The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/MRL/802/01-FINAL
September 2001

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SPECTINOMYCIN

SUMMARY REPORT (4)

1. Spectinomycin is an aminocyclitol antibiotic produced by *Streptomyces spectabilis*. It exerts its bacteriostatic effect by binding to the 30S subunit of bacterial ribosomes and inhibiting the translation of protein synthesis. Spectinomycin is indicated for use by the oral and intramuscular route, often in conjunction with lincomycin, in the treatment of a variety of enteric, respiratory and other infections of cattle, sheep, pigs and poultry. In cattle including lactating cows, products are given by intramuscular injection at of 30 mg/kg bw/day or subcutaneous injection at 15 mg/kg bw/day, both for 5 consecutive days. In pigs, spectinomycin is administered in the diet at 22 mg/kg feed for 21 consecutive days or by intramuscular injection at 11 mg/kg bw/day. In sheep, 50 mg/animal is administered to new-born lambs. In chickens, spectinomycin is administered orally in drinking water and feed at doses equivalent to 100 mg/kg bw/day for 3 to 7 days.

   A microbiological ADI of 40 µg/kg (i.e. 2400 µg/person) has previously been established by the Committee for Veterinary Medicinal Products. The hydrochloride and sulphate salts are similar in their acute toxicity and pharmacokinetics, and so a single MRL for spectinomycin base was considered justified.

   Spectinomycin is currently entered into 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
Spectinomycin	Spectinomycin	Bovine, porcine, chicken	1000 µg/kg 5000 µg/kg 300 µg/kg 500 µg/kg	Liver Kidney Muscle Fat	
		Bovine	200 µ/kg	Milk	

   Spectinomycin is also currently entered into Annex III of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Spectinomycin	Spectinomycin	Ovine	2000 µg/kg 5000 µg/kg 300 µg/kg 500 µg/kg	Liver Kidney Muscle Fat	Provisional MRLs expire on 1 January 2002. Not for use in animals producing milk for human consumption.
		Chicken	200 µg/kg	Eggs	

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This assessment addresses only the additional data provided in respect to sheep.

2. Pharmacokinetic data indicate that absorption is poor *via* the oral route in humans and in animals, but rapid and extensive after intramuscular injection. After oral administration of 100 and 500 mg/kg bw to dogs, mean peak serum concentrations were around 22 µg/ml and 80 µg/ml respectively. Spectinomycin is not extensively bound to proteins either in serum or in milk. Plasma elimination half lives range from 1 to 3 hours in various species (sheep, cattle, dog, and human) when administered via the oral, intramuscular and intravenous routes. Spectinomycin is rapidly and extensively excreted in the urine. The data available suggest that spectinomycin is not extensively metabolised in animals or in humans.

3. After administration of 10 mg spectinomycin (plus 5 mg lincomycin)/kg bw to sheep by intramuscular and intravenous routes the areas under the curves (AUC) were 71 and 73 µg·h/ml, respectively. After intramuscular administration the Cmax was 23 µg/ml and the tmax was 0.8 hours with all of the dose being bioavailable.

4. Sheep were given intramuscular doses 30 mg spectinomycin/kg bw/day for 5 consecutive days the groups of 4 animals were killed on days 1, 3, 7, 10, 14 and 18 after the last (5th) dose. The spectinomycin concentrations in tissue samples were determined by a validated method based on HPLC with colorimetric detection. The average spectinomycin concentrations in liver, kidney muscle and fat were 4 780, 100 000, 434 and 610 µg/kg, 1 day after the last dose. These residue concentrations depleted as follows: 3 179, 47 419, 253, and less than 250 µg/kg, at 3 days; 1 242, 10 314, less than 65 and less than 119 µg/kg, at 7 days; 903, 3 890, less than 65 and less than 119 µg/kg at day 10; 834, 1 754, less than 65 and 461 µg/kg at day 14 and less than 500, 781, less than 65 and less than 119 µg/kg, 18 days after the last dose. Over the same withdrawal period injection site (5th) muscle tissue spectinomycin concentrations depleted from 16 300 to 168 µg/kg. The high low and average spectinomycin concentrations were reported; no other raw data were presented.

   In another study, sheep were treated with 10 mg spectinomycin/kg bw (plus 5 mg lincomycin) by intravenous route, then 3 weeks later by intramuscular route. Groups for 5 sheep were killed at 8 hours, 7, 14 and 21 days after administration of the second dose. The concentrations of spectinomycin in tissues were determined by HPLC. Eight hours after treatment the highest spectinomycin concentrations were found in kidney, followed by liver, muscle and fat (12 000, 630, 288 and 194 µg/kg, respectively). The spectinomycin concentrations in kidney, liver, muscle and fat were 514, 104, less than 40 and less than 40 µg/kg at 7 days; 96, 72, less than 40 and less than 40 µg/kg at 14 days and less than 40 µg/kg in all tissues at 21 days.

5. In a new study, sheep were dosed with 11 mg spectinomycin and 5.5 mg lincomycin/kg bw per day for 3 consecutive days. Sheep were killed on days 0, 1, 2, 5 and 15 after dosing. The concentrations of spectinomycin and total antimicrobial residue were determined by HPLC and microbiological assay respectively. Mean spectinomycin concentrations in kidney were 8270, 5360, 3580, 3050 and 130 µg/kg on days 0, 1, 2, 5 and 15 days after dosing. Mean spectinomycin concentrations in liver were 490, 368, 324, 178 and 51 µg/kg on days 0, 1, 2, 5 and 15 days after dosing. Mean spectinomycin concentrations in muscle 136 and 55 µg/kg on days 0 and 1 after dosing and not detected thereafter. Mean spectinomycin concentrations in fat were 66 and 37 on days 0 and 1 after dosing and not detected thereafter.

   Spectinomycin represented about 80% of the total residue with antimicrobial activity in ovine kidney for up to 5 days after treatment; residues in liver, muscle and fat were too low for the percentage in these tissues to be determined.

6. An analytical method based on HPLC with residue derivatisation and UV detection to determine spectinomycin in ovine tissues and milk has been validated in accordance with Volume VI of the Rules Governing Medicinal Products in the European Community and presented in the ISO 78/2 format. The limits of quantification of the method were 500 µg/kg in liver, 1000 µg/kg in kidney, 100 µg/kg in muscle, 100 µg/kg in fat and 100 µg/kg in sheep milk