DATE OF APPROVAL LETTER: FEB 28, 2002

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 97-505

Lincomycin Feed Medications (LINCOMIX® 20, LINCOMIX® 50)

"…for the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*"

SPONSORED BY:

Pharmacia & Upjohn Company

I. GENERAL INFORMATION

NADA number:	97-505
Sponsor:	Pharmacia & Upjohn Company 7000 Portage Rd. Kalamazoo, MI 49001
Established Name:	Lincomycin hydrochloride
Proprietary Name:	LINCOMIX® 20 LINCOMIX® 50
Marketing Status:	Over-The-Counter (OTC).
Effect of Supplement:	To add the label claim for the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis.*

II. INDICATIONS FOR USE

SWINE: For the treatment and control of swine dysentery.

For the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*.

For reduction in the severity of swine mycoplasmal pneumonia.

For increase in rate of weight gain in growing-finishing swine.

III. DOSAGE

Dosage Form: LINCOMIX® 20 and LINCOMIX® 50 are Type A medicated articles.

Route of Administration: Oral, in feed

Recommended Dosage: For the treatment of swine dysentery, and the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*: Feed 100 grams of lincomycin per ton of complete feed as the sole ration for three weeks, or until signs of disease (watery, mucoid or bloody stools) disappear.

For the treatment and control of swine dysentery, and the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*: Feed 100 grams of lincomycin per

ton of complete feed as the sole ration for three weeks, or until signs of disease (watery, mucoid or bloody stools) disappear, followed by 40 grams of lincomycin per ton.

For the control of swine dysentery and porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*: Feed 40 grams of lincomycin per ton of complete feed as the sole ration. For use in animals or on premises with a history of swine dysentery, but where symptoms have not yet occurred.

III. EFFECTIVENESS

DOSE JUSTIFICATION

Dose Selection Study – Swine: Pharmacia & Upjohn Study Reports 768-9690-97-002 and 768-9690-98-003.

1. Type of Study: An induced challenge model study.

2. Investigators:

   Cornell CP, Kratzer DD, Evans RA. Pharmacia & Upjohn, Kalamazoo, MI 49001
   NL Winkelman. Swine Services Unlimited Inc., Morris, MN 56267.

3. Study Design:

   The study was designed to evaluate the effectiveness of 20 grams, 40 grams, and 100 grams of lincomycin per ton of complete feed for the prevention and control of porcine proliferative enteropathies (ileitis) in an induced-challenge model. One hundred weaned commercial crossbred pigs (Landrace/York), 4 to 5 weeks old, were used in the study. The source herd was serologically negative for *Lawsonia intracellularis*, TGE virus, and PRRS virus. Pigs were randomly assigned to treatment groups by weight. A randomized complete block design was used; pigs in each weight group were assigned to one of four pens within a location in the building. Treatment (0 grams, 20 grams, 40 grams, or 100 grams of lincomycin per ton of feed) was randomly assigned to pens of pigs in each location. There were five pigs per pen and five replicates of each treatment, including non-medicated controls. All clinical personnel involved in making and recording observations were blinded to treatments.

   All pigs received the assigned test diet *ad libitum* for 21 days, beginning on Day -4. A total dose of 1.2×10^8 *Lawsonia intracellularis* organisms was administered as an oral intestinal mucosal homogenate to each pig on the two challenge days (Days 0 and 1). Each pig also received an IM injection of prednisolone (10 mg/kg body weight) on both challenge days to facilitate pathogenesis. After the 21-day treatment period, all pigs were fed an unmedicated diet *ad libitum* and observed for an additional 14 days.

Variables measured were mortality, abnormal clinical impression score days, abnormal diarrhea score days, ileal/jejunal lesion length and lesion incidence, average daily gain (ADG), average daily feed intake (ADFI), and feed conversion efficiency (ADFI/ADG).

4. Results: Feed assay results for lincomycin content of the 20 g/ton diet were unacceptably low (≈ 4 g/ton), therefore the data from this group were not evaluated. The challenge was very severe and resulted in high mortality (52%) for the control group pigs. The 40 g/ton and 100 g/ton medicated groups demonstrated improvement over the controls in clinical scores and gain variables.

