Approval Date: February 24, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-833

B. Sponsor

Merck & Co., Inc.
P.O. Box 2000
Rahway, New Jersey 07065

C. Proprietary Name

Ivomec® Plus Injection for Cattle

D. Established Name

ivermectin and clorsulon

E. Dosage

1) DOSAGE FORM
IVOMEC PLUS is a sterile solution available in 50, 200, 500, and 1000 mL plastic bottles. Each milliliter contains 10 mg/mL ivermectin and 100 mg/mL clorsulon.

2) ROUTE OF ADMINISTRATION
IVOMEC PLUS should be administered by subcutaneous injection.

3) APPROVED DOSAGES
200 g ivermectin and 2 mg clorsulon/kg body weight (1 mL/110 lb body weight).

F. Indication

Gastrointestinal Roundworms (adults and 4th stage larvae):

•*Ostertagia ostertagi* (including inhibited *O. ostertagi*)

•*O. lyrata*

•*Haemonchus placei*

•*Trichostrongylus axei*

•*T. colubriformis*

•*Cooperia oncophora*

•*C. punctata*

•*C. pectinata*

•*Oesophagostomum radiatum*

•*Bunostomum phlebotomum*

•*Nematodirus helvetianus* (adults only)

•*N. spathiger* (adults only)

Lungworms (adults and fourth-stage larvae):

•*Dictyocaulus viviparous*

Liver Flukes

•*Fasciola hepatica* (adults only)

•**Cattle Grubs** (parasitic stages):

Hypoderma bovis

•*H. lineatum*

Sucking Lice:

•*Linognathus vituli*

•*Haematopinus eurysternus*

•*Solenopotes capillatus*

Mites (Scabies):

•*Psoroptes ovis (syn. P. communis* var*. bovis)*

•*Sarcoptes scabiei* var*. bovis*

Additional indications contained in this supplemental NADA are for control of infections of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment, and *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

G. Effect of Supplement

New claims for persistent control of gastrointestinal roundworms and lungworms.

II. EFFECTIVENESS

IVOMEC Injection for Cattle is identical to IVOMEC PLUS except that it does not contain clorsulon. Because clorsulon is not active against nematodes, the two products would be expected to show similar efficacy. Data demonstrating the effectiveness of IVOMEC PLUS Injection for Cattle for previously registered therapeutic indications are discussed in the parent NADA 140-833 FOI Summary (approval date September 17, 1990). In this original approval, demonstration of equivalence of IVOMEC and IVOMEC PLUS was considered sufficient for the therapeutic claims. For the persistence claims for IVOMEC PLUS, only one

study in a representative parasite species was necessary to include all species that were granted a persistence claim under NADA 128-409. The effectiveness of IVOMEC Injection for Cattle for the persistent efficacy indications listed above was demonstrated by data discussed in the supplemental NADA 128-409 FOI Summary (approval date xxxxx).

Data from the following dose confirmation trials demonstrate that IVOMEC PLUS Injection for Cattle given at the recommended dosage is similar to IVOMEC Injection for Cattle with respect to control of infections of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment, and *Haemonchus placei, Trichostrongylus axei, Cooperia punctata* and *Cooperia oncophora* for 14 days after treatment. The claim for *Oesophagostomum radiatum* is granted based on the premise that at least one study was accomplished in a representative species of parasite for IVOMEC PLUS. There were sufficient studies using IVOMEC PLUS to show efficacy against 6 of the 7 parasites for which the additional persistence claims are warranted for IVOMEC.

A. Dose Confirmation
Trial ASR 15065

1. Type of study

   Dose confirmation study in cattle with induced infections of gastrointestinal roundworms

2. Investigator:

   Bruce N. Kunkle, D.V.M., M.S., Ph.D.
   Merck & Co., Inc.
   Fulton, Missouri

3. General design:

   a. Purpose:

      To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

   b. Animals:

      Thirty (30) Holstein calves (10 per group). Animals were approximately 4 to 5 months old and weighed 157 to 234 kg at the start of the study. Animals were free of patent infections at the time of treatment.

   c. Controls:

      Negative controls received the vehicle for IVOMEC Injection for Cattle subcutaneously at 1 mL/50 kg body weight.

