Approval Date: July 27, 1995

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-974

B. Sponsor

Merck Research Laboratories

C. Proprietary Name

IVOMEC® Premix for Swine

D. Established Name

Ivermectin

E. Dosage Form, Route of Administration, and Recommended Dosage

See available labeling.

F. Dispensing Status

OTC

G. 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), kidney worms (*Stephanurus dentatus* , adults and fourth-stage larvae), lungworms (*Metastrongylus* spp., adults), lice (*Haematopinus suis*) and mange mites (*Sarcoptes scabiei* var. *suis*) when incorporated into complete swine feeds at the level listed in the table. Follow mixing directions when preparing complete feeds.

H. Effect of Supplement

To add the label claim for treatment of breeding swine.

II. EFFECTIVENESS

A. Endoparasites (Nematodes)-Dose Confirmation

Study ASR 14160 was conducted in the United States to confirm that IVOMEC Premix is effective against nematodes in adult pigs when administered at 0.1 mg/kg bodyweight daily for 7 consecutive days. Twelve adult swine with natural infections were divided into two groups of six each. One group was not treated; the other group received ivermectin in the feed at 0.1 mg/kg/day for 7 consecutive days. The animals were necropsied 7 days following the termination of the 7-day treatment

period and the reductions in the numbers of nematodes are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes	**% Reduction at 0.1 mg/kg 7 for days**
Ascaris suum , adult	100%
Ascarops strongylina , adult	97%
Hyostrongylus rubidus , adult	99%
Metastrongylus spp., adult	100%
Oesophagostomum spp., adult	100%
Oesophagostomum spp., L4	100%
Stephanurus dentatus , adult	100%

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B. Ectoparasites (Sarcoptic Mange Mites)

Study ASR 14048 was conducted in the United States to confirm the efficacy of IVOMEC Premix against *Sarcoptes scabiei* var. *suis* in adult swine when administered at 0.1 mg/kg bodyweight daily for 7 consecutive days. Fourteen adult swine with natural infestations of sarcoptic mange mites were divided into two groups of seven each. One group was not treated and the other received ivermectin in the feed at 0.1 mg/kg/day for 7 consecutive days. The animals were housed individually in solid wall pens. Mites from preselected locations were counted on Days -3, 14, 28 and 42 of the study. No living mites were found on any of the ivermectin treated pigs after the Day -3 count. The medicated feed was readily consumed. No adverse reactions were observed during the study.

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C. Field Studies

Field trials were not required for this supplemental claim.

III. ANIMAL SAFETY

A. Boar Reproductive Safety

Study ASR 14075 was conducted in the United States to assess the safety of IVOMEC Premix for adult breeding boars when included in the ration at a dose of 0.3 mg/kg/day (3X the recommended use level) for 7 consecutive days. Twenty adult boars selected on the basis of successful test mating and breeding soundness evaluation were used. They were ranked by testicle size and age into two age

groups, penned individually and assigned to replicates of two animals each. Within each replicate, the boars were allocated randomly to a non-medicated treatment group or a medicated treatment group to begin treatment on Day 0.

Semen was collected from each boar on Days -22 or -21, -14, -7 and 0 as part of the breeding soundness evaluation and then on Day 7 and weekly to Day 56 to determine any effects of the 7-day ivermectin treatment. The semen evaluations included measurements of volume, color, sperm concentration, percent progressively motile sperm, total sperm ejaculated, and sperm morphology. Testicular size was also measured at each semen evaluation.

Following treatment, there were no overall treatment differences or treatment by day interactions between the treated and control groups for testicular size, total number of sperm per ejaculate, or percentage of sperm with proximal droplets, abnormal heads, or abnormal midpieces. Other categories of sperm abnormalities (abnormal acrosomes, detached heads, coiled tails) were observed relatively infrequently and appeared to occur at a similar rate in the treated and control groups. Weight gain of the control boars from Day -1 to 7 was not significantly different from that of the treated boars. Percentage of normal sperm in the control group in the post-treatment period ranged from 91.5 to 96.1%. For the treated group post-treatment, the range was 92.8 to 94.7%.

No adverse treatment effects were exhibited on spermatogenesis or libido in boars receiving a 3X dose of ivermectin in the feed for 7 days.

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B. Sow Reproductive Safety

Study ASR 14074 was conducted in the United States to assess the safety of the IVOMEC Premix for adult female breeding swine in all phases of reproduction. One hundred fifty non-pregnant lactating females (1 to 4 years of age with proven breeding histories) were used in the study. Twelve boars with proven breeding histories were used for breeding by artificial insemination. There were two groups, an untreated control receiving unmedicated feed (Group 1) and an ivermectin-treated group (Group 2). The treated group received ivermectin at 0.3 mg/kg bodyweight/day in the feed for 7 days, four times with a four week interval between dosing periods, under five schedules which started in the premating period and ended in the late fetal development period as follows.