   There were no reports of drug-related adverse effects in this study.

5. Conclusions:

   Lincomycin doses of 40 g/ton and 100 g/ton of feed were effective in preventing the clinical signs of PPE in an induced challenge model study when compared to non-medicated control animals.

DOSE CONFIRMATION

B. Dose Confirmation Study: Pharmacia & Upjohn Study Report a0075523.

1. Type of Study: This study was a clinical trial using an induced model infection of *Lawsonia intracellularis*.

2. Investigators:

   Crane JP, Kratzer DD, Evans RA, Dame KJ, Buckham SL. Pharmacia & Upjohn, Kalamazoo, MI 49001
   NL Winkelman. Swine Services Unlimited Inc., Morris, MN 56267.

3. Study Design:

   a. Purpose: This induced-challenge model study was conducted to evaluate the clinical effectiveness of lincomycin at 40 g/ton and 100 g/ton of complete feed, for the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*.

   b. Experimental Animals: One hundred and eighty weaned commercial crossbred pigs (Large White/Landrace), approximately 5 weeks old, were used in the study. The source herd was serologically negative for *Lawsonia intracellularis* and PRRS virus.

c. Randomization: A randomized complete block design was used. There were a total of 6 pigs per pen with 10 replicates of each treatment group (non-medicated control, 40 grams lincomycin per ton of feed, and 100 grams lincomycin per ton of feed). Pigs were housed in two adjacent barns. All clinical personnel involved in making and recording observations were blinded to treatments.

d. Dosage Form, Route, and Duration of Administration: LINCOMIX® 20 Feed Medication was mixed with swine feed to produce medicated test diets containing 40 grams and 100 grams of lincomycin per ton of feed. A swine feed of the same dietary composition as the medicated test diets but without lincomycin was used as a negative control diet in one group of pigs. All pigs were fed a non-medicated feed *ad libitum* from Day 0 to Day 7.

e. Entrance Criteria: Treatment was initiated once at least 10% of pigs in each barn manifested either Grade 3 diarrhea scores or Grade 2 clinical impression scores.

   1) Diarrhea was scored as follows: 1 = no diarrhea; 2 = semi-solid, no blood; 3 = watery stool, runs through the floor slats, no blood; 4 = blood tinged feces, loose or formed; 5 = profuse diarrhea with blood or very dark tarry feces.

   2) Clinical impression scores were obtained from the sum of the pig demeanor score (PDS) and the abdominal appearance score (AAS) divided by two. PDS were scored as follows: 1 = normal; 2 = slightly to moderately depressed, listless, will stand; 3 = severely depressed, recumbent, will not stand. AAS were scored as follows: 1 = normal; 2 = moderately gaunt; 3 = severely gaunt.

f. Challenge: A total dose of 1.8×10^9 *Lawsonia intracellularis* organisms was administered as an oral intestinal mucosal homogenate to each pig over the two challenge days (Days 0 and 1). Each pig also received an IM injection of prednisolone (10 mg/kg body weight) on both challenge days to facilitate pathogenesis.

g. Study Duration: Treatment was initiated on Day 7. The test diets were then provided *ad libitum* for 21 consecutive days. The study duration was 28 days.

h. Variables Measured: The primary variables for determining effectiveness were a comparison of mortality, abnormal clinical impression days, and abnormal diarrhea days between the treated and control groups. Clinical impression score was considered abnormal if either pig demeanor scores were ≥2 or abdominal appearance scores were ≥2. Diarrhea score was considered abnormal if ≥2. Other variables measured were lesion incidence, lesion length, average daily gain (ADG), average daily feed intake (ADFI), and feed conversion efficiency (ADFI/ADG).

4. Statistical methods used: Mixed model ANOVA procedures were used to analyze the data. Rates per pen for mortality, abnormal diarrhea scores, and abnormal clinical impression scores were computed for the entire 21-day treatment period. Freeman-Tukey arcsine transformations were applied if necessary. Analyses were conducted using a model with Treatment as a fixed effect and Weight block as a random effect. Pairwise comparisons were made between the lincomycin treatment groups and the nonmedicated control group. Two-sided tests were used for the pairwise comparisons.