   d. Infection:

      Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Ostertagia ostertagi* (1000 per day for 21 days).

e. Dosage form:
The dosage form of IVOMEC PLUS was an injectable solution containing 10 mg ivermectin and 100 mg clorsulon per mL.

f. Route of administration:

Subcutaneous injection

g. Dose:

Ten animals received IVOMEC PLUS at 1 mL/50 kg body weight (200 mcg ivermectin and 2 mg clorsulon/kg body weight) once and ten animals received IVOMEC at 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight).

h. Test duration:

49 to 50 days after treatment

i. Pertinent variables measured:

Worm counts were determined at necropsy which was 49 to 50 days after treatment and 28 to 29 days after the last larvae were administered.

4. Results

The following parasites had a minimum of six adequately infected control animals:

	Arithmetic mean (percent reduction)		
Parasite	**Control**	**IVOMEC**	**IVOMEC PLUS**
Ostertagia ostertagi	1258.0	82.0 (93.5%)	68.9 (94.5%)

5. Statistical methods:

Nematode percentage efficacies were calculated for each medication using the following formula:

[Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in each group of medicated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

Under the conditions of this study, both IVOMEC PLUS and IVOMEC Injection for Cattle controlled infections of *Ostertagia ostertagi* for 21 days after treatment.

7. Adverse reactions:

One animal died 22 days after treatment. The apparent cause of death was an esophageal impaction, which was not believed to be related to the experimental treatment.

Trial ASR 15071

1. Type of study:

   Dose confirmation study in cattle with induced infections of gastrointestinal roundworms and lungworms.

2. Investigator:

   Bruce N. Kunkle, D.V.M., M.S., Ph.D.
   Merck & Co., Inc.
   Fulton, Missouri

3. General design:

   a. Purpose:

      To determine the period after treatment during which infections of gastrointestinal roundworms and lungworms are controlled.

   b. Animals:

      Thirty (30) crossbred calves (10 per group). Animals were approximately 8 to 9 months old and weighed 235 to 275 kg at the start of the study. Animals were free of patent infections at the time of treatment.

   c. Controls:

      Negative controls received the vehicle for IVOMEC Injection for Cattle subcutaneously at 1 mL/50 kg body weight.

   d. Infection:

      Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Haemonchus placei* (500 per day for 14 days); *Trichostrongylus axei* (1000 per day for 14 days); and *Cooperia punctata* (1000 per day for 14 days).

   e. Dosage form:

      The dosage form of IVOMEC PLUS was an injectable solution containing 10 mg ivermectin and 100 mg clorsulon per mL.

   f. Route of administration:

      Subcutaneous injection

   g. Dose:

Ten animals received IVOMEC PLUS at 1 mL/50 kg body weight (200 mcg ivermectin and 2 mg clorsulon/kg body weight) once and ten animals received IVOMEC 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight).

h. Test duration:

42 or 43 days after treatment

i. Pertinent variables measured:

Worm counts were determined at necropsy which was 42 or 43 days after treatment and 28 or 29 days after the last larvae were administered.

4. Results

The following parasites had a minimum of six adequately infected control animals:

	Arithmetic mean (percent reduction)		
Parasite	**Control**	**IVOMEC**	**IVOMEC PLUS**
Haemonchus placei	1022.0	16.0 (98.4%)	2.0 (99.8%)
Trichostrongylus axei	1578.0	4.0 (99.7%)	4.0 (99.7%)
Cooperia punctata	1996.2	11.0 (99.4%)	0.0 (100%)

5. Statistical methods:

Nematode percentage efficacies were calculated for each medication using the following formula:

[Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in each group of medicated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

Under the conditions of this study, both IVOMEC PLUS and IVOMEC Injection for Cattle controlled infections *Haemonchus placei, Trichostrongylus axei* and *Cooperia punctata* for 14 days after treatment.

7. Adverse reactions:

One animal exhibited lameness of the left rear leg during the trial. This event was not believed to be related to the experimental treatments.

Trial ASR 15073

1. Type of study

Dose confirmation study in cattle with induced infections of gastrointestinal roundworms and lungworms.

