I. GENERAL INFORMATION

A. File Number

NADA 140-974

B. Sponsor

Merck Sharp & Dohme Research Laboratories
2100 Ronson Road
Iselin, New Jersey 08830-3077

C. Proprietary Name

IVOMEC® Premix for Swine

D. Established Name

ivermectin

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

Add IVOMEC Premix to starter, grower and finisher feeds at 300 g per ton to supply 1.8 g ivermectin per ton (2 ppm) of feed. Use this Type C Medicated Feed as the only feed for 7 consecutive days. This provides approximately 100 mcg of ivermectin per kg of bodyweight per day.

300g

Required amount of IVOMEC Premix (Type A) Medicated Article 0.6 % to medicate one ton of complete (Type C) Medicated Feed

1.8g

Required level of ivermectin per ton of complete (Type C) Medicated Feed.

IVOMEC Premix should be thoroughly and evenly mixed in the feed in accordance with good manufacturing practices for medicated feeds. Dispersion of ivermectin in the feed is enhanced by diluting 1 part ivermectin Type A Medicated Article with 14 parts of finely ground feed ingredients to provide an intermediate premix. Ten lb of this intermediate premix is used to provide 1.8 g ivermectin in one ton of complete Type C Medicated Feed.

F. Dispensing Status

Over the Counter (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), kidneyworms (*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 below. Follow mixing directions when preparing complete feeds.

II. EFFECTIVENESS

Several formulations of ivermectin, including an injectable formulation for swine, are currently marketed by Merck & Co., Inc. as effective antiparasitic agents for various animal species. Data collected from a development program that included 26 clinical studies conducted in diverse areas of the United States as well as a number of international sites demonstrate that ivermectin as a 0.6% w/w Type A medicated article added to the ration at a rate to provide 2 ppm ivermectin (equivalent to approximately 100 mcg/kg/day) and fed to pigs for seven consecutive days effectively controls a wide range of economically important endo- and ectoparasites of growing swine. All of the studies involving efficacy evaluations against parasites were conducted as controlled studies. Both ecto-and endoparasite counts of treated swine were compared with those of untreated controls. The pigs were either experimentally or naturally infected with one or more species of ectoparasites (lice and mites) or endoparasites (nematodes). Each claim for a parasite species was supported by at least two controlled studies. Efficacy was expressed as percentage (%) reduction of parasites as compared to controls. The % reduction was calculated as follows:

$$\text{Percentage Reduction of Parasites} = \frac{(\text{Arithmetic mean number of parasites in control swine} - \text{Arithmetic mean number of parasites in treated swine})}{\text{Arithmetic mean number of parasites in control swine}} \times 100$$

The efficacy of ivermectin was at least 93% for each endoparasite claim except for the fourth-stage larvae of *Oesophagostomum* spp. (90%) while ectoparasite populations were reduced following treatment. Data from United States and international studies supports the claim that ivermectin administered in the ration of growing swine at 2 ppm for seven consecutive days is effective against adult and larval stages of the important nematode and arthropod parasites that affect swine.

A. Dose Titration

Dose titration studies were conducted to determine the amount of ivermectin that would be required in a seven-day treatment regimen to control swine endo- and ectoparasites. One ectoparasite study, and two endoparasite studies, each including eight controls and 24 medicated swine were conducted. Ivermectin dosages of 0, 50, 100 or 200 mcg/kg/day for seven consecutive days were evaluated. Local procedures were followed regarding animal husbandry during the studies and standard procedures were used for allocating animals, collecting samples, enumerating and identifying parasites and performing necropsies. The endoparasite studies used induced infections but naturally infested animals were used in the ectoparasite study. Based on the data collected, the optimum dose was determined to be 100 mcg/kg/day for seven days.

Ectoparasite Dose Titration

Study 12581 was conducted in the United States to establish the optimum level of ivermectin effective against *Sarcoptes scabiei* var *suis* . Thirty-two pigs with natural infestations were randomly allocated into four groups and fed ivermectin in feed at 0, 50, 100 or 200 mcg/kg/day for seven consecutive days, followed by nonmedicated ration until the study was terminated. Mites in scrapings from specified areas of the skin were counted. Mite infestation was markedly reduced in all ivermectin-treated pigs at seven days after the termination of treatment and these animals were free of infestation on Day 42 of the study. The medicated rations were readily consumed. No adverse reactions were observed during the course of the study. Data from the controls and pigs treated with ivermectin are listed below.

