

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 34-025

LINCOCIN[®] Sterile Solution

LINCOMIX[®] Injectable

(Lincomycin Hydrochloride)

Sponsored by:

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

Date of Approval: _____

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I. GENERAL INFORMATION

NADA NUMBER: 34-025

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

ACCEPTED DRUG NAME: lincomycin hydrochloride

TRADE NAME: LINCOCIN[®] Sterile Solution; LINCOMIX[®] Injectable

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.

II. INDICATIONS FOR USE

Dogs and Cats--Infections caused by Gram-positive organisms, particularly streptococci and staphylococci.

Swine--Treatment of infectious arthritis and mycoplasma pneumonia.

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

As discussed in the Freedom of Information (FOI) Summary for the original approval of NADA 34-025 dated June 6, 1967.

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. Total and Parent Lincomycin Residue Depletion and Determination of Tolerances

Because the tolerance in swine liver for all uses of lincomycin is determined from the data for the injectable dosage form, only data from the intramuscularly treated animals are summarized in Item 1 below.

1. Determination of Lincomycin in the Liver of Intramuscularly and Orally treated swine by GC/MS Analysis
 - a. Report Number: 768-9760-89-001
 - b. Study Completion: February 27, 1989
 - c. Investigator: J.L. Nappier
Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001
 - d. Substance and Dosage Form: Lincomycin was provided either by intramuscular administration or in medicated feed.
 - e. Species and Strain of Animal Used: Yorkshire-Hampshire cross swine.
 - f. Number of Animals: 12 animals were used in the intramuscular administration portion of the study and 27 animals were used in the oral administration portion of the study.
 - g. Levels and Duration of Dosing: Intramuscularly administered lincomycin was dosed at 5 mg lincomycin freebase/lb (11 mg/kg) body weight once daily for 3 days. Orally administered lincomycin was dosed at 20, 40, 100, and 200 g lincomycin freebase/ ton complete feed and fed for 7 days.
 - h. Route of Administration: Lincomycin was administered either intramuscularly or in the feed.
 - i. Study parameters. Total and parent residues of lincomycin were measured.
 - j. Radioisotope used in this study: ¹⁴C labeled lincomycin hydrochloride.
 - k. Measured residue concentrations: Total residues were determined by HPLC with a radioactive flow detector. Parent lincomycin residues were determined by gas chromatography with mass spectrometric detection.

1. Results: The highest residues occurred after intramuscular administration of lincomycin. The intramuscular data were therefore used for determination of tolerance.

Table 1. Mean lincomycin residues in the livers of swine following intramuscular administration of lincomycin hydrochloride at a dose of 5 mg/lb body weight once daily for 3 days

Withdrawal time (hours)	Total lincomycin residues (ppm)	Parent lincomycin residues (ppm)
12	17.5	1.14
24	13.6	0.32
48	3.84	0.02

Using the data summarized in Table 1, depletion curves for both total lincomycin residues and for parent lincomycin residues were determined.

2. Determination of Tolerances for Lincomycin Hydrochloride in Swine.

The residue depletion data for total and parent lincomycin residues from report 768-9760-89-001 were used together with the new lincomycin Safe Concentration of 15 ppm in the liver (target tissue) to determine the tolerance (R_m) for parent lincomycin (marker residue). Based on these data a tolerance of 0.6 ppm 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 an Intramuscular Injection of Lincomycin Hydrochloride (U-10149A) at 11 mg of Lincomycin Free Base Equivalents per kg of Body Weight.
 - a. Report Number: 768-7926-95-004
 - 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 as an injectable solution.
 - 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 (52 total).
- g. Levels and Duration of Dosing: Animals were treated once daily at a dose of 5 mg/lb (11 mg/kg) body weight for 3 consecutive days.
- h. Route of Administration: Intramuscular.
- i. Parameters: Study parameters included assay of parent lincomycin residues in the liver and kidneys of swine at various times after the final dosing. Residue levels were determined by a gas chromatographic method with mass spectrometric detection.
- j. Results:

Table 2. Mean levels of parent lincomycin in the livers of swine (ppm) following intramuscular administration of LINCOMIX® Injectable at a dose of 5 mg/lb (11 mg/kg) once daily for 3 days

Treatment	0 hr	3 hr	6 hr	12 hr	24 hr	48 hr	144 hr
Control	<0.02	- ^a	-	-	-	-	-
LINCOMIX® 100 ^b	-	6.37	4.37	2.42	0.32	0.06	<0.02
LINCOMIX® 300 ^b	-	4.71	4.86	2.48	0.55	0.07	<0.02

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

b-100 and 300 refer to 100 mg/mL or 300 mg/mL formulations of lincomycin injectable.

Mean residue levels were found to be below the tolerance at 24 hours after the final dose.

2. Calculation of Withdrawal Times

Applying its statistical method for determining withdrawal periods to the data sets for LINCOMIX® 100 and LINCOMIX® 300, FDA found that the 99% tolerance limit, with 95% confidence, would be below 0.6 ppm in liver at 39 hours and 36 hours, respectively. Each of those statistically derived times permits the assignment of a 2-day withdrawal period for swine treated intramuscularly with lincomycin at 5 mg/lb BW.

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 kilogram 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.

According to 21 CFR 514.106(b)(2)(xi), this is a Category II supplement. The approval of this change required a re-evaluation of 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.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, the approval for food-producing animals for LINCOCIN[®] Sterile Solution and LINCOMIX[®] Injectable (NADA 34-025) 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 tolerance for lincomycin in swine liver for which the supplemental application was approved.

LINCOCIN[®] Sterile Solution/LINCOMIX[®] Injectable are not under any unexpired U.S. patents.