5. Results: The results for the 21-day treatment period are summarized in Table 4.1.

Table 4.1: Summary of results for the 21-day treatment period

Study Group	Least Squares Mean Pen Rate (2-sided p-value vs. control)		
	Non-Medicated Controls	Lincomycin 40 g/ton	Lincomycin 100 g/ton
% mortality	2.5	3.3 (0.67)	0 (0.35)
% abnormal diarrhea score pig days	39.5	30.4 (0.04)	24.6 (<0.01)
% abnormal clinical impression score pig days	13.8	11.0 (0.42)	6.7 (0.02)

Mortality was numerically lower in the 100 grams lincomycin per ton of feed treatment group compared to the non-medicated group. There was a statistically significant decrease in abnormal diarrhea score pig days and abnormal clinical impression score pig days in the 100 grams lincomycin per ton of feed treatment group compared to the non-medicated group.

There were no reports of drug-related adverse effects in this study.

6. Conclusions: Lincomycin, fed at a level of 100 g/ton of feed for 21 consecutive days, was effective in the control of PPE in swine challenged with an oral *Lawsonia intracellularis* intestinal mucosal homogenate.

C. Dose Confirmation Study: Pharmacia & Upjohn Study Report a0075522.

1. Type of Study: This study was a clinical trial using an induced infection of *Lawsonia intracellularis*.

2. Investigators:

   Crane JP, Kratzer DD, Meeuwse DM, Dame KJ, Buckham SL. Pharmacia & Upjohn, Kalamazoo, MI 49001.
   NL Winkelman. Swine Services Unlimited Inc., Morris, MN 56267.

3. Study Design:

   a. Purpose: This study was conducted to evaluate the clinical effectiveness of lincomycin at 40 g/ton and 100 g/ton of feed, for the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis*, using an induced-challenge model.

   b. Experimental Animals: One hundred and thirty-two weaned commercial crossbred pigs (Large White/Landrace/Duroc), 4½ to 5 weeks old, were used in the study. The source herd was serologically negative for *Lawsonia intracellularis* and PRRS virus.

   c. Randomization: A randomized incomplete block design was used. There were a total of 12 pigs per pen with 4 replicates of both the non-medicated control and 40 grams of lincomycin per ton of feed treatment groups, and 3 replicates of the 100 grams lincomycin per ton of feed treatment group. All clinical personnel involved in making and recording observations were blinded to treatments.

   d. Dosage Form, Route, and Duration of Administration: LINCOMIX® 20 Feed Medication was mixed with swine feed to produce medicated test diets containing 40 grams and 100 grams of lincomycin per ton of feed. A swine feed of the same dietary composition as the medicated test diets but without lincomycin was used as a negative control diet in one group of pigs. All pigs were fed a non-medicated feed *ad libitum* from Day 0 to Day 7.

   e. Entrance Criteria: Treatment was initiated once at least 20% of pigs manifested either ≥ Grade 2 diarrhea scores or ≥ Grade 2 clinical impression scores, with at least one pig per pen expressing these criteria.

      1) Diarrhea was scored as follows: 1 = no diarrhea; 2 = semi-solid, no blood; 3 = watery stool, runs through the floor slats, no blood; 4 = blood tinged feces, loose or formed; 5 = profuse diarrhea with blood or very dark tarry feces.

      2) Clinical impression scores were obtained from the sum of the pig demeanor score (PDS) and the abdominal appearance score (AAS) divided by two. PDS were scored as follows: 1 = normal; 2 = slightly to moderately depressed, listless, will stand; 3 = severely depressed, recumbent, will not stand. AAS were scored as follows: 1 = normal; 2 = moderately gaunt; 3 = severely gaunt.

f. Challenge: A total dose of 5 x 10^9 cells of *Lawsonia intracellularis* was administered as an oral intestinal mucosal homogenate to each pig over the two challenge days (Days 0 and 1).

g. Study Duration: Treatment was initiated on Day 7. The test diets were then provided *ad libitum* for 21 consecutive days. The study duration was 28 days.

h. Variables Measured: The primary variables for determining effectiveness were a comparison of mortality, abnormal clinical impression days, and abnormal diarrhea days between the treated and control groups. Clinical impression score was considered abnormal if either pig demeanor scores were ≥2 or abdominal appearance scores were ≥2. Diarrhea score was considered abnormal if ≥2.