Sarcoptes scabiei

Dose Level	**% Efficacy (Range Day 14-42)**
50 mcg/kg	99-100
100 mcg/kg	99-100
200 mcg/kg	100-100

Investigator:

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Endoparasite Dose Titration

Study 12583 was conducted in the United States to establish the optimum level of ivermectin in feed against nematodes. Thirty-two pigs were artificially infected and randomly allocated to four groups of equal size. When the nematodes were in the fourth larval stage (L4), the groups were given ivermectin in feed at 0, 50, 100 or 200 mcg/kg/day for seven days followed by nonmedicated ration until the study was terminated. Necropsies were performed 16 to 17 days after the termination of treatment and the reductions in nematode counts are summarized below. The medicated rations were readily consumed. No adverse reactions were observed during the course of the study.

Percent Reduction Relative to Controls

Nematode (L4)	**Ivermectin (50 mcg/kg/day)**	**Ivermectin (100 mcg/kg/day)**	**Ivermectin (200 mcg/kg/day)**
Ascaris suum	100	100	100
Hyostrongylus rubidus	99	100	100
Oesophagostomum spp.	94	96	92

Investigator:

Dr. R. Alva-Valdes
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Study 12443 was conducted in West Germany to establish the optimum level of ivermectin in feed against immature *Hyostrongylus rubidus* . Thirty-two pigs with induced infections were randomly allocated to four groups of equal size. When the nematodes were in the fourth larval stage (L4), the groups were given ivermectin in feed at 0, 50, 100 or 200 mcg/kg/day for seven days, followed by nonmedicated ration until the study was terminated. Necropsies were performed 35-37 days after the termination of treatment and the findings listed below recorded. The medicated ration was readily consumed. No adverse reactions were observed during the course of the study.

Percent Reduction Relative to Controls

Nematode (L4)	**Ivermectin (50 mcg/kg/day)**	**Ivermectin (100 mcg/kg/day)**	**Ivermectin (200 mcg/kg/day)**
Hyostrongylus rubidus	93	99	99

Investigator:

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Lauterbach, West Germany

Justification of Dose Selection

Results from the above dose titration studies showed that 100 mcg/kg/day for seven days was adequate to control *Sarcoptes scabiei* var *suis* as well as L4 nematodes. Dose responses observed against L4 nematodes in two separate studies support the selection of 100 mcg/kg/day.

B. Dose Confirmation

Eight dose confirmation studies were conducted with ectoparasites (mange mites and swine lice). The studies included 105 ivermectin-treated pigs and 105 controls. The infestations were naturally acquired in five studies and induced in three. The parasite numbers were recorded from selected sample sites. The reductions of *Sarcoptes scabiei* var *suis* and *Haematopinus suis* are summarized in Table 1.

Confirmation of the dose selected for endoparasites (gastrointestinal, pulmonary and kidney nematodes) was affirmed in 15 controlled studies. The dose-confirmation data were obtained using 181 ivermectin-treated pigs and 181 controls. Infections were acquired naturally in eight of the studies and were induced in seven. All pigs were killed 14 to 180 days after treatment for parasite recoveries. Table 2 contains a summary of the reductions obtained.

Table 1 Reductions of Ectoparasites on Swine Given Ivermectin In Feed at 2 ppm for Seven Days Compared to Controls

Parasite	**Days After Treatment**	**No. of Trials**	**Range of % Reduction**
Sarcoptes scabiei var *suis* 3 (total no.)	14 days	3	100
Sarcoptes scabiei var *suis* 3 (total no.)	21 days	1	100
Sarcoptes scabiei var *suis* 3 (total no.)	28 days	2	100
Haematopinus suis 5 (total no.)	14 days	5	95-100
Haematopinus suis 5 (total no.)	21 days	1	92-95
Haematopinus suis 5 (total no.)	28 days	3	95-100

Table 2 Reductions of Endoparasites in Swine Given Ivermectin In Feed at 2 ppm for Seven Days Compared to Controls

Parasite	**No. of Trials**	**% Reduction**
Oesophagostomum spp. Adults	5	98.2
Oesophagostomum spp. L4	2	90.3
Ascaris suum adults	7	100.0
Ascaris suum L4	1	100.0
Hyostrongylus rubidus adults	3	96.9
Hyostrongylus rubidus L4	2	95.0
Ascarops strongylina adults	5	96.4
Metastrongylus spp. adults	4	100.0
Stephanurus dentatus adults	2	100.0
Stephanurus dentatus L4	2	100.0

