Date of Approval Letter: April 1, 1999

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 128-409

IVOMEC® Injection for Cattle
(ivermectin)

"...has been proved to effectively control infections and to protect from reinfection with *Dictyocaulus viviparus* for 28 days after treatment."

Sponsored by:

MERIAL LIMITED

I. GENERAL INFORMATION

NADA Number:	128-409
Sponsor:	Merial Limited 2100 Ronson Road Iselin, New Jersey 08830
Established Name:	ivermectin
Trade Name:	IVOMEC® Injection for Cattle and Swine
Marketing Status:	over-the-counter (OTC)
Effect of Supplement:	Extend the period of persistent activity against *Dictyocaulus viviparus* from 21 days to 28 days after treatment.

II. INDICATIONS FOR USE: For the treatment and control of the following in cattle.

Gastrointestinal roundworms	*Ostertagia ostertagi*	Adults and fourth-stage larvae
	Ostertagia ostertagi	Inhibited fourth-stage larvae
	Ostertagia lyrata	Adults and fourth-stage larvae
	Haemonchus placei	Adults and fourth-stage larvae
	Trichostrongylus axei	Adults and fourth-stage larvae
	Trichostrongylus colubriformis	Adults and fourth-stage larvae
	Cooperia oncophora	Adults and fourth-stage larvae
	Cooperia punctata	Adults and fourth-stage larvae
	Cooperia pectinata	Adults and fourth-stage larvae
	Oesophagostomum radiatum	Adults and fourth-stage larvae
	Bunostomum phlebotomum	Adults and fourth-stage larvae
	Nematodirus helvetianus	Adults
	N. spathiger	Adults
Lungworms	*Dictyocaulus viviparus*	Adults and fourth-stage larvae
Grubs	*Hypoderma bovis* *H. lineatum*	
Sucking Lice	*Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus*	
Mange mites	*Psoroptes ovis (*syn. *P. communis* var. *bovis)* *Sarcoptes scabiei* var. *bovis*	

IVOMEC® Injection has been proved to effectively control infections and to protect cattle from re-infection with *Dictyocaulus viviparus* for 28 days after treatment; *Ostertagia ostertagi* for 21 days after treatment; *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata,* and *Cooperia oncophora* for 14 days after treatment.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. Dosage Form: IVOMEC® Injection is a sterile solution containing 10 mg ivermectin/mL.

B. Route of Administration: IVOMEC® Injection should be administered by subcutaneous injection.

C. Approved Dose: 200 mcg ivermectin/kg body weight (1 mL/110 lb body weight)

IV. EFFECTIVENESS

Data demonstrating the effectiveness of IVOMEC® Injection for Cattle for previously approved indications are discussed in the parent NADA 128-409 FOI Summary (approval date February 7, 1984, and in the supplemental NADA 128-409 FOI Summary (approval date February 24, 1997). Data from the following dose confirmation trials demonstrate that IVOMEC® Injection for Cattle given at the recommended dosage controls infection and protects against reinfection 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:

[Arithmetic mean number of nematodes in control cattle) - (Arithmetic mean number of nematodes in ivermectin-treated cattle)] ÷ (Arithmetic mean number of nematodes in control cattle) × 100 = 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 ivermectin 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 IVOMEC Injection for Cattle 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

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

4. Adverse reactions: No adverse reactions to treatment were observed.

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

B. Dose Confirmation: Trial ASR 15100

1. Investigator: Edward G. Johnson, D.V.M., Johnson Research, Parma, Idaho

2. General design:

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

b. Animals: Twenty (20) Holstein calves (10 per group). Animals were no more than 8 months old and weighed 187 to 254 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.

c. Controls: Vehicle for IVOMEC Injection SC 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: *Dictyocaulus viviparus* (100 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. 1 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 days after treatment and 21 days after the last *Dictyocaulus viviparus* larvae were administered.

