European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

LINCOMYCIN

SUMMARY REPORT (2)

1. Lincomycin is an antibiotic derived from *Streptomyces lincolnensis*. It belongs to the lincosamide group which also includes pirlimycin and clindamycin. In veterinary medicine, it is used in mono-preparations and in combination product with other antibiotics such as spectinomycin, sulfadimidine and gentamicin. It is administered to poultry orally, sometimes in the feed or drinking water, at doses equivalent to up to 50 mg/kg bw/day for up to 7 days. It is administered to swine orally, at doses of up to 10 mg/kg bw/day for up to 21 days, or intramuscularly at a dose of 15 mg/kg bw/day for up to 7 days. In calves and sheep, it is administered intramuscularly at doses of up to 15 mg/kg bw/day for up to 4 days. There is also a preparation containing lincomycin, neomycin and methylprednisolone for intramammary administration to dairy cattle; 1 tube (200 mg lincomycin) is administered per teat. Most of the safety studies used either premix grade lincomycin or lincomycin complying with the specification in the US Pharmacopoeia. The grades differed in their lincomycin factor B content, up to 5% in the case of the USP grade and up to 10% in the "premix" grade. It was considered that the differences in specification would not result in significant differences in toxicity.

   In humans, the usual dosage is 500 mg to 2 g lincomycin, orally per day for 7 to 10 days. It may also be administered by intramuscular injection, at doses of 600 to 1800 mg/person/day. Lincomycin has been largely replaced by clindamycin in human therapy.

   A microbiological ADI of 10 µg/kg bw, i.e. 600 µg/person, was previously established for lincomycin.

   Lincomycin is currently entered into Annex I of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Lincomycin	Lincomycin	Bovine	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg 150 µg/kg	Muscle Fat Liver Kidney Milk	

[1] Correction introduced in July 2008 in paragraph 7 concerning sacrifice times, replacing days by hours.

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Currently, lincomycin is also included in Annex III of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Lincomycin	Lincomycin	Porcine	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg	Muscle Skin+fat Liver Kidney	Provisional MRLs expire on 1.1.2001
		Ovine	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg 150 µg/kg	Muscle Fat Liver Kidney Milk	
		Chicken	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg 50 µg/kg	Muscle Skin+fat Liver Kidney Eggs	

Further data were provided to support an entry of lincomycin in Annex I of Council Regulation (EEC) No 2377/90 for pigs, sheep and chicken.

2. The following pharmacokinetic studies were carried out in target species:

   In chickens (1/sex/time point) given twice daily oral boluses of ^{14}C-lincomycin (simulating a dietary dose of 1 mg/bird/day) for 35 days approximately 75% of the administered dose was radiometrically detected in the excrement 1 to 3 days after dosing while approximately 30% was detectable by microbiological assay. When chickens (2/time point) were fed a diet containing 11 mg ^{14}C-lincomycin/kg for 35 days then 2 times 0.5 mg ^{14}C-lincomycin/day by oral bolus, the 'total' residue concentrations in bile ranged from 5 194 to 10 µg equivalents/kg after 1 hour to 3-day withdrawal periods, respectively.

   In pigs, oral doses of 4.4, 11 (the therapeutic dose), and 22 mg lincomycin/kg bw resulted in therapeutic serum concentrations being reached by 0.5 hour after dosing. Peak serum concentrations of 1.8, 3.9 and 5.1 mg/ml were reached within an hour and less than 4% of the plasma lincomycin was protein bound. In studies where pigs were administered lincomycin by intravenous or oral routes the distribution of liver metabolites were determined by thin layer chromatography (TLC) to have been quantitatively the same. An oral bolus or intravenous injection of 10 mg lincomycin/kg bw resulted in plasma t½ values of 3.4 and 2.0 hours, respectively. In another pig study, the half-life for liver and kidney tissues after oral administration of lincomycin was reported to have been 24 and 29 hours, respectively.

   In sheep, intramuscular injection of 20 mg lincomycin/kg bw resulted in a plasma C_{max} of 12.3 µg/ml after 1 hour and a milk C_{max} of 25 200 µg/l after 2 hours.

3. When chickens (2/time point) were fed a diet containing 11 mg lincomycin/kg for 35 days then 2 times 0.5 mg ^{14}C-lincomycin/day by oral bolus for 12 days, followed by 1 hour, 1, 2 and 3 day withdrawal periods, 'total' tissue residue concentrations were highest in the liver (mean values 165, 30, 13, and 5 µg equivalents/kg, respectively). Kidney tissues contained mean residue concentrations of 101, 21, 8, and 4, respectively. Skin and fat tissues all contained total residue concentrations below 5 µg equivalents/kg.