Ectoparasite Dose-Confirmation Studies

1. Study 12751 was conducted in the United States to confirm the efficacy of ivermectin in feed against *Sarcoptes scabiei* var *suis* . Fifty-six pigs with natural infestations were allocated to two groups and housed four animals per pen. One group was the nonmedicated control and received the basal ration, the other group was given ivermectin in feed at 2 ppm for seven days followed

by nonmedicated feed until the study terminated. Mites from preselected locations were counted biweekly until study termination on Day 42. No living mites were found on any of the ivermectin-treated pigs after Day 0. The medicated feed was readily consumed. No adverse reactions were observed during the study.

Parasite	**% Efficacy on Day 14**	**% Efficacy on Day 28**	**% Efficacy on Day 42**
S. scabiei	100	100	100

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2. Study 12760 was conducted in the United States to confirm the efficacy of ivermectin in feed against *Sarcoptes scabiei* var *suis* . Twenty pigs with naturally acquired infestations were randomly allocated to two groups of equal size. One group was not treated and the other received ivermectin in feed at 2 ppm for seven days. Mites from preselected locations were counted on Days -2, 14, 28 and 42 of the study. No live mites were found on the ivermectin-treated pigs during any of the last three examinations. The medicated feed was readily consumed. No adverse reactions were observed. The data from this study are summarized below.

Parasite	**% Efficacy on Day 14**	**% Efficacy on Day 28**	**% Efficacy on Day 42**
S. scabiei	100	100	100

Investigator: Dr. D.P. Bane
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3. Study 12772 was conducted in the United States to confirm the efficacy of ivermectin in feed against *Sarcoptes scabiei* var *suis* . Twenty pigs with natural infestations were allocated to two groups of equal size. One group was not treated and the other received ivermectin in feed at 2 ppm for seven days. Mites from preselected locations were counted on Days -1, 7 and 21 of the study. No live mites were found on the ivermectin-treated pigs on either Day 7 or 21. The medicated feed was readily consumed. No adverse reactions were observed. The data are summarized below.

Parasite	**% Efficacy on Day 7**	**% Efficacy on Day 14**
S. scabiei	100	100

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4. Study 12461 was conducted in West Germany to confirm the efficacy of ivermectin in feed against *Haernatopinus suis.* Sixteen pigs with induced infestations were allocated to two groups of equal number. Pigs in one group were not treated and those of the other group received ivermectin in feed at 2 ppm for seven days. The lice on each pig were counted weekly and the results are summarized below. The medicated feed was readily consumed. No adverse reactions were observed. The lice that appeared on the ivermectin-treated pigs on Days 14-28 of the study originated from eggs that hatched during the posttreatment period.

Parasite	**% Efficacy on Day 7**	**% Efficacy on Day 14**	**% Efficacy on Day 21**	**% Efficacy on Day 28**
H. suis	100	95	92	95

Investigator:

Dr. E.M. Heinze-Mutz
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5. Study 12593 was conducted in the United States to confirm the efficacy of ivermectin against swine lice. Twenty pigs with natural infestations of *Haernatopinus suis* were allocated to two groups of equal number. Pigs in one group were not treated and those of the other group received ivermectin in feed at 2 ppm for seven days. The lice on each pig were counted on Days -2, 7, 14 and 28, and the results are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Parasite	**% Efficacy on Day 7**	**% Efficacy on Day 14**	**% Efficacy on Day 28**
H. suis	100	100	100

Investigator:

Dr. H.N. Becker
Becker Veterinary Clinic
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6. Study 12763 was conducted in the United States to confirm the efficacy of ivermectin in feed against swine lice. Twenty pigs with induced infestations of *H. suis* were allocated to two groups of equal size. Pigs in one group received ivermectin in feed at 2 ppm for seven days and those of the other group were not treated. The lice on each pig were counted on Days -1, 7, 14 and 28 and the results are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Parasite	**% Efficacy on Day 7**	**% Efficacy on Day 14**	**% Efficacy on Day 28**
H. suis	100	100	100

Investigator:

Dr. R.E. Williams
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7. Study 13038 was conducted in the United States to confirm that ivermectin in feed is effective against swine lice. Twenty pigs with natural infestations of *Haematopinus suis* were allocated to two groups of equal number. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. The lice on each pig were counted on Days 0, 7, 14 and 28 and the results are listed below. The lice that appeared on the ivermectin-treated pigs on Day 28 originated from eggs that hatched during the posttreatment period. The medicated feed was readily consumed. No adverse reactions were observed.