2. Investigator:

Edward G. Johnson, D.V.M.
Johnson Research
Parma, Idaho

3. General design:

a. Purpose:

To determine the period after treatment during which infections of gastrointestinal roundworms and lungworms are controlled.

b. Animals:

Thirty (30) crossbred calves (10 per group). Animals were approximately 6 to 10 months old and weighed 215 to 283 kg at the start of the study. Animals were free of patent infections at the time of treatment.

c. Controls:

Negative controls received the vehicle for IVOMEC Injection for Cattle subcutaneously at 1 mL/50 kg body weight.

d. Infection:

Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Haemonchus placei* (500 per day for 14 days); *Trichostrongylus axei* (1000 per day for 14 days); *Cooperia punctata* (1000 per day for 14 days); *Cooperia oncophora* (1000 per day for 14 days); and *Dictyocaulus viviparus* (50 per day for 21 days).

e. Dosage form:

The dosage form of IVOMEC PLUS was an injectable solution containing 10 mg ivermectin and 100 mg clorsulon per mL.

f. Route of administration:

Subcutaneous injection

g. Dose:

Ten animals received IVOMEC PLUS at 1 mL/50 kg body weight (200 mcg ivermectin and 2 mg clorsulon/kg body weight) once and ten animals received IVOMEC at 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight).

h. Test duration:

42 or 43 days after treatment

i. Pertinent variables measured:

Worm counts were determined at necropsy which was 42 or 43 days after treatment, 28 or 29 days after the last *Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* larvae were administered, and 21 or 22 days after the last *Dictyocaulus viviparus* larvae were administered.

4. Results

The following parasites had a minimum of six adequately infected control animals:

	Arithmetic mean (percent reduction)		
Parasite	**Control**	**IVOMEC**	**IVOMEC PLUS**
Haemonchus placei	1353.5	10.0 (99.3%)	136.0 (90.0%)
Trichostrongylus axei	1202.0	0.0 (100%)	8.0 (99.3%)
Cooperia punctata	3067.8	0.7 (>99.9%)	0.0 (100%)
Cooperia oncophora	696.0	0.7 (>99.9%)	6.0 (99.1%)
Dictyocaulus viviparus	32.4	0.0 (100%)	0.0 (100%)

5. Statistical methods:

Nematode percentage efficacies were calculated for each medicated group using the following formula:

[Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in each group of medicated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

Under the conditions of this study, both IVOMEC PLUS and IVOMEC Injection for Cattle controlled infections of *Dictyocaulus viviparus* for 21 days after treatment, and *Haemonchus placei, Trichostrongylus axei, Cooperia punctata* and *Cooperia oncophora* for 14 days after treatment.

7. Adverse reactions:

Signs of respiratory disease, arthritis and bloat were seen in two animals during the trial. These health problems were not believed to be related to the experimental treatments.

III. ANIMAL SAFETY

As discussed in the parent NADA 140-833 FOI Summary (approval date September 17, 1990).

IV. HUMAN SAFETY

As discussed in the parent NADA 140-833 FOI Summary (approval date September 17, 1990) and in the supplement to NADA 128-409 FOI Summary (IVOMEC Injection for Cattle; approval date September 12, 1994).

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of section 512 of the Act and demonstrate that ivermectin and clorsulon injection, when used under the proposed conditions of use, is safe and effective for the control of infections of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment, and *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

For cattle the tolerance of residues are specified in 21 CFR 556.344 and 21 CFR 556.163. A tolerance for the marker residue (22, 23-dihydro-avermectin B1a) of ivermectin is 100 ppb in the liver (target tissue) and the tolerance for clorsulon (marker residue) in kidney (target tissue) is 1.0 ppm. The withdrawal time is 49 days following one subcutaneous injection of IVOMEC PLUS as specified in 21 CFR 522.1193.

The original approval of ivermectin and clorsulon injection was as an over-the-counter 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 retain over-the-counter marketing status.

Under the Center's supplemental approval policy 21 CFR 514.106(b)(2)(v), this is a Category II change. The approval of this change did not require a reevaluation of the safety or effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals 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 claim for the control of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment and *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment for which the supplemental application was approved.

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.