Date of Approval: August 16, 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 128-409

IVOMEC (ivermectin) Injection for Cattle and Swine

"In cattle to extend the period of persistent effect for *Oesophagostomum radiatum* from 14 to 28 days and for *Trichostrongylus axei* and *Cooperia punctata* from 14 to 21 days."

Sponsored by:
Merial Ltd.

1. GENERAL INFORMATION:

a.	File Number:	NADA 128-409
b.	Sponsor**:**	Merial Ltd. 3239 Satellite Blvd., Bldg. 500 Duluth, GA. 30096-4640 Drug Labeler Code: 050604
c.	Established Name:	Ivermectin
d.	Proprietary Name**:**	IVOMEC (ivermectin) Injection for Cattle and Swine
e.	Dosage Form:	Sterile injectable solution
f.	How supplied:	50 mL rubber-capped bottle, and 200, 500, 2 X 500, and 1000 mL soft collapsible packs for use with an automatic syringe
g.	How Dispensed:	Over-the-counter (OTC)
h.	Amount of Active Ingredients:	10 mg (1%) ivermectin/mL
i.	Route of Administration:	Subcutaneous
j.	Species/Class:	Cattle, Swine, Reindeer, American Bison. This supplemental approval only affects cattle.
k.	Recommended Dosage:	Cattle: 1 mL for each 50 kg (110 lb) or 200 mcg ivermectin of body weight per kg
l.	Pharmacology Category:	Antiparasitic
m.	Indications:	For the treatment and control of the following parasites in cattle: **Gastrointestinal Roundworms** (adults and fourth-stage larvae) *Ostertagia ostertagi* (including inhibited *O. ostertagi),* *O. lyrata* *Haemonchus placei* *Trichostrongylus axe* *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 viviparus

Cattle Grubs (parasitic stages):
Hypoderma bovis
H. lineatum

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites (scabies)
*Psoroptes ovis (*syn. *P. communis* var. *bovis)*
Sarcoptes scabiei var. *bovis*

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

n. Effect of Supplement: To extend the persistent effect periods of *Oesophagostomum radiatum* from 14 to 28 days after treatment and *Cooperia punctata* and *Trichostrongylus axei* from 14 to 21 days after treatment. At this time, the labeling is being revised to reflect updated environmental information and to add the veal calf warning statement to the residue information section.

2. EFFECTIVENESS

a. Dose Characterization

Effectiveness studies were presented in the original NADA 128-409 FOI Summary approval dated February 13, 1984, establishing the recommended dosage of IVOMEC (ivermectin) Injection for Cattle and Swine for the treatment and control of internal and external parasites.

b. Substantial Evidence for Persistent Effectiveness against Endoparasites

Three studies (ASR 1505, 15110, and 15111) conducted to evaluate the persistent activity of IVOMEC (ivermectin) Injection for Cattle and Swine were previously submitted and evaluated using arithmetic means. Subsequent to the original review, the VICH guidance #90 "Effectiveness of Anthelmintics: General Recommendations VICH GL 7" was finalized on March 26, 2001. It allowed for the evaluation of parasite effectiveness studies using geometric means. For each study, the effectiveness was determined by comparing the geometric mean worm counts of the treated groups with those of an untreated control group for each parasite species present in at least six adequately infected control animals. P-values were computed for each parasite species using contrasts in a one-way analysis of variance or unequal-variance t-tests on log-transformed counts, or using Wilcoxon's rank-sum test. The period of persistent activity was defined as the time during which the effectiveness against a genus-species was $\geq$90%.

For an indication to be granted, a minimum of two studies is required that have the following characteristics: an adequate level of infection in six control animals, a statistically significant difference between treated and control animals at $P<0.05$, and 90% or higher efficacies using geometric means for each genus species of parasite and at each persistent effect period. If there are more than 2 studies, then the percent efficacy against a genus species of parasite from each study is added together and divided by the number of studies with that genus species of parasite. If the average is greater than or equal to 90%, then the claim may be granted. These three studies met the above criteria and were reevaluated using geometric means. The overall percent efficacies from three studies for *Trichostrongylus axei* and *Cooperia punctata* at 21 days are 93% and 90%, respectively. Two studies at 28 days for *Oesophagostomum radiatum* both demonstrated percent efficacy $\geq$90%. The following claims are granted for IVOMEC (ivermectin) Injection for Cattle and Swine: To extend the persistent effect periods for *Oesophagostomum radiatum* from 14 to 28 days and *Cooperia punctata* and *Trichostrongylus axei* from 14 to 21 days after treatment. The three studies are individually summarized below.

B.1 Study 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.
Merial Limited
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), approximately 4 to 5 months old and weighing 157 to 234 kg at the start of the study were used. All animals were treated with another anthelmintic during the acclimation period to eliminate existing infections.

c. Treatment Groups: There were 3 treatment groups. One group received IVOMEC (ivermectin) Injection for Cattle and Swine. The negative controls received no treatment. One group received a medication which is not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment according to the following schedule: 1000 L_3 *Trichostrongylus axei* and *Cooperia* spp. Days 1 to 21 and 100 L_3 *Oesophagostomum radiatum* Days 1 to 28. There were larvae of other genus species given for various lengths of time that are not pertinent to this approval and are not reported.

e. Dosage Form: IVOMEC (ivermectin) Injection for Cattle and Swine, 10 mg ivermectin/mL.

f. Route of Administration: Subcutaneous.

g. Dose: 1 mL/50 kg bodyweight (200 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 to 50 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 to 50 days after treatment, 28 to 29 days after the last *Trichostrongylus axei* and *Cooperia* spp. larvae were administered and 21 to 22 days after the last *Oesophagostomum radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for the following two genus species. The results are summarized in Table 2.1:

Table 2.1 Study ASR 15065 – Percent Efficacy IVOMEC (ivermectin) Injection for Cattle and Swine 21-Day Persistent Effect Period.