Parasite	**% Efficacy on Day 7**	**% Efficacy on Day 14**
H. suis	100	100

Investigator:

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8. Study 13039 was conducted in the United States to confirm the efficacy of ivermectin in feed against natural infestations of *Haematopinus suis,* the swine louse. Eighteen pigs with naturally acquired infestations were randomly allocated to two groups of equal number. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. The lice on each pig were counted weekly and the results are listed below. The lice that appeared on the ivermectin-treated pigs on Days 21-28 originated from eggs that hatched during the posttreatment period. The medicated feed was readily consumed. No adverse reactions were observed.

Parasite	**% Efficacy on Day 7**	**% Efficacy on Day 14**	**% Efficacy on Day 21**	**% Efficacy on Day 28**
H. suis	100	100	99	97

Investigator:

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Endoparasite Dose Confirmation Studies

1. Study 12461 was conducted in West Germany to confirm that ivermectin in feed is effective against nematodes. Sixteen pigs with induced infections were randomly allocated to two groups of equal number. When the nematodes became adults, one group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 21-23 days after termination of treatment and the reductions in counts of adult nematodes are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Hyostrongylus rubidus	98
Oesophagostomum spp.	98
Metastrongylus spp.	100

Investigator:

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2. Study 12593 was conducted in the United States to confirm that ivermectin in feed is effective against nematodes. Twenty pigs with natural infections were randomly allocated to two groups of equal number. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 21 days after the termination of treatment and the reductions in nematode counts are summarized below. The medicated feed was consumed readily. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Oesoph. quadrispinulatum	99

Investigator:

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3. Study 12760 was conducted in the United States to confirm that ivermectin is effective against nematodes. Twenty pigs with natural infections were randomly allocated to two groups of equal size. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 35 days after the termination of treatment and the reductions in nematode counts are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Ascarops strongylina	99

Investigator:

Dr. D.P. Bane
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4. Study 12761 was conducted in the United States to confirm that ivermectin in feed is effective against nematodes. Twenty pigs with natural infections were randomly allocated to two groups of equal size. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 14 days after the termination of treatment and the reductions in counts of adult nematodes are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Metastrongylus spp.	100
Ascarops strongylina	99

Investigator:

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5. Study 12764 was conducted in the United States to confirm that ivermectin in feed is effective against nematodes. Twenty pigs with naturally acquired infections were randomly allocated to two groups of equal size. One group was given ivermectin in feed at 2 ppm for seven days and the other group was not treated. Necropsies were performed 14-15 days after the termination of treatment and the reduction in counts of adult *Ascaris suum* is shown below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100

Investigator:

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6. Study 12772 was conducted in the United States to confirm that ivermectin in feed is effective against adult nematodes. Twenty pigs with natural infections were randomly allocated to two groups of equal size. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 14-15 days after the termination of treatment and the reductions in nematode counts are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Ascarops strongylina	99
Hyostrongylus rubidus	100
Metastrongylus spp.	100
Oesophagostomum spp.	100

Investigator:

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7. Study 12777 was conducted in the United States to confirm that ivermectin in feed is effective against adult nematodes. Twenty pigs with natural infections were randomly allocated to two groups of ten animals. One group received ivermectin in feed at 2 ppm for seven days and the other group was not treated. Necropsies were performed 14 days after termination of treatment and the reductions in nematode counts are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Ascarops strongylina	93
Hyostrongylus rubidus	99
Metastrongylus spp.	100
Oesophagostomum spp.	100

Investigator:

Dr. T.B. Stewart
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Louisiana State University
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8. Study 13039 was conducted in the United States to confirm that ivermectin in feed is effective against adult nematodes in swine. Eighteen pigs with natural infections were randomly allocated to two groups of equal size. One group was not treated and the other group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 21 days after termination of treatment and the reductions in nematode counts are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Ascarops strongylina	99
Metastrongylus spp.	100
Oesophagostomum spp.	99

Investigator:

Dr. J.E. Holste
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9. Study 12755 was conducted in the United States to confirm that ivermectin in feed is effective against immature nematodes in swine. Fifty-six pigs with induced infections were randomly allocated to two groups of equal size. When the infections had reached the fourth larval stage, one group received ivermectin in feed at 2 ppm for seven days and the other group was not treated. Necropsies were performed 21-23 days after the termination of treatment and the reductions in counts of fourth-stage larvae (L4) are summarized below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (L4)	**% Reduction at 2ppm/7days**
Ascaris suum	100
Hyostrongylus rubidus	100
Oesophagostomum spp.	84