In another radiometric chicken study (3/sex/time point), birds were dosed with 5.1 to 6.6 mg ^{14}C-lincomycin/kg bw/day for 7 consecutive days in drinking water. The mean total residue concentrations at 0, 0.5, 1, 2, 4 and 7 day time points after treatment were determined to have been: 1580, 503, 224, 107, 28 and 20 µg equivalents/kg in liver; 1260, 560, 230, 100, 30 and 10 in µg equivalents/kg in kidney; 52, 27, 27, less than 5, less than 5, less than 5 µg equivalents/kg in muscle and 132, 51, 65, 28, 17 and 5 µg equivalents/kg in skin plus fat, respectively. In this study, lincomycin in the liver accounted for 20 and 5 % of the total residues at 0 and 96 hour time points respectively. At the same time points, liver samples also contained lincomycin sulphoxide (40 and 6 %), N-desmethyl-lincomycin (4% to less than the limit of quantification), N-desmethyl-lincomycin sulphoxide (4% and 4%) and lincomycin-3-5'-adenylate (18 to 57%). The tissue residue distribution in this study was different from that found in the non-radiolabelled studies conducted in other species, hence was not used when elaborating MRLs.

4. In a non-radiolabelled chicken study, residues in tissues from birds (4/time point) dosed with 264 mg lincomycin/l in the drinking water for 7 days were determined by a microbiological assay. It was claimed that all tissues contained lincomycin concentrations below the limit of quantification (not given), between 0 and 48 hours after treatment, except for one liver (980 µg/kg at 0 hour withdrawal) and one kidney (850 µg/kg at 6 hour withdrawal) sample.

5. In laying hens (6 animals per time point), oral boluses of 0.55 mg ^{14}C-lincomycin every 12 hours for 12 consecutive days resulted in whole egg total residue concentrations ranging from 1.2 to 12.0 µg equivalents/kg during the treatment period and 1 to 4 µg equivalents/kg 3 days after treatment (the yolk concentrations were approximately 3 times those in egg white). In the same study, mean tissue residue concentrations at 4, 28 and 76 hours after treatment were found to be 141, 24 and 6 µg equivalents/kg in liver; 152, 21, and 6 µg equivalent/kg in kidney; 20, 13, and 10 µg equivalents/kg in muscle and 19, 14, and 3 µg equivalents/kg in skin/fat, respectively.

6. In pigs (3 animals per time point) dosed intramuscularly with 11 mg ^{14}C-lincomycin/kg bw/day for 3 days, mean tissue residue concentrations 12, 24 and 48 hours after treatment were determined by liquid scintillation counting (LSC) to have been 17 300, 13 600 and 3 840 µg equivalents/kg in liver; 12 000, 5 750, and 3 080 µg equivalents/kg in kidney; 393, 127, and 138 µg equivalents/kg in muscle, 590, 260, and 200 µg equivalents/kg in fat and 1 050, 863, and 585 µg equivalents/kg in injection site muscle tissue, respectively.

   In another radiometric pig study (3 animals per sex and time point), where animals were fed as diet containing 20 to 200 mg/kg lincomycin, a microbiological assay detected less than 10% of the total tissue residues determined by LSC.

7. In pigs dosed via their feed (3 animals per sex and time point: approximately 1.3 to 2.3 mg lincomycin/kg bw/day for 61 days) the lincomycin concentrations (microbiological assay) were highest in kidney tissues (maximum values of 280 µg/kg) at 0 withdrawal, respectively. All other tissues contained lincomycin concentrations below the limits of quantification of the microbiological assay method (less than 100 µg/kg). In another non-radiolabelled pig study, the animals (3/sex/time point) were dosed via their drinking water: 7.8 to 10.7 mg/kg bw/day for 10 days. The lincomycin concentrations (microbiological assay) were highest in kidney tissues (maximum values of 250 µg/kg) at 0 days withdrawal. All other tissues contained lincomycin concentrations below the limit of quantification (50 µg/kg) of the analytical method. In both studies the lincomycin concentrations determined by microbiological assay were the same as those later determined by GC/MS.

   Following intramuscular administration of 11 mg lincomycin/kg bw to pigs (3 animals per time point) all tissue sample were reported to have contained lincomycin concentrations below 100 µg/kg 1 day after treatment and at time points thereafter (method of analysis not given).

   Three further non-radiolabelled residue depletion studies, using the updated and validated GC/MS routine analytical method were presented.

Pigs (4 animals per time point) were intramuscularly injected, daily for 3 consecutive days, with 10 mg lincomycin/kg bw and sacrificed at 3, 6, 12, 24, 48 and 144 hours after treatment. Liver samples contained mean concentrations of 4 710, 4 860, 2 480, 552, 65 and less than 17 µg lincomycin/kg, respectively. Kidney samples contained 20 900, 18 400, 7 470, 1 360, 239 and less than 60 µg lincomycin/kg, respectively. Muscle samples contained 2 460, 1 840, 638, 85, less than 17 and less than 17 µg lincomycin/kg, respectively. Fat samples contained 468, 456, 204, 39, less than 17 and less than 17 µg lincomycin/kg, respectively. Twelve days after treatment the theoretical maximum daily intake of microbiologically active residue was 151 µg (25% ADI), these data were used in-part when determining MRLs for porcine tissues.