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

Table 4.2. Arithmetic mean worm counts of *Dictyocaulus viviparus* recovered for each group and percent efficacy

	Arithmetic Mean		Percent
Parasite	Control	IVOMEC	efficacy
Dictyocaulus viviparus	14.7	0.0	100

4. Adverse reactions: No adverse reactions were observed during these studies.

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

V. ANIMAL SAFETY

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

VI. HUMAN SAFETY

A. Toxicology, Acceptable Daily Intake (ADI), and Target Tissue Tolerance

The basic toxicology and residue chemistry studies that support the use of ivermectin in cattle are summarized in the FOI Summaries for the original and supplemental approvals of the parenteral and oral dosage forms of ivermectin under NADA 128-409 and NADA 137-006. An ADI of 1 mcg/kg/day and the safe concentrations for total residues were assigned to cattle on the basis of the toxicology studies. The residues and metabolism studies established 100 ppb as the tolerance for residues of ivermectin B1a (the marker residue) in liver (the target tissue).

B. Assignment of a Muscle Tolerance

A muscle tolerance of 10 ppb ivermectin B1a was assigned following review of a number of pivotal residue studies with the various dosage forms of the drug, which contained values for ivermectin B1a in cattle muscle.

Data in two total residue studies, RN-189 (NADA 137-006) and RN-190 (NADA 128-409) showed that the B1a component of ivermectin represents approximately 70% of the residues present in muscle tissue in the first one or two weeks post dosing. Those results confirm that ivermectin B1a can serve as the marker residue in muscle tissue.

The muscle tolerance value of 10 ppb was obtained using the values for ivermectin B1a in study CA-129, the withdrawal study submitted with the original NADA 128-409 for the injectable formulation in cattle. Of all the studies examined, the muscle residue data in CA-129 were best suited for the muscle tolerance assignement. CA-129 was the withdrawal study with the highest residue values and was the only study that reported values in muscle at relatively short withdrawal times. The 10 ppb tolerance represents the upper tolerance limit obtained by CVM's standard statistical procedure (99% tolerance limit with 95% confidence) at approximaely 22 days of withdrawal.

That interval was chosen for the tolerance assignment rather than the withdrawal time of 35 days so that the tolerance value would be well above the limit of quantitation of the assay in muscle. The choice of 10 ppb as the muscle tolerance for ivermectin makes it possible to identify animals that have been treated with the drug and slaughtered shortly thereafter.

The 10 ppb muscle tolerance applies to samples collected remotely from sites of injection with the injectable product. Muscle tissue collected at the site of injection of the ivermectin injectable product may contain ivermectin residues that significantly exceed 10 ppb, even though the animals were withheld from slaughter for the required period. A higher safe concentration for residues at injection site is allowed based on acute toxicity considerations and the minimal chance of that type tissue being

consumed in a single serving. See the FOI Summary for a Supplement to NADA 128-409 approved on September 12, 1994, for a statement on the human food safety assessment of ivermectin injection site residues.

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 implementing regulations at Part 514 of Title 21, Code of Federal Regulations (21 CFR 514) to demonstrate that IVOMEC® 1% Injection Solution for Cattle, when used under the proposed conditions of use, is safe and effective to control infections and to protect cattle from reinfection with *Dictyocaulus viviparus* for 28 after treatment.

For cattle, a tolerance of 100 ppb for 22, 23-dihydro-avermectin B1a (marker residue of ivermectin) in liver (target tissue) is codified at 21 CFR 556.334. The preslaughter withdrawal time is 35 days following one subcutaneous injection of IVOMEC® 1% Injection for Cattle, as specified at 21 CFR 522.1192. Although no new toxicology or residue chemistry studies were submitted with this supplement, CVM used the opportunity to assign a tolerance for residues of ivermectin in cattle muscle. A value of 10 ppb ivermectin B1a is assigned as the tolerance in cattle muscle tissue.

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® 1% Injection for Cattle is under U.S. patent number 4,199,569, which expires on October 3, 1999, and patent number 4, 853,372, which expires August 1, 2006.

VIII. APPROVED PRODUCT LABELING (attached)

A. Facsimile base label and package outsert – 1,000 mL container

B. Facsimile bottle label and package insert – 50, 200, 500 mL containers

C. Facsimile box carton – 50 mL container