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10. Study 12853 was conducted in the United States to confirm that ivermectin in feed is effective against L4*Oesophagostomum* spp. in swine. Fifty-six pigs with induced infections were randomly allocated to two groups of equal size. When the infection had reached the fourth larval stage, one group received ivermectin in feed at 2 ppm for seven days and the other group was not treated. Necropsies were performed 17-19 days after the termination of treatment and the reduction in counts of L4 *Oesophagostomum* spp. is shown below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (L4)	**% Reduction at 2ppm/7days**
Oesophagostomum spp.	96

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11. Study 13073 was conducted in the United Kingdom to confirm that ivermectin in feed is effective against immature *Hyostrongylus rubidus* . Sixteen pigs with induced infections were randomly allocated to two groups of 8 pigs. When the infections reached the fourth larval stage, one group received ivermectin in feed at 2 ppm for seven days and the other group was not treated. Necropsies were performed 14 days after the termination of treatment and the reduction in counts of L4 *H. rubidus* is shown below. The medicated feed was readily consumed. No adverse reactions were observed.

Nematodes (L4)	**% Reduction at 2ppm/7days**
Hyostrongylus rubidus	88

Investigator:

Dr. R.M. Connan
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Madingley Road, Cambridge CB3 OES, England

12. Study 12778 was conducted in the United States to confirm that ivermectin in feed is effective against immature *Stephanurus dentatus* . Thirty pigs with induced infections were randomly allocated to three groups of ten. When infections had reached the fourth larval stage, one group was not treated and one group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 13-18 days after the termination of treatment and the reduction in counts of L4 *S. dentatus* is shown below. The medicated feed was readily consumed. No adverse reactions were observed. The third group of pigs was given an injectable formulation of ivermectin; however, the data from that treatment are not pertinent to this summary and have been omitted.

Nematodes (L4)	**% Reduction at 2ppm/7days**
Stephanurus dentatus	100

Investigator:

Dr. D.J. Moncol
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Raleigh, North Carolina 27606

13. Study 12833 was conducted in the United States to confirm that ivermectin in feed is effective against immature *Stephanurus dentatus* . Thirty pigs with induced infections were randomly allocated to three groups of ten. When the infection had reached the fourth larval stage, one group was not treated and one group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed approximately 180 days after the termination of treatment when all nematodes in treated and nontreated animals were adults, and the reduction in counts of L4 *S. dentatus* is shown below. The medicated feed was readily consumed. No adverse reactions were observed. The third group of pigs was given an injectable formulation of ivermectin; however, the data from that treatment are not pertinent to this summary and have been omitted.

Nematodes (L4)	**% Reduction at 2ppm/7days**
Stephanurus dentatus	100

Investigator:

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14. Study 12594 was conducted in the United States to confirm that ivermectin in feed is effective against adult *Stephanurus dentatus* . Thirty-three sows with natural infections were randomly allocated to three groups of equal size. One group was not treated and one group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 21 days after the termination of treatment and the reduction in counts of adult *S. dentatus* is shown below. The medicated feed was readily consumed. No adverse reactions were observed. The third group of pigs was given an injectable formulation of ivermectin; however, the data from that treatment are not pertinent to this summary and have been omitted.

Nematodes (L4)	**% Reduction at 2ppm/7days**
Stephanurus dentatus	100

Investigator:

Dr. H.N. Becker
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15. Study 12832 was conducted in the United States to confirm that ivermectin is effective against adult *Stephanurus dentatus* . Thirty pigs with induced infections were randomly allocated to three groups of equal size. One group was not treated and one group received ivermectin in feed at 2 ppm for seven days. Necropsies were performed 21 days after the termination of treatment and the reduction in counts of adult *S. dentatus* is shown below. The medicated feed was readily consumed. No adverse reactions were observed. The third group of pigs was given an injectable formulation of ivermectin; however, the data from that treatment are not pertinent to this summary and have been omitted.

Nematodes (adult)	**% Reduction at 2ppm/7days**
Stephanurus dentatus	100

Investigator: Dr. R. Alva-Valdes
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C. Field Studies

Three field studies were conducted in the United States in which ivermectin in feed was administered at use level (Table 3). Three hundred six pigs were given ivermectin in feed at 2 ppm for seven days and 76 were untreated controls.