Nematode Species	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy IVOMEC Injection
Cooperia punctata	3169.8	67.9	98
Trichostrongylus axei	3826.9	83.3	98

5) Adverse Reactions: There were no adverse reactions in the IVOMEC (ivermectin) Injection for Cattle and Swine group.

B.2 Study ASR 15110

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

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 are controlled.

b. Animals: Thirty (30) Holstein male calves (24 castrated and 6 intact), approximately 4 to 12 months old and weighing 130 to 186 kg at the start of the study were used. Animals were clear of patent infections at the time of treatment.

c. Treatment Groups: There were three groups (10 animals per group). One group received IVOMEC (ivermectin) Injection for Cattle and Swine. The negative controls received no treatment. One group received a medication which is not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of the treatment according to the following schedule: *Cooperia punctata* (1000 per day for 21 days), *Trichostrongylus axei* (1000 per day for 21 days), and *Oesophagostomum radiatum* (100 per day for 28 days). There were larvae of other genus species given for various lengths of time that are not pertinent to this approval and are not reported.

e. Dosage Form: The dosage form was IVOMEC (ivermectin) Injection for Cattle and Swine, 10 mg ivermectin/mL.

f. Route of Administration: Subcutaneous.

g. Dose: 1 mL/50 body weight (200 mcg ivermectin/ kg body weight) once.

h. Test Duration: 49 days of treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 days after treatment, 28 days after the last *Cooperia* spp. and *Trichostrongylus axei* larvae were administered and 21 days after the last *Oesophagostomum radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least six control animals for *Cooperia punctata, Trichostrongylus axei,* and *Oesophagostomum radiatum.* Efficacy is summarized in Table 2.2:

Table 2.2 Study ASR 15110 – Percent Efficacy IVOMEC (ivermectin) Injection for Cattle and Swine 21-day or 28-day persistent effect periods

Nematode Species	Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Injection
Cooperia punctata	21	1470.7	374.4	75
Trichostrongylus axei	21	588.7	109.7	81
Oesophagostomum. radiatum	28	278.8	24.0	91

5) Adverse Reactions: There were no adverse reactions to treatment.

B.3 Study ASR 15111

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.
Merial Limited
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 heifer calves, approximately 5 to 6 months old and weighing 165 to 268 kg at the start of the study were used. Animals were free of patent infections at the time of infection.

c. Treatment Groups: There were 3 treatment groups (10 animals per group). One group received IVOMEC (ivermectin) Injection for Cattle and Swine.

The negative controls received no treatment. One group received a medication which was not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Cooperia punctata* (1000 per day for 21 days), *Trichostrongylus axei* (1000 per day for 21 days), and *Oesophagostomum radiatum* (100 per day for 28 days). There were larvae of other genus species given for various lengths of time that were not pertinent to this approval and are not reported.

e. Dosage Form: The dosage form was IVOMEC (ivermectin) Injection for Cattle and Swine, 10 mg ivermectin/mL.

f. Route of Administration: Subcutaneous.

g. Dose: 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 days after treatment, 28 days after the last *Cooperia* spp. and *Trichostrongylus axei* larvae were administered and 21 days after the last *Oesophagostomum radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for *Cooperia punctata, Trichostrongylus axei,* and *Oesophagostomum radiatum*. Efficacy is summarized in Table 2.3:

Table 2.3. Study ASR 15111 – Percent Efficacy IVOMEC (ivermectin) Injection for Cattle and Swine 21-day or 28-day persistent effect periods

Nematode Species	Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Injection
Cooperia punctata	21	2917.8	33.5	99
Trichostrongylus axei	21	2122.8	9.9	99
Oesophagostomum radiatum	28	174.2	2.0	99

5) Adverse Reactions: There were no adverse reactions to treatment.

3. TARGET ANIMAL SAFETY

No further target animal safety data were required from the original approval as discussed in the parent NADA 128-409 FOI summary approval dated February 13, 1984.

4. HUMAN SAFETY

No further human safety data were required from the original approval as discussed in the parent NADA 128-409 FOI summary dated February 13, 1984. There is a 35-day withdrawal period for slaughter, a withdrawal period for milk has not been established, and a withdrawal period has not been established for pre-ruminating calves.

5. 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 (ivermectin) Injection for Cattle and Swine when administered to cattle once at 200 mcg ivermectin/kg body weight is safe and effective for the extension of the following persistent effect periods: for *Oesophagostomum radiatum* from 14 to 28 days after treatment, and *Cooperia punctata* and *Trichostrongylus axei* from 14 to 21 days after treatment.

The following has been added to the residue information section of the labeling: "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal".

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

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did require a reevaluation of safety or effectiveness data in the parent application. Previously submitted studies were reevaluated using geometric means allowing the persistent effect period for 3 nematode species to be extended.

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. The three years of marketing exclusivity applies only to the extension of the 3 already approved persistent effect indications listed above. Three studies were conducted to provide substantial evidence for these supplemental indications.

No patent information was submitted with this application.

6. ATTACHMENTS

Facsimile Labeling is attached as indicated below:

A. 50, 200, and 500 mL – container label and box carton
B. 2 X 500 mL box carton
C. 1000 mL – base label, outsert, and box carton
D. Package insert for 50, 200, and 500 mL container sizes.