Approval Date: August 9, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-079

B. Sponsor

Merial Ltd.
2100 Ronson Rd.
Iselin, New Jersey 08830-3077

C. Proprietary Name

Ivomec® Eprinex™ Pour-On for Beef and Dairy Cattle

D. Established Name

Eprinomectin

E. Pharmacological Category

Anticoccidial, antimicrobial, antiparasitic, etc.

F. Dosage Form

Pour on

G. Dispensing Status

OTC

H. Route of Administration

Topical

I. Indication

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.

J. 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. 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 longispicularis*	100	0	100
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.

III. TARGET 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.

IV. HUMAN FOOD 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 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 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.

V. 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.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.