The percentage of fecal samples with nematode eggs was markedly reduced after treatment with ivermectin. The effects of ivermectin on fecal nematode eggs, *Sarcoptes scabiei* var *suis* and *Haematopinus suis* in these studies are summarized in Table 4. No adverse reactions were observed following treatment. All medicated rations were readily consumed.

Table 3 Field Studies

Trial No.	**Location**	**Total # Pigs**	**# Pigs Treated with 2 ppm Ivermectin in Feed**
12943[a]	Stillwater, OK	127	102
13031[b]	Pittsfield, IL	130	104
13035[c]	Kingdom City, MO	125	100

[a]Investigator: Dr. J.A. Hair, Research Cooperators Stillwater, Oklahoma 74074
[b]Investigator: Dr. J.E. Hoiste, R. Ghrist Farm Pittsfield, Illinois 62363
[c]Investigator: Dr. J.E. Hoiste, J. Gilmore Farm Kingdom City, Missouri 65252

Table 4 Summary of Parasite Evaluation in Field Studies

Study Number	# With Positive EPG/# Evaluated - Control	# With Positive EPG/# Evaluated - Ivermectin	# With Lice Present/# Evaluated – Control	# With Lice Present/# Evaluated – Ivermectin	# With Mites Present/# Evaluated - Control	# With Mites Present/# Evaluated - Ivermectin
ASR 12943 Day 1	12/22	54/67	20/25	47/72	25/25	30/72
ASR 12943 Day 19-20	9/22	5/61	23/25	2/72	13/25	9/72
ASR 13031 Day 0	25/26	23/26	26/26	26/26	-	-
ASR 13031 Day 21	25/26	2/26	26/26	8/26	-	-
ASR 13035 Day 0	7/25	5/25	25/25	25/25	-	-
ASR 13035 Day 21	13/25	0/25	13/25	0/25	-	-

III. TARGET ANIMAL SAFETY

Study 12768 was conducted in the United States to assess the safety of the in-feed formulation of ivermectin in pigs when included in the ration at levels up to 10 ppm (five times the recommended dose) for 21 consecutive days (three times the recommended treatment period). Twelve castrated males and an equal number of female eight-week old pigs were assigned randomly to four treatment groups and housed individually. They were fed a basal ration that contained ivermectin in feed at 0, 2, 6 or 10 ppm for 21 days. Weight gain, feed consumption and clinical health during the study were recorded. Blood was collected for clinicopathologic evaluation.

No treatment-related adverse findings were observed during routine clinical evaluation or during necropsy and histopathological review. No significant treatment effects on weight gain and feed consumption were detected.

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IV. HUMAN FOOD SAFETY

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 lowest no-observable-effect-levels (NOEL) in the battery of toxicity studies described above were determined in the multigeneration study in rats (0.1 mg/kg/day) and in the oral teratogenic study in the mouse (0.1 mg/kg/day for maternotoxicity and 0.2 mg/kg/day for teratogenicity). The minimum safety margins required for the effects observed in these studies are 100x for the multigeneration study and for the maternotoxicity in the mouse teratological study and 1000x for the teratological effects also seen in the latter study. Due to the significance of the terata (cleft palate) seen in the teratology study the 1000x safety factor was used for determining an acceptable daily intake (ADI) of up to 0.2 micrograms per kg per day of ivermectin residue by an individual in food.

ADl = 0.2 mg/kg/day / 1000 safety factor = 0.2 mcg/kg/day

A safe concentration in muscle tissue of swine is calculated from the acceptable daily intake, assuming the average weight of man to be 60 kg and the daily human intake of muscle to be 500 g, as follows:

safe concentration in muscle = (60 kg)(0.2 mcg/kg/day) / 500 g/day = 24 ppb

When rounded to the nearest 5 ppb, the safe concentration in muscle then becomes 25 ppb. The safe concentration of residues in liver, kidney and fat are determined from this number using appropriate food consumption values (food factor) for these tissues. Therefore, the safe concentrations are:

Liver: 25 ppb x 3 (food factor) = 75 ppb
Kidney: 25 ppb x 4 (food factor) = 100 ppb
Fat: 25 ppb x 4 (food factor) = 100 ppb

C. Metabolism and Total Residue Depletion Studies

Total radioactive residue (averaged value from three animals) in edible tissues of swine dosed with 3H-labeled MK-933 orally at 100 g/kg body weight/day for 7 days in the feed is shown in the table below:

