Approval Date: August 10, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-974

B. Sponsor

Merial Limited
2100 Ronson Road
Iselin, New Jersey 08830-3077

C. Proprietary Name

IVOMEC® Premix for Swine

D. Established Name

ivermectin

E. Dosage Form

Type A medicated article to be mixed with feed to produce a Type B or C medicated feed.

F. Dispensing Status

Over the Counter (OTC)

G. Dosage Regimen

0.1 mg ivermectin/kg (2.2 lb) of body weight daily for 7 consecutive days.

H. Route of Administration

Orally, through feed

I. Indication

For the treatment and control of gastrointestinal roundworms (*Ascaris suum*, adults and fourth-stage larvae; *Ascarops strongylina*, adults; *Hyostrongylus rubidus*, adults and fourth-stage larvae; *Oesophagostomum* spp., adults and fourth-stage larvae), kidneyworms (*Stephanurus dentatus*, adults and fourth-stage larvae), lungworms (*Metastrongylus* spp., adults), lice (*Haematopinus suis*), and mange mites (*Sarcoptes scabiei* var *suis*). Additional indications contained in this supplemental NADA are for treatment and control of threadworms (*Strongyloides ransomi*, adults and somatic larvae, and prevention of transmission of infective larvae to piglets, *via* the colostrum or milk, when fed during gestation).

J. Effect of Supplement

New claim for the treatment and control of threadworms (*Strongyloides ransomi*, adults and somatic larvae, and prevention of transmission of infective larvae to

piglets via the colostrum or milk, when fed during gestation) and use of Type C medicated feed as a top dress for adult swine.

II. EFFECTIVENESS

Data demonstrating the effectiveness of IVOMEC® Premix for Swine for previously approved indications are discussed in FOI Summaries for NADA 140-974 dated September 23, 1993 (58 FR 58652; Nov. 3, 1993), and June 29, 1995 (60 FR 39847; Aug. 4, 1995). Data from the following dose confirmation trials demonstrate that IVOMEC® Premix for Swine given at the recommended dosage controls infections of adult *Strongyloides ransomi* and prevents transmission of infective *S.ransomi* larvae from sows to piglets, via the colostrum or milk, when IVOMEC® Premix is given in the feed during gestation.

A. Confirmation of effectiveness of ivermectin in swine feed for threadworms (*S.ransomi*)

Note: Percent effectiveness was calculated using the formula:

$$\frac{(Arithmetic\ mean\ number\ of\ nematodes\ in\ non-medicated\ swine) - (Arithmetic\ mean\ number\ of\ nematodes\ in\ ivermectin-treated\ swine)}{(Arithmetic\ mean\ number\ of\ nematodes\ in\ non-medicated\ swine)\ x\ 100} = Percent\ Efficacy$$

1. Trial ASR 14712 and Trial ASR 14774

   (i) Type and purpose of study: Induced infection in pregnant sows to determine the effect of ivermectin treatment during gestation on transcolostral transmission of larvae.

   (ii) Investigator:

   Marlene Drag, D.V.M.
   Merck & Co., Inc.
   Fulton, Missouri

   James Arends, M.S., Ph.D.
   2340 Sanders Road
   Willow Spring, NC 27592

   (iii) General design:

   a. Animals: Twenty-four (24) crossbred sows (8 per group) each had at least one previous litter and were bred over a known three-day interval.

   b. Induced infection: Infective larvae of *S.ransomi* were given by subcutaneous injection to each animal on three occasions during the interval from Days 63 to 80 (ASR 14712) or Day57 to 78 (ASR 14774) of gestation. On each occasion approximately 250,000 larvae were given.

   c. Dosage form and dose of test articles: Type C medicated feed fed to deliver 100mcg ivermectin/kg body weight/day for seven consecutive days. One group received ivermectin from Days 0 to 7 and the other group received it from Days 11 to 18, with Day 0 being the 92nd day of gestation. Control animals received feed containing vehicle of the IVOMEC® Premix for Swine on Days 0 to 7.

d. Test duration: For each sow, until 14 days after parturition.

e. Pertinent variables measured: Worm counts for up to 4 piglets per sow at 14 days of age; and larval counts in sow colostrum or milk at 1, 2 and 7 days after parturition.

