be made by USDA pursuant to 7 CFR 1.27(d). Instructions for submitting CBI to the National List Petition process are presented in the instructions below:

(a) Financial or commercial information the petitioner does not want disclosed for competitive reasons may be claimed as CBI. Applicants must submit a written justification to support each claim.

N/A

(b) "Trade secrets" (information relating to the production process, such as formulas, processes, quality control tests and data, and research methodology) may be claimed as CBI. This information must be (1) commercially valuable, (2) used in the applicant's business, and (3) maintained in secrecy.

The information presented in section 5 contains confidential information of commercial value to the business of Merial Limited. We hereby request that this information be maintained in secrecy pursuant to 7 CFR 1.27(d).

(c) Each page containing CBI material must have "CBI Copy" marked in the upper right corner of the page. In the right margin, mark the CBI information with a bracket and "CBI."

N/A

(d) The CBI-deleted copy should be a facsimile of the CBI copy, except for spaces occurring in the text where CBI has been deleted. Be sure that the CBI deleted copy is paginated the same as the CBI copy (The CBI-deleted copy of the application should be made from the same copy of the application which originally contained CBI). Additional material (transitions, paraphrasing, or generic substitutions, etc.) should not be included in the CBI-deleted copy.

N/A

(e) Each page with CBI-deletions should be marked "CBI-deleted" at the upper right corner of the page. In the right margin, mark the place where the CBI material has been deleted with a bracket and "CBI-deleted."

N/A

(f) If several pages are CBI-deleted, a single page designating the numbers of deleted pages may be substituted for blank pages. (For example, "pages 7 through 10 have been CBI-deleted.")

N/A

(g) All published references that appear in the CBI copy should be included in the reference list of the CBI deleted copy. Published information cannot be claimed as confidential.

N/A

(h) Final determination regarding whether to afford CBI treatment to submitted petitions will be made by USDA pursuant to 7 CFR 1.27(d). If a determination is made to deny CBI treatment, the petitioner will be afforded an opportunity to withdraw the submission.

N/A