Total Residue (ppb)

Tissue	**Days Off Drug - 0**	**Days Off Drug - 3**	**Days Off Drug - 7**	**Days Off Drug - 14**	**Days Off Drug - 21**
Liver	237	43	11	4	3
Fat	207	64	18	8	5
Kidney	117	20	3	0	0
Muscle	58	12	3	1	0

Examination of the residue data and unaltered drug depletion patterns shows that fat and liver generally contain the highest and most persistent residue. The fat residue levels are slightly higher than the liver at almost all time points, although the unaltered drug depletion pattern in both tissues is essentially similar, i.e., the unaltered drug is a satisfactory marker substance. Because of the integrity of the

liver as one organ and the relative difficulty in extracting and isolating the marker substance from fat, the liver is considered the preferred target tissue. The radioactive residue in the edible tissues examined is essentially all extractable into organic solvents indicating that there is very little, if any, intractable, covalently bound residue in these tissues. The unaltered drug (H2B1a and H2Blb, respectively) acoounts for about 45% (33 + 12%) and 34% (26 + 8%) of the total radioactive residue in liver on-drug and 3 days off-drug, respectively. In fat, the unaltered drug accounts for about 77% (66 + 11%) of the total residue on-drug and 64% (56 + 8%) at 3 days off-drug.

Livers from two on drug (1 barrow and 1 gilt) and three 3-day off-drug (1 barrow and 2 gilts) swine were used for metabolism studies. In these samples, unaltered drug accounts for about 38 and 34% [by normal-phase (NP) HPLC] of the residue, respectively. Metabolites can be separated into a polar group (17 and 12%, respectively), 3"-O-desmethyl and drug-like (43 and 50%, respectively) and nonpolar (4 and 5%, respectively). By reversed-phase high performance liquid chromatography (RP-HPLC), H2Bla component comprised about 34% of the total radioactivity in the on-drug livers and about 28% in the 3-day off-drug livers. The H2Blb component coeluted with 3"-O-desmethyl-H2Bla, but these compounds were separated by NP-HPLC. The H2Blb component comprised about 7% of the radioactivity in the on-drug and about 6% in 3-day off-drug livers while the 3"-O-desmethyl H2B1a component was about 27% and 30% of the radioactivity in the on-drug and 3-day off-drug livers, respectively. There were at least two metabolites that eluted in the polar fraction during the NP-HPLC where the 24-hydroxymethyl metabolites would be expected. Metabolites less polar than the H2B1a component comprised only 3-7% of the radioactivity in any of the liver samples. The remainder of the radioactivity in the livers, about 12% on-drug and about 16% 3-days off-drug, was comprised of at least two "drug-like" components, one of which was identified as 3"-0-desmethyl-H2Blb by its chromatographic behavior on NP and RP-HPLC. None of the unidentified components of the residue in liver represented as much as 10% of the total residue nor were present at a concentration of >0.1 ppm.

The metabolism of MK-933 in swine fat is qualitatively similar to that in the swine liver. The compositions of the radioactive residues (determined by NP-HPLC) in on-drug and 3-day off-drug swine fat samples are respectively; unaltered drug, 75 and 64%; non-polar metabolites, 10 and 23%; drug-like metabolites, 11 and 9%; and polar metabolites, 7 and 6%. The distribution of radioactive components in the livers and fat of the swine fed ivermectin is qualitatively similar to the distribution of components following subcutaneous dosing.

Comparative metabolism studies indicate that the metabolism of MK-933 in swine and rat, the toxicity test species, is qualitatively similar. In both species, the unaltered drug is the major residue. The HPLC profiles of the radioactive residue in the liver are qualitatively similar with respect to the metabolite components, but quantitatively different in the abundance of some metabolite components. The major metabolites in swine liver are 3"-O-desmethyl-H2B1a and 3"-O-desmethyl-H2B1b, whereas in rat liver, the major polar metabolites are 24-hydroxymethyl-H2B1a and 24-hydroxymethyl-H2B1b. The presence of 24-hydroxymethylH2B1a and 24-hydroxymethyl-H281b in the on-drug and 3 days off-drug livers of the swine dosed orally with MK-933 in feed is indicated by radioactive peaks with

retention times characteristic of these components. The presence of a small amount of 3"-O-desmethyl products in rat liver is suggested by the presence of a small radioactive peak with retention time identical to the 3"-O-desmethyl compounds. Thus, the test species is exposed to the major drug residue components known to be present in swine tissues.

