Approval Date: April 1, 1999

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-833

B. Sponsor

Merial Limited
2100 Ronson Road
Iselin, New Jersey 08830

C. Proprietary Name

Ivomec® Plus Injection for Cattle

D. Established Name

ivermectin and clorsulon

E. Dosage Form

IVOMEC® PLUS Injection is a sterile solution containing 10 mg ivermectin and 2 mg clorsulon/mL.

F. Dosage Regimen

200 mcg ivermectin and 2 mg/kg body weight (1 mL/110 lb body weight)

G. Route of Administration

IVOMEC® PLUS Injection should be administered by subcutaneous injection.

H. Indication

Gastrointestinal roundworms

- *Ostertagia ostertagi* (Adults and forth-stage larvae)
- *Ostertagia ostertagi* (Inhibited forth-stage larvae)
- *Ostertagia lyrata* (Adults and forth-stage larvae)
- *Haemonchus placei* (Adults and forth-stage larvae)
- *Trichostrongylus axei* (Adults and forth-stage larvae)
- *Trichostrongylus colubriformis* (Adults and forth-stage larvae)
- *Cooperia oncophora* (Adults and forth-stage larvae)
- *Cooperia punctata* (Adults and forth-stage larvae)
- *Cooperia pectinata* (Adults and forth-stage larvae)
- *Oesophagostomum radiatum* (Adults and forth-stage larvae)
- *Bunostomum phlebotomum* (Adults and forth-stage larvae)
- *Nematodirus helvetianus* (Adults)
- *N. spathiger* (Adults)

Lungworms

- *Dictyocaulus viviparus* (Adults and fourth-stage larvae)

Liver Flukes

- *Fasciola hepatica* (Adults)

Grubs

- *Hypoderma bovis* (Parasitic stages)
- *H. lineatum*

Sucking Lice

- *Linognathus vituli*
- *Haematopinus eurysternus*
- *Solenopotes capillatus*

Mange mites

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

IVOMEC® PLUS Injection has been proved to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment; *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

II. EFFECTIVENESS

IVOMEC® Injection for Cattle is identical to IVOMEC® PLUS Injection for Cattle 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® Injection for Cattle and IVOMEC® PLUS Injection for Cattle was considered sufficient for the therapeutic claims. For the persistence claims for IVOMEC® PLUS Injection for Cattle, 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 February 24, 1997).

Data from the following dose confirmation trial demonstrate that IVOMEC® PLUS Injection for Cattle given at the recommended dosage is similar to IVOMEC® Injection for Cattle with respect to effective control of infections and protection from re-infection with *Dictyocaulus viviparus* for 28 days after treatment.

Note: Nematode percentage efficacies were calculated if there were six adequately infected controls using the following formula:

$$\frac{\text{(Arithmetic mean number of nematodes in control cattle)} - \text{(Arithmetic mean number of nematodes in ivermectin/clorsulon – treated cattle)}}{\text{(Arithmetic mean number of nematodes in control cattle)}} \times 100 = \text{Percent Effectiveness}$$

A. Dose Confirmation: Trial ASR 15065

1. **Investigator**: Bruce N. Kunkle, D.V.M., M.S. Ph.D., Merial Limited, Fulton, Missouri

2. **General design**:

   a. **Purpose**: To evaluate the persistent efficacy of IVOMEC® PLUS against artificially induced infections of *Dictyocaulus viviparus*.

   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, having been raised under parasite-free conditions and treated with fenbendazole on Days –41 and -18.

   c. **Controls**: Control animals received the vehicle for IVOMECÒ Injection for Cattle (the same vehicle used for IVOMEC® PLUS) at 1 mL/50 kg body weight. One group received a medication which is not pertinent to this document.

   d. **Infection**: Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Dictyocaulus viviparus* (50 larvae per day for 28 days).

   e. **Test article administration**: The approved formulation of injectable solution containing 10 mg ivermectin per mL was administered by subcutaneous injection. One mL/50 kg body weight (200 mcg ivermectin/kg body weight) was given once.

   f. **Pertinent variables measured**: Worm counts were determined at necropsy which was 49 to 50 days after treatment, 21 to 22 days after the last *Dictyocaulus viviparus* larvae were administered.

3. **Results -** *Dictyocaulus viviparus* was present in adequate numbers for a determination of efficacy.

   Table 4.1. Arithmetic mean worm counts of *Dictyocaulus viviparus* recovered for each group and percent efficacy

Parasite	**Arithmetic Mean Control**	**Arithmetic Mean IVOMEC PLUS**	**Percent efficacy**
Dictyocaulus viviparus	20.3	0.0	100

4. **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.

5. **Conclusion**: This study is adequate to establish a level of persistent efficacy for *Dictyocaulus viviparus* for 28 days.

III. TARGET ANIMAL SAFETY

As discussed in the parent NADA 128-409 FOI Summary (approval date February 7, 1984).

IV. HUMAN FOOD 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 (approval date September 12, 1994).

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 implementing regulations at Part 514 of Title 21, Code of Federal Regulations (21 CFR 514) to demonstrate that IVOMEC® PLUS Injection for Cattle, when used under the proposed conditions of use, is safe and effective to control infections and to protect cattle from re-infection with Dictyocaulus viviparus for 28 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 10 ppb in the muscle, 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 Injection for Cattle as specified in 21 CFR 522.1193.

The agency has concluded that this product shall retain over-the-counter marketing status because adequate directions for use have been written for the layman and the conditions for use prescribed on the label are likely to be followed in practice.

In accordance with 21 CFR 514.106(b)(2), this is a Category II change which did not require a reevaluation of the safety or effectiveness data in the parent application.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals qualifies for three (3) 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 which the supplemental application is approved.

IVOMEC® PLUS Injection for Cattle is under U.S. patent number 4,853,372, which expires on August 1, 2006.

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.