4. Statistical methods used: Mixed model ANOVA procedures were used to analyze the data. Rates per pen for mortality, abnormal diarrhea scores, and abnormal clinical impression scores were computed for the entire 21-day treatment period. Freeman-Tukey arcsine transformations were applied if necessary. Analyses were conducted using a model with Treatment as a fixed effect and Weight block as a random effect. Pairwise comparisons were made with each lincomycin treatment group and the nonmedicated control group. Two-sided tests were used for the pairwise comparisons.

5. Results: The results for the 21-day treatment period are summarized in Table 4.2.

Table 4.2: Summary of results for the 21-day treatment period

	Least Squares Mean Pen Rate (2-sided p-value vs. control)		
Study Group	Non-Medicated Controls	Lincomycin 40 g/ton	Lincomycin 100 g/ton
% mortality	22.9	21.6 (0.89)	14.1 (0.32)
% abnormal diarrhea score pig days	84.6	58.7 (<0.01)	55.5 (<0.01)
% abnormal clinical impression score pig days	76.5	52.7 (<0.01)	49.4 (<0.01)

Mortality was numerically lower in the 40 grams and 100 grams lincomycin per ton of feed treatment groups compared to the non-medicated group. There was a statistically significant decrease in % abnormal diarrhea score pig days for both the 40 grams ($p<0.01$) and 100 grams ($p<0.01$) lincomycin per ton of feed treatment groups relative to the non-medicated group. In addition, there was a statistically

significant decrease in % abnormal clinical impression score pig days for both the 40 grams ($p<0.01$) and 100 grams ($p<0.01$) lincomycin per ton of feed treatment groups relative to the non-medicated group.

There were no reports of drug-related adverse effects in this study.

6. Conclusions: Lincomycin, fed at a level of 40 g/ton of feed or 100 g/ton of feed for 21 consecutive days, was effective in the control of PPE in swine challenged with an oral *Lawsonia intracellularis* intestinal mucosal homogenate.

V. ANIMAL SAFETY

No animal safety data were required for the approval of this supplement.

VI. HUMAN FOOD SAFETY

No human safety data were required for the approval of this supplement. It was determined by the Agency that this submission, requesting an additional label claim for LINCOMIX® (lincomycin) Type A medicated article, has at this time satisfied the requirements for microbial safety with respect to resistance and pathogen load issues. No additional information was required for this supplemental approval.

VII. 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 LINCOMIX® Type A Medicated Article is effective for the control of porcine proliferative enteropathies (ileitis) caused by *Lawsonia intracellularis* when administered as follows:

1) Feed 100 grams of lincomycin per ton of complete feed as the sole ration for three weeks, or until signs of disease (watery, mucoid or bloody stools) disappear,

2) Feed 100 grams of lincomycin per ton of complete feed as the sole ration for three weeks, or until signs of disease (watery, mucoid or bloody stools) disappear, followed by 40 grams of lincomycin per ton, or

3) Feed 40 grams of lincomycin per ton of complete feed as the sole ration.

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

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals qualifies for THREE 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 the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new claim for the control of porcine proliferative enteropathies (ileitis), for which the supplemental application was approved.

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did not require a reevaluation of the safety or effectiveness data in the parent application.

There are currently no U.S. patents for LINCOMIX® 20 and LINCOMIX® 50 Type A Medicated Articles.

VIII. APPROVED LABELING

Copies of facsimile Type A medicated article labeling and specimen (Blue Bird) Type B and Type C medicated feed labels are attached to this document.

A. LINCOMIX® 20 Type A Medicated Article

B. LINCOMIX® 50 Type A Medicated Article

C. Blue Bird Type B Medicated Feed Swine Mix

D. Blue Bird Type C Medicated Feeds: Swine Ration L20, Swine Ration LC, Swine Ration L100, and Swine Ration PLC

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

Freedom of Information Staff (HFI-35)
Food and Drug Administration, Room 12A16
5600 Fishers Lane
Rockville, Maryland 20857