D. Studies Demonstrating a Withdrawal Time

A tissue residue depletion study was performed to determine the marker residue (component H2B1a) concentration in swine tissues resulting from the feeding of animals continuously for seven days with ivermectin premlx combined in a complete feed at 2 ppm. Three barrows and two gilts were sacrificed at each withdrawal time. The withdrawal times following the end of the medication period were 0 (on the seventh day of medication), 0.5, 1, 1.5, 2, 2.5, 3, 5 and 7 days. Another set of five animals served as unmedicated controls.

Marker residue assays were conducted on swine livers (the target tissue) for selected withdrawal times using the high pressure liquid chromatography-fluorescence determinative method. The average marker residue concentrations found were as follows:

	Withdrawal Day 0	**Withdrawal Day 1.0**	**Withdrawal Day 1.5**	**Withdrawal Day 2.0**	**Withdrawal Day 2.5**	**Withdrawal Day 3.0**	**Withdrawal Day 5.0**	**Control**
ppb Found	38	22	19	14	10	12	3	0

The analytical method used to determine the marker residue has a lower limit of reliable measurement of 10 ppb. The Rm value (marker residue concentration tolerance) for swine derived from toxicity and metabolism data has been determined to be 20 ppb, which is the same tolerance established for swine in NADA 135-008. Statistical analysis of the depletion data, using the upper tolerance limit containing 99 percentile of the population with 95% confidence, yields a withdrawal period of 5 days.

E. Regulatory Methods

Ivermectin Determinative Assay Scheme

The determinative assay measures the marker residue, 22,23-dihydroavermectin Bla by high pressure liquid chromatography (HPLC) of a fluorescent derivative. The marker residue is extracted into isooctane from an aqueous acetone homogenate of liver tissue. The isooctane is removed by evaporation and the extract purified by a series of acetonitrile-hexane-water partitions. The fluorescent derivative is formed by heating with an acetic anhydride + methylimidazole reagent. A chloroform solution is purified over a silica column and concentrated by evaporation; reverse phase HPLC is performed using methanol/water and fluorescence detection. Quantitation is obtained by using a standard curve for the marker residue carried through the derivatization and subsequent steps. Recoveries are in the range of 75-95% with a lower limit of reliable measurement of 10 ppb.

Ivermectin Confirmatory Assay Scheme

The sample preparation and purification steps of the confirmatory assay are essentially the same as the determinative assay. The specificity is obtained by the production of two new species just prior to derivatization. The new species are produced by removing one of the saccharide groups with 1% sulfuric acid in isopropanol to form the monosaccharide or removing both saccharide groups with 1% sulfuric acid in methanol to form the aglycone of 22,23-dihydroavermectin B1a. Since these two treatments are so similar, the formation of the two new species and their chromatographic properties are unique and hence confirm the presence of the marker residue.

In the confirmatory test, the liver extract is split into three parts. One part is used for each of the sulfuric acid treatments. These samples are separated from sulfuric acid by extractions and the fiuorescent derivatives of the two new compounds are made. The third aliquot is derivatized without pretreatment. All three derivatives are then extracted into hexane with a small amount of isobutyl alcohol present. The high pressure liquid chromatography determination is made as in the determinative assay. Three separate peaks are observed at three separate retention times which are compared with standards run through the procedure from the sulfuric acid addition step onward. Presence of and quantitation of the three peaks is confirmation that ivermectin is present.

Validation

The determinative and confirmatory methods were validated satisfactorily by FDA and USDA laboratories utilizing bovine and ovine tissue. It was not deemed necessary to repeat these methods trials with porcine tissue. 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 original NADA comply with the requirements of section 512 of the Act and demonstrate that ivermectin 0.6% Type A medicated artide 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 100 mcg/kg body weight 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; *Haernatopinus suis;* and *Sarcoptes scabiei* var. *suis*.

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 compound, parent ivermectin, with a tolerance of 20 ppb in swine liver (21 CFR 556.344).

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 Section 512(c)(2)(F)(ii) of the FFDCA, this approval for food producing animals qualifies for THREE 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.

VI. ATTACHMENTS

Front Panel: Ivomec® Premix for Swine, Type A Medicated Article, 50# bag (22.68 kg).
Back Panel; Ivomec® Premix for Swine, Type A Medicated Article, 50# bag (22.68 kg).

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.