FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 111-636

LINCOMIX® Soluble Powder

(Lincomycin Hydrochloride)

Sponsored by:

Pharmacia and Upjohn Animal Health.
7000 Portage Road
Kalamazoo, Michigan 49001

Date of Approval:_____

I. GENERAL INFORMATION

NADA NUMBER:	111-636
SPONSOR:	Pharmacia and Upjohn Animal Health 7000 Portage Road Kalamazoo, Michigan 49001
ACCEPTED DRUG NAME:	lincomycin hydrochloride
TRADE NAME:	LINCOMIX® Soluble Powder
MARKETING STATUS:	Over-the-counter
EFFECT OF SUPPLEMENT:	This supplemental approval provides for the assignment of a tolerance of 0.6 ppm for lincomycin in swine liver, a tolerance of 0.1 ppm for lincomycin in swine muscle, and the assignment of an Acceptable Daily Intake (ADI) of 25 micrograms per kilograms per body weight per day for the total residues of lincomycin. In addition, this supplement reduces the slaughter period for drinking water uses of lincomycin in swine from 6 days to 0 days.

II. INDICATIONS FOR USE

Swine--For treatment of swine dysentery (bloody scours).

Broiler chickens--For the control of necrotic enteritis caused by *Clostridium prefringens* susceptible to lincomycin.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

As discussed in the Freedom of Information (FOI) Summary for the original approval of NADA 111-636 dated January 28, 1983.

IV. HUMAN SAFETY

A. Toxicity Studies

Toxicity studies conducted for lincomycin were described in the FOI Summary for NADA 97-505 dated June 1, 1990.

An ADI of 1.5 mg per 60 kg person per day (equivalent to 0.025 mg/kg body weight per day) was assigned based on procedures described in the *Guideline for Establishing a Safe Concentration* (FR 37499-37500, July 22, 1994) and the CVM document, *Guidance: Microbiological Testing of Antimicrobial Drug Residues in Food* (FDA/CVM, January 1996).

B. Calculations of Safe Concentrations (SC):

Based on the procedures described in the CVM document *Guideline for Establishing a Safe Concentration* dated July 1994, safe concentrations of total residues of lincomycin may be calculated:

$$\text{Safe Concentration (SC)} = \frac{\text{Acceptable Daily Intake (ADI)}}{\text{Consumption Value}}$$

The daily consumption values of edible tissues are approximated as 300 g (0.3 kg) for muscle, 100 g (0.1 kg) for liver, 50 g (0.05 kg) for fat/skin, and 50 g (0.05 kg) for kidney.

$$\text{SC (muscle)} = \frac{1.5 \text{ mg/day}}{0.3 \text{ kg/day}} = 5 \text{ mg/kg} = 5 \text{ ppm in muscle}$$

$$\text{SC (liver)} = \frac{1.5 \text{ mg/day}}{0.1 \text{ kg/day}} = 15 \text{ mg/kg} = 15 \text{ ppm in liver}$$

$$\text{SC (fat/skin)} = \frac{1.5 \text{ mg/day}}{0.05 \text{ kg/day}} = 30 \text{ mg/kg} = 30 \text{ ppm in fat/skin}$$

$$\text{SC (kidney)} = \frac{1.5 \text{ mg/day}}{0.05 \text{ kg/day}} = 30 \text{ mg/kg} = 30 \text{ ppm in kidney}$$

C. Determination of Tolerances

Based on data from studies described in the 1998 FOI Summary for NADA 34-025, a tolerance of 0.6 part per million is established for parent lincomycin (marker residue) in the liver (target tissue) of swine. In addition, FDA is retaining the currently codified tolerance of 0.1 ppm for lincomycin in muscle.

D. Withdrawal Times

1. Determination of the Residue Decline of Lincomycin in the Liver Tissue of Swine Treated with Lincomycin Hydrochloride (U-10149A) at 250 mg of Lincomycin Freebase Equivalents per Gallon of Drinking Water

   a. Report Number: 768-7926-95-005

   b. Study Completion: February 13, 1996

   c. Investigator: J.L. Nappier
   Pharmacia & Upjohn Company
   Kalamazoo, Michigan 49001

   d. Substance and Dosage Form: Lincomycin was provided in drinking water.

   e. Species and Strain of Animal: Yorkshire-Hampshire cross swine.

   f. Number of Animals per Group: Two pigs of each sex per dose per time point (24 total).

   g. Levels and Duration of Dosing: Medicated water was provided for 7 consecutive days.

   h. Route of Administration: Orally, via water.

   i. Parameters: Study parameters included assay of parent lincomycin residues in the liver and kidneys of swine at various times after the withdrawal of medicated water. Residue levels were determined by a gas chromatographic method with mass spectrometric detection.

j. Results:

Table 1. Mean levels of parent lincomycin in the livers of swine (ppm) following administration of LINCOMIX® in drinking water for 7 days

Treatment	0 hr	3 hr	6 hr	12 hr	24 hr	48 hr
Control	<0.02	-[a]	-	-	-	-
250 mg/gal.	-	0.20	0.11	0.05	0.02	<0.02

a. - indicates that samples were not taken at that dose/time point

Mean residue levels were found to be below the tolerance at all time points, even at 3 hours after the final dose.

2. Calculation of Withdrawal Times

Applying its statistical method for determining withdrawal periods to the data sets for lincomycin soluble powder, FDA found that the 99% tolerance limit, with 95% confidence, would be below 0.6 ppm in liver at 4 hours. This statistically derived time permits the assignment of a zero-day withdrawal period for swine treated with lincomycin soluble powder at 250 mg/gallon.

E. Regulatory Method:

Refer to the FOI Summary for NADA 97-505 dated February 25, 1976, for information regarding the regulatory method.

V. AGENCY CONCLUSIONS

Based on the revised consumption values provided in the *Guideline for Establishing a Safe Concentration* (FR 37499-37500, July 22, 1994) and the CVM document, *Guidance: Microbiological Testing of Antimicrobial Drug Residues in Food* (FDA/CVM, January 1996), the Center has established new safe concentrations and tolerances for total residues in edible tissues. The acceptable daily intake (ADI) (25 micrograms per kilograms of body weight per day) and the marker residue tolerance of 0.6 ppm for lincomycin in swine liver (target tissue) will be codified under 21 CFR 556.360. In addition, the currently codified tolerance of 0.1 ppm will be retained for lincomycin in swine muscle.

In addition, the slaughter withdrawal period for drinking water uses of lincomycin in swine has been reduced from 6 days to 0 days. The LIMITATIONS section in 21 CFR 520.1263c will be amended to reflect the 0-day withdrawal period.

According to 21 CFR 514.106(b)(2)(x) and (xi), this is a Category II supplement. The approval of this change required a re-evaluation of the slaughter withdrawal period and the tolerance according to current food safety guidance, but did not require a reevaluation of target animal safety or effectiveness data in the parent application.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

LINCOMIX® Soluble Powder is not under any unexpired U.S. patents.

VI. APPROVED PRODUCT LABELING

A copy of the draft facsimile labeling is attached to this document.

A. LINCOMIX® Soluble Powder Packet Labels (40 and 80 gram sizes)

B. LINCOMIX® Soluble Powder Carton Labels (40 and 80 gram sizes)