Schedule	**# of Sows**	**Treatment Period - 1 Day**	**Treatment Period - 2 days**	**Treatment Period - 3 days**	**Treatment Period - 4 days**
1	15	0-6	35-41	70-76	105-111
2	15	7-13	42-48	77-83	112-118
3	15	14-20	49-55	84-90	119-125
4	15	21-27	56-62	91-97	126-132

Schedule	**# of Sows**	**Treatment Period - 1 Day**	**Treatment Period - 2 days**	**Treatment Period - 3 days**	**Treatment Period - 4 days**
5	15	28-34	63-69	98-104	133-139

The study was conducted in five consecutive phases with 30 sows per phase. In each phase, 15 replicates of two sows were formed based on parity (1, 2, 3, or 4+) and initial weight. There were 3 sows assigned to each treatment schedule in each of the 5 phases for a total of 15 sows per treatment schedule. Day 0 was the first day of the trial for each phase. All sows of each phase had farrowed a previous litter within 1 to 16 days prior to Day 0 for that phase. For estrus synchronization, the piglets of the previous litter were all weaned on Day 32. Sows were checked for estrus once daily and observations recorded. Breeding was by artificial insemination. Each sow was inseminated with semen from the same boar on the first, second, and third day of estrus, and both sows in the same replicate were bred to the same boar. The semen was evaluated for motility, color and physical condition prior to use. Observation for estrus continued for a period of 31 to 32 days following weaning. Within this interval, if a sow returned to estrus after being bred once, she was rebred with semen from the same boar. Those sows not observed in estrus during the 31 to 32 days following weaning were not bred. Primary parameters of interest were number of pigs born per litter, number of live pigs born per litter, proportion of dead pigs born per litter, proportion of pigs with abnormalities per litter, average birth weight of live pigs, and weight gain from birth to weaning. Estrus rate, conception rate and farrowing rate were evaluated.

Following treatment, the percent of sows exhibiting estrus of all sows available for breeding (estrus rate) for the control sows was 96% and for the treated sows 93%. The percent of sows that were bred and diagnosed pregnant (conception rate) for the control sows was 93% and for the treated sows 90%. The percent of sows that farrowed of those bred for the control sows was 93% and for the treated sows 86%. The farrowing parameters (pigs born per litter, live pigs born per litter, birth weight, pigs weaned per litter, weaning weight), which are the primary parameters for this study, were all similar between the treated and control groups. There was no evidence of any teratogenicity in the pigs born to ivermectin treated sows. The effect on nursing pigs was also taken into account in that all sows treated before breeding were nursing pigs. The weaning weights were comparable for the pigs (born prior to the initiation of the trial) weaned from the ivermectin treated sows and the control sows.

The study shows that ivermectin premix, when incorporated in feed and fed to sows during any stage of the reproductive cycle, does not have an adverse effect on breeding or farrowing parameters.

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IV. HUMAN FOOD SAFETY

The human food safety requirements and results are the same as in the original approved NADA for 140-974 FEDERAL REGISTER, November 3, 1993, (58FR 58652).

A. Toxicity Tests

The toxicology studies conducted to support the safe concentration of ivermectin in swine edible tissues are summarized in NADA 135-008.

B. Safe Concentration of Residues

The withdrawal period for swine is 5 days. The safe concentration for total ivermectin residues in uncooked edible swine tissues has been established as 25 ppb in muscle, 75 ppb in liver, 100 ppb in kidney, and 100 ppb in fat. A regulatory tissue residue method has been developed for the determination of the marker residue, the B1a component of the parent ivermectin, with a tolerance of 20 ppb in swine liver (21 CFR 556.344).

Validation

The validated regulatory analytical methods for detection of residues of ivermectin are filed in the Food Additives Manual on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of section 512 of the Act and demonstrate that ivermectin 0.6% Type A medicated article when used under the proposed conditions of use, is safe and effective. These data from the controlled studies demonstrate the effectiveness of ivermectin for its labeled indications in swine feeds when fed at 0.1 mg/kg body weight per day for a period of 7 consecutive days. These studies demonstrate the efficacy of a 7 consecutive day regimen for treatment and control of *Ascaris suum*-adult and fourth-stage larvae; *Ascarops strongylina*-adults; *Hyostrongylus rubidus*-adult and fourth-stage larvae; *Oesophagostomum* spp.-adult and fourth-stage larvae; *Stephanurus dentatus* -adult and fourth-stage larvae; *Metastrongylus* spp.-adult; *Haematopinus suis*; and *Sarcoptes scabiei* var. *suis*.

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Ivermectin products for use in food producing animals are generally over-the-counter products. Accurate diagnosis can be made with reasonable degree of certainty by the layman. 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 have over-the-counter marketing status.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)(v)), this is a Category II change. The approval of this change is not expected to have any adverse effect

on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

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 application contains reports of new clinical or field investigations essential to the approval of the application and conducted or sponsored by the applicant. The THREE years of marketing exclusivity applies only to the claim for the treatment of breeding swine, for which the supplemental application was approved.

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.