Pigs (4/time point) were fed a diet containing 220 mg lincomycin/kg for 7 days and sacrificed on days 3, 6, 12, 24 and 48 after the end of treatment. Liver samples contained mean concentrations of 272, 169, 75, 40 and less than 17 µg lincomycin/kg, respectively. Kidney samples contained 904, 427, 278, 108 and less than 60 µg lincomycin/kg, respectively. Muscle samples contained 74, 31, less than 17, less than 17 and less than 17 µg lincomycin/kg, respectively. Fat samples contained 31, 17, less than 17, less than 17, and less than 17 µg lincomycin/kg, respectively. Three days after treatment the theoretical maximum daily intake of microbiologically active residue was 96 µg (16% ADI), these data were used in-part when determining MRLs for porcine tissues.

Pigs (4/time point) were given water containing 66 mg lincomycin/l for 7 days and sacrificed on days 3, 6, 12, 24 and 48 after the end of treatment. Liver samples contained mean concentrations of 204, 105, 53, 17 and less than 17 µg lincomycin/kg, respectively. Kidney samples contained 647, 296, 161, less than 60 and less than 60 µg lincomycin/kg, respectively. Muscle samples contained 42, 28, less than 17, less than 17 and less than 17 µg lincomycin/kg, respectively. All fat samples contained less than 17 µg lincomycin/kg. Three days after the end of treatment the theoretical maximum daily intake of microbiologically active residue was 66 µg (11% ADI), these data were used in-part when determining MRLs for porcine tissues. Data for porcine skin plus fat in natural proportions were not provided.

8. A further non-radiolabelled residue depletion study in sheep, using the updated and validated GC/MS routine analytical method was presented.

   Sheep (5/time point) were intramuscularly injected with 5 mg lincomycin/kg bw (and 10 mg/kg spectinomycin) for 3 consecutive days and sacrificed at 8 hours, 7, 14, and 21 days after the last treatment. Liver samples contained mean residues of 4 340, 27, less than 17 and less than 17 µg lincomycin/kg, respectively. Kidney samples contained 9 150, less than 17, less than 17 and less than 17 µg lincomycin/kg, respectively. Residue depletion data for muscle and fat samples were not presented. Notwithstanding the absence of data for sheep muscle and fat samples, the MRLs established for bovine and proposed for porcine tissues are also proposed for ovine tissues as the relative distribution of lincomycin in the 8 hour liver and kidney samples were the same as that observed in bovine and porcine tissues at later time points.

9. Lactating sheep (n = 5) were intramuscularly dosed alternatively with 20 mg lincomycin/kg bw and 20 mg clindamycin/kg bw in a crossover regime at 3 week intervals, then with 15 mg lincomycin/kg bw or 15 mg clindamycin/kg bw in a crossover regime at 2 hour intervals. During the treatment period when a 20 mg lincomycin/kg bw dose was applied, milk concentrations reached a C_{max} of 25 200 µg/l after 2 hours.

10. A routine analytical method for the determination of the marker residue, lincomycin, based on GC with MS detection was described in ISO 78/2 format. The method had been validated in accordance with Volume VI of the Rules Governing Medicinal Products in the European Community for all edible porcine, ovine and chicken tissues, chicken eggs, and ovine milk. The limits of quantification of the method were 17, 35, 60 and 60 µg/kg in porcine muscle, skin + fat, liver and kidney; 17, 35, 17, 17 and 35 µg/kg in ovine muscle, fat, liver, kidney and milk; and 17, 35, 17, 17 and 31 µg/kg in chicken muscle, skin + fat, liver, kidney and eggs.

Conclusions and recommendation

Having considered that:

- a microbiological ADI of 10 µg/kg bw, i.e. 600 µg/person, has previously been established,
- lincomycin represents all of the microbiological activity of incurred residues in tissues, milk and eggs; the parent compound is therefore recommended as the marker residue in all target species,
- the routine analytical method, based on GC-MS, has now been validated for all edible porcine, ovine and chicken tissues, chicken eggs, and ovine milk,
- the tissue distribution of lincomycin being the same in bovine, ovine and porcine species,
- the distribution of total residues in chickens indicated that the daily consumption of residues would be below the ADI at all time points after treatment,

the Committee recommends the inclusion of lincomycin in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Lincomycin	Lincomycin	Porcine	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg	Muscle Skin + fat Liver Kidney	
		Ovine	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg 150 µg/kg	Muscle Fat Liver Kidney Milk	
		Chicken	100 µg/kg 50 µg/kg 500 µg/kg 1500 µg/kg 50 µg/kg	Muscle Skin + fat Liver Kidney Eggs	

Based on these MRL values the maximum daily intake of microbiologically active residue will be 383 µg/person/day equivalent to 64% of the ADI.