(iv) Results: Trial results are summarized in Tables 4.1 and 4.2.

Table 4.1. Mean worm counts and percent worm reduction at 14days of age in up to 4 piglets/sow from 8 sows fed either control ration or ration containing 100mcg ivermectin/kg body weight/day for seven consecutive days

Treatment Group	**Adult *S. ransomi*[a]**	**Percent reduction**
Trial ASR ASR 14712 Vehicle Control	3274.4	-
IVOMEC Premix (Days 92 to 99)	0	100
IVOMEC Premix (Days 103 to 110)	0	100
Trial ASR ASR 14774 Vehicle Control	828.1	-
IVOMEC Premix (Days 92 to 99)[b]	0	100
IVOMEC Premix (Days 103 to 110)	0	100

[a]Arithmetic mean
[b]Some sows were treated from Day 93 to 100 of gestation.

Table 4.2. *S. ransomi* larval counts in colostrum or milk at 1, 2, and 7 days after parturition from sows fed either control ration or ration containing 100mcg ivermectin/kg body weight/day for seven consecutive days

Treatment Group	Day of Sample					
	Day 1		Day 2		Day 7	
	Number larvae	Percent reduction	Number larvae	Percent reduction	Number larvae	Percent reduction
Trial ASR ASR 14712 Vehicle Control	117.0	-	10.0	-	5.2	-
IVOMEC Premix (Days 92 to 99)	0	100	0.1	98.8	0	100
IVOMEC Premix (Days 103 to 110)	0	100	0	100	0	100
Trial ASR ASR 14774 Vehicle Control	83.0	-	35.5	-	0	-
IVOMEC Premix (Days 92 to 99)[b]	0	100	0	100	0	-
IVOMEC Premix (Days 103 to 110)	0	100	0	100	0	-

(v) Conclusion: Under the conditions of this study, IVOMEC® Premix for Swine prevented transmission of *S.ransomi* larvae from sows to piglets, *via* the colostrum or milk, when given in the feed of sows during gestation.

(vi) Adverse reactions: No adverse events related to treatments were observed.

2. Trials ASR 14775 and ASR 14820

(i) Type of study: Induced infections of *S.ransomi* to determine the efficacy of treatment against patent infections of *S.ransomi* in growing pigs.

(ii) Investigator:

James Arends, M.S., Ph.D.
2340 Sanders Road
Willow Spring, NC 27592

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

(iii) General design:

a. Animals: In each trial there were twenty female and male-castrate crossbred pigs (10 per group). Trial-ASR 14775 animals were approximately 12 weeks old and weighed 25.4 to 52.0kg at the start of the study. Trial-ASR 14820 animals were approximately 8 weeks old and weighed 11.4 to 22.4kg at the start of the study.

b. Induced infection: Approximately 2500 infective larvae of *S.ransomi* were given by subcutaneous injection to each animal ten days before the start of treatment.

c. Dosage form and dose of test article: TypeC medicated feed fed to provide 100mcg ivermectin/kg body weight/day for 7 days. Controls animals received feed containing vehicle of the IVOMEC® Premix fed daily for 7 days.

d. Test duration and pertinent variables measured: Worm counts were determined at necropsy 14 days after start of treatment.

(iv) Results: Trial results are summarized in Tables 4.5.

Table 4.5. Mean worm counts and percent efficacy in growing pigs fed 100 mcg ivermectin/kg body weight/day for 7 days

Trial	Treatment Group	Adult S. ransomi[a]	Percent reduction
Trial ASR 14775	Vehicle Control	869.3	-
Trial ASR 14775	IVOMEC® Premix	0	100
Trial ASR 14820	Vehicle Control	2126.0	-
Trial ASR 14820	IVOMEC® Premix	3.0	>99

[a]Arithmetic mean

(v) Conclusion: Under the conditions of this study, IVOMEC® Premix for Swine controlled infections of adult *Strongyloides ransomi*.

(vi) Adverse reactions: No adverse events related to treatments were observed.

