Date of Approval: April 21, 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-833

IVOMEC Plus Injection for Cattle
(ivermectin and clorsulon)

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 140-833
b. Sponsor:	Merial Ltd. 3239 Satellite Blvd., Bldg. 500, Duluth, GA 30096-4640 Drug Labeler Code: 050604
c. Established Name:	Ivermectin and clorsulon
d. Proprietary Name:	IVOMEC Plus Injection for Cattle
e. Dosage Form:	Sterile injectable solution
f. How Supplied:	50 mL rubber capped bottle, and 200, 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 and 100 mg (10%) clorsulon/mL
i. Route of Administration:	Subcutaneous
j. Species/Class:	Cattle
k. Recommended Dosage:	1 mL for each 50 kg (110 lb) of body weight, or 200 mcg ivermectin and 2 mg clorsulon per kg
l. Pharmacological Category:	Antiparasitic

m. Indications: For the effective 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 axei
T. colubriformis
Cooperia oncophora
C. punctata
C. pectinata
Bunostomum phlebotomum
Nematodirus helvetianus (adults only)
N. spathiger (adults only)
Oesophagostomum radiatum

Lungworms (adults and fourth-stage larvae):
Dictyocaulus viviparus

Liver Flukes:
Fasciola hepatica (adults only)

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

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites (cattle scab):
Psoroptes ovis (syn. *P. communis* var. bovis)
Sarcoptes scabiei var. *bovis*

Persistent Activity
IVOMEC Plus 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 for *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 140-833 FOI Summary approval dated September 17, 1990, establishing the recommended effective dose of IVOMEC Plus Injection for the treatment and control of internal and external parasites.

b. Substantial Evidence for Persistent Effectiveness against Endoparasites

IVOMEC Plus Injection for Cattle is identical to IVOMEC Injection for Cattle except that it contains clorsulon. For the purposes of the therapeutic claims for the original approval of IVOMEC Plus dated September 17, 1990, effectiveness of clorsulon against *Fasciola hepatica* was demonstrated and noninterference of clorsulon with ivermectin was demonstrated. It was concluded that IVOMEC Injection and IVOMEC Plus were equivalent with regards to the effectiveness of ivermectin for treatment and control of various nematodes and ectoparasites. All the therapeutic claims for IVOMEC Injection were granted to IVOMEC Plus. Since these formulations are equivalent with regards to the effectiveness of ivermectin, it was decided that all the persistence claims granted to IVOMEC Injection could be granted to IVOMEC Plus with one persistent effect study conducted with IVOMEC Plus in a representative parasite species. In the original approval of IVOMEC Plus for persistent effect, studies were conducted in 6 of the 7 parasites approved for IVOMEC Injection.

Three studies (ASR 15065, 15110, and 15111) conducted to evaluate the persistent activity of IVOMEC Injection were previously evaluated using arithmetic means. Subsequent to the original review, the VICH guidance #90 "Effectiveness of Anthelmintics: General Recommendations VICH GL7" was finalized March 26, 2001. It allowed for the evaluation of parasite effectiveness studies using geometric means. For each study, the efficacy 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 efficacy against a genus species was ≥ 90%.

For an indication to be granted, a minimum of two studies is required that have the following: an adequate level of infection in 6 control animals, a statistically significant difference between treated and control animals at $P<0.05$, and 90% efficacy using geometric means for each genus species of parasite and at each persistent effect period. If there are more than 2 studies, then the geometric means of 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 this 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 ≥ 90%. The

following are granted for IVOMEC Injection and IVOMEC Plus: To extend the 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 three trials are individually summarized below.

B.1 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.
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. The treated groups received IVOMEC Injection or IVOMEC Plus. The negative controls received no treatment.

   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 Injection, 10 mg ivermectin/mL and IVOMEC Plus, 10 mg ivermectin/mL and 100 mg clorsulon/mL.

   f. Route of Administration: Subcutaneous

   g. Dose: 1 mL/50 kg body weight for both formulations given once, 200 mcg ivermectin per kg for IVOMEC Injection or 200 mcg ivermectin and 2 mg clorsulon per kg for IVOMEC Plus.

   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. Only the results for the IVOMEC Injection group are reported as the extension of the persistent effect periods for IVOMEC Plus are based upon those proven for IVOMEC Injection. Efficacy is summarized in Table 2.1:

Table 2.1 Trial ASR 15065 - Percent Efficacy IVOMEC Injection 21-day Persistent Effect Period

Nematode Species	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of 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 Injection group. One animal in the IVOMEC Plus group died 22 days after treatment. The apparent cause of death was esophageal impaction, which was not believed to be related to the experimental treatment.

B.2 Trial 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 3 treatment groups (10 animals per group). One group received IVOMEC Injection. 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: *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 Injection, 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 *T. axei* larvae and 21 days after the last *O. radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for *C. punctata, T. axei,* and *O. radiatum*. Efficacy is summarized in Table 2.2:

Table 2.2 Trial ASR 15110 - Percent Efficacy IVOMEC Injection 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
C. punctata	21	1470.7	374.4	75
T. axei	21	588.7	109.7	81
O. radiatum	28	278.8	24.0	91

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

B.3 Trial 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 Injection. 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 Injection, 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 *T. axei* larvae and 21 days after the last *O. radiatum* larvae were administered.

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

Table 2.3 Trial ASR 15111 - Percent Efficacy IVOMEC Injection 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
C. punctata	21	2917.8	33.5	99
T. axei	21	2122.8	9.9	99
O. 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 140-833 FOI Summary approval dated September 17, 1990.

4. HUMAN SAFETY

No further human food safety data were required from the original approval as discussed in the parent NADA 140-833 FOI summary approval dated September 17, 1990. There is a 49-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 Plus Injection for Cattle when administered once at 200 mcg ivermectin and 2 mg clorsulon/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 3 already approved persistent effect indications listed above. Three studies were conducted to provide substantial evidence for these 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. 1000 mL – base label and outsert
C. Package insert for 50, 200, and 500 mL container sizes