LINCOMYCIN

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ADDENDUM

To the monograph and addendum prepared by the 54th and 58th meetings of the Committee and published in the FAO Food and Nutrition Papers 41/13 and 41/14

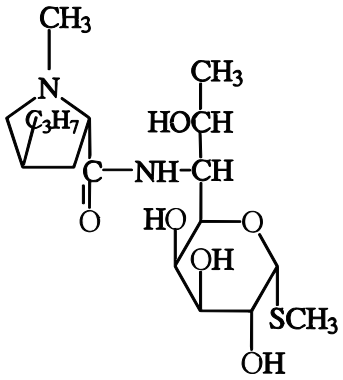
IDENTITY

Chemical Name: Methyl 6,8-dideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-D-erythro-∝-D-galacto-octopyranoside, monohydrochloride monohydrate (CAS name); CAS No. 154-21-2 (Lincomycin), 7179-49-9 (Lincomycin hydrochloride monohydrate); 859-18-7 (Lincomycin hydrochloride anhydrous)

Methyl 6,8-dideoxy-6-(1-methyl-trans-4-propoyl-L-2-pyrolidone-carboxamido)-1-thio-D-erythro-∝-D-galacto-octopyranoside monohydrochloride monohydrate, (IUPAC Name)

Synonyms: Lincomycin, Lincomycin hydrochloride, Upjohn: PNU-10149A, Albiotic® Non-Proprietary name: Lincocin

Structural formula:



Molecular formula: $C_{18}H_{34}N_2O_6S$

Molecular weight: 406.56

INTRODUCTION

Lincomycin is a member of the lincosamide antibiotics is produced by Streptomyces linconensis. It is used alone or in combination with other drugs in poultry and pigs for oral treatment of bacterial enteric infections, control of respiratory infections and growth enhancement. Intramuscular preparations are available for treatment of bacterial enteric and respiratory disease in calves. Combination preparations with neomycin are used as intramammary applications in lactating dairy cattle for treatment of acute mastitis.

Lincomycin was previously considered by the Committee at its fifty–fourth and fifty-eighth meetings. At its fifty-fourth meeting, the Committee established an ADI of 0 – 30 μg/kg body weight and recommended temporary MRLs for cattle, sheep and chicken tissues, and full MRLs for pig tissues. The temporary MRLs that were recommended for cattle tissues are: muscle 100 μg/kg, liver 500 μg/kg, kidney 1500 μg/kg, fat 100 μg/kg. The MRL recommended for milk was 150 μg/kg.

The Committee at the fifty-fourth meeting, also requested information on the following:

1. Data from residue depletion studies in cattle, sheep and chickens which show that lincomycin is the major microbiologically active residue in the edible tissues
2. Data from residue depletion studies showing that lincomycin is the major microbiologically active residue in chickens eggs
3. The results of a residue depletion study in which GC-MS is used to analyse residues in chickens eggs.

At the fifty-eighth meeting, data from new studies with broiler chickens and pigs were provided for evaluation and were used for reviewing the MRLS for chickens and pigs. Since lincomycin was determined in the new studies using three different analytical detection principles, namely, radioactivity, mass spectra and inhibition of microbial growth, it was concluded from the observed dose-linearity that parent lincomycin is the major microbiologically active residue in liver and kidney. From this approach, the Committee recommended full MRLs for chickens and pigs. However, the temporary MRLs for muscle, liver, kidney and fat for cattle and sheep recommended at the fifty-fourth meeting were withdrawn, as the requested information was not provided.

At the sixty-second meeting, the sponsor provided data from four cattle studies of which one was a new study (Barbiers and Smith, 1981), and three were studies that had been evaluated by the fifty fourth meeting (Weber et al, 1981; Hoffman et al, 1996, De Greave et al, 1997). One of the three previously evaluated studies was entirely on pharmacokinetics (Weber et al, 1981) and not tissue residues.

RESIDUES IN FOOD AND THEIR EVALUATION

Metabolism

Metabolic studies of lincomycin were evaluated during the fifty-fourth meeting. No data from cattle studies were available. Data from studies in pigs and chicken have shown that metabolism of lincomycin is rapid and lincomycin is the major component of the total residues.

Residue Depletion Studies with Unlabelled Drug

In the new study, 17 calves were given lincomycin by intramuscular administration at a dose of 5 mg per kg body weight twice on the first day of treatment followed by a single dose of 5 mg/kg body weight per day for four consecutive days (Barbiers and Smith, 1981). Groups of animals were killed at 1, 7, 14, 21 and 28 days after the last treatment. Samples of liver, kidney, muscle, fat and injection site were assayed for lincomycin residues using a microbiological method with a limit of detection (LOD) of 0.1 mg/kg. Results of the microbiological assay are shown in Table 1.