B. Effectiveness of the top dress

Specific studies addressing the effectiveness of IVOMEC® Premix for Swine when used as a top dress intake were not required because 1)the formulation of Type C feeds with respect to feed ingredients is not specified; 2)treated animals are not ill or otherwise demonstrating poor appetite; 3)the labeling states that the top dress is for individually-fed adult and breeding swine; and 4) with respect to the concentration of the drug, the Type C feed is palatable as demonstrated in non-pivotal palatability studies previously submitted to the parent application which included doses up to 6X of the high end of the allowable concentration of the Type C medicated feed.

III. TARGET ANIMAL SAFETY

Animal safety is discussed in FOI Summaries for NADA 140-974 dated September 23, 1993 (58 FR 58652; Nov. 3, 1993), and June 29, 1995 (60 FR 39847; Aug. 4, 1995).

IV. HUMAN FOOD SAFETY

Human food safety is discussed in FOI summaries for NADA 140-974 dated September 23, 1993 (58 FR 58652; Nov. 3, 1993), and June 29, 1995 (60 FR 39847; Aug. 4, 1995).

Based on a battery of toxicological studies, an Acceptable Daily Intake (ADI) of 1 mcg/kg body weight/day has been established for ivermectin. A tolerance of 20 ppb for residues of 22, 23-dihydroavermectin B1a (the marker residue) in liver (the target tissue) has been codified at 21 CFR 556.344. Concentrations of marker residue below the tolerance in the target tissue indicate that the total residues of the drug in all edible tissues are below their respective safe concentrations.

No additional residue studies were conducted for the top dress because the Agency concluded that, given the feeding practices for sows, there would be no significant difference in tissue residue levels of ivermectin at the prescribed withdrawal period (5 days) resulting from feeding via a top dress as compared to feeding in a complete feed. Data summarized in Sections 6.C and 6.D of the September 23, 1993, FOI Summary for this NADA support this conclusion.

As part of the approval of this supplement, the Agency has taken the opportunity to update the human food safety information on this product and codify the Acceptable Daily Intake (ADI) of 1 mcg/kg body weight/day and a muscle tolerance of 20 ppb for residues of 22, 23-dihydro-avermectin B1a. Residues of 22, 23-dihydro-avermectin B1a below 20 ppb in muscle indicate that total residues of the drug in muscle are below the muscle safe concentration. Muscle residues of drug at or below the muscle tolerance are not indicative of the safety of other edible tissues in swine for human consumption.

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Act and demonstrate that IVOMEC® Premix for Swine when used under the proposed conditions of use, is safe and effective for treatment and control of threadworms (*Strongyloides ransomi*, adults and somatic larvae, and prevention of transmission of infective larvae to piglets, via the colostrum or milk, when fed during gestation). No additional data was required for the use of Type C medicated feed as a top dress for adult swine due to data contained in the parent application.

The preslaughter withdrawal period following 7 consecutive days of feeding ivermectin to swine at a level of 0.1mg/kg body weight per day remains at 5days. As described in SectionVI., a muscle tolerance of 20 ppb is established for residues of 22, 23-dihydro-avermectin B1a.

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.

In accordance with 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.

This action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.33(a)(1) and (7).

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 approval of the supplement and conducted or sponsored by the applicant. The three years of marketing exclusivity only applies to the claim for treatment and control of threadworms (*Strongyloides ransomi*, adults and somatic larvae, and prevention of transmission of infective larvae to piglets, *via* the colostrum or milk, when fed during gestation).

VI. APPROVED PRODUCT LABELING

1. Facsimile labeling for Ivomec® Premix for swine
   - Type A medicated article, 0.6%, 50# bag (22.68 kg)
2. Bluebird labeling for Type B medicated feed
   - Ivermectin at 18.2-1180 g/ton
3. Bluebird labeling for Type C medicated feed
   - Ivermectin at 1.8 g/ton for Weaned, Growing, and Finishing Pigs
   - Ivermectin at 1.8-11.8 g/ton for Adult and Breeding Swine
   - Ivermectin at 18.2-1180 g/ton for Top Dress Use for Adult and Breeding Swine

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 2085

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.