Table 1: Mean residue concentrations of lincomycin in tissues of calves given intramuscular injections of lincomycin (5 mg/kg body of weight) two times on the first day followed by one injection (5 mg/kg body of weight) daily for four consecutive days

Withdrawal time (days)	Mean residue concentrations (mg/kg)				
	Muscle	Liver	Kidney	Fat	Injection site
1	<LOD (5)	0.56 (5)	0.34 (5)	<LOD (3), * (2)	0.26 (5)
7	<LOD (3)	<LOD (3)	<LOD (3)	<LOD (3)	<LOD (3)
14	NA	NA	NA	NA	<LOD (3)
21	NA	NA	NA	NA	NA
28	NA	NA	NA	NA	NA

LOD: limit of detection (0.1 mg/kg - microbiological assay)
NA = samples were not analysed
* Zones did not resemble lincomycin
( ) Number of animals in a group

The second non-GLP study involved twenty veal calves allocated to four groups each of five animals (Hoffman et al, 1996). All the four groups were given lincomycin by intramuscular administration at a dose of 5 mg per kg body weight, the first two doses at 12 hours interval, followed by four doses at 24 hours interval. The animals were killed at 8 hours, 7, 14 and 21 days after the last dose and tissue samples taken and analysed for lincomycin using a validated GC/MS method with a limit of quantitation (LOQ) of 40-47 µg lincomycin free base equivalent /kg tissue. The results are summarised in Table 2.

Table 2: Mean residue concentrations of lincomycin in tissues of calves given intramuscular injections of lincomycin (5 mg/kg body of weight) and spectinomycin (10 mg/kg body of weight) two injections at an interval of 12 hours followed by four injections (5 mg/kg body of weight) at an interval of 24 hours.

Withdrawal time	Mean residue concentrations (mg/kg)				
	Muscle	Liver	Kidney	Fat	Injection site
8 hours	0.72	0.30	3.34	0.10	2.42
7 days	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
14 days	<LOQ	0.07*	<LOQ	<LOQ	<LOQ
21 days	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

* One sample, the remaining 4 assayed were <LOQ
LOQ: limit of quantification (0.040 – 0.047 mg/kg - GC/MS)

In another study conducted according to GLP, sixteen cows were given three consecutive intramammary infusions of 330 mg of lincomycin into each of the four quarters of the udder at 12- hour intervals (De Grave et al, 1997). The animals were killed at 1, 7, 14 and 21 days after treatment and tissue samples taken and analysed by GC/MS, the results are summarised in Table 3.

Table 3: Mean residue concentrations of lincomycin in tissues of lactating cows given at 12-hour intervals three consecutive intramammary infusions containing lincomycin (300 mg) in each quarter

Withdrawal time (days)	Mean residue concentrations (mg/kg)			
	Muscle	Liver	Kidney	Fat
1	0.037	0.23	0.60	<LOQ
7	<LOQ	0.058	<LOQ	<LOQ
14	<LOQ	0.026	<LOQ	<LOQ
21	<LOQ	0.029	<LOQ	<LOQ

LOQ: limit of quantification (0.015 mg/kg - GC/MS)

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

The various methods that have been used to determine the concentrations of lincomycin in foods of animal origin include microbiological assay, thin-layer chromatography-bio-autography, GC with alkaline flame detector and GC/MS. These were reviewed during the fifty-fourth meeting of the Committee. No new methods were submitted for review in the present meeting.

APPRAISAL

The Committee reviewed the data from the new study, and took into consideration the studies that were evaluated during the fifty-fourth meeting. These studies, taken together were considered insufficient to allow any extrapolation, such as the relationship between dose and extrapolated concentration at time zero after drug administration. Thus, the approach used for pig and chicken data during the fifty-eighth meeting of estimating parameters that fit a similar relationship irrespective of the method of residue analysis cannot be applied on the cattle data submitted. Establishment of dose-linearity relationship using data generated by radioactivity measurements, GC/MS and microbiological assay was sufficient to confirm that lincomycin is the major microbiologically active residue in edible tissues of pigs and chicken.

The sponsor has attempted to compare data from two calf studies (Barbiers and Smith, 1981; Hoffman et al, 1996) by estimating tissue residues in different tissues using plasma half-life obtained from a pharmacokinetic study of lincomycin in cows (Weber et al, 1981), but the Committee noted that data from non-ruminating calf studies could not be used to support data from studies on intramammary administration of the drug in cows. Residues of the drug were detected in liver for up to 21 days in cows, unlike in calves where the drug was detected in day one only.

In an attempt to establish MRLs, data from other species were also considered. This was however not possible since studies in pigs and chickens have shown significant differences between animal species in the kinetics of lincomycin residues in tissues. In pigs for example, concentrations of the drug in kidney were three times higher than those in liver, whereas in chickens, the concentrations were similar. At comparable doses, the concentrations of residues in muscle and skin/fat were also higher in pigs than in chickens. Therefore, the Committee concluded that it was not possible to extrapolate the kinetics of lincomycin residues between animal species.

MAXIMUM RESIDUE LIMITS

Since the available information was inadequate, the present Committee could not recommend MRLs for lincomycin in cattle tissues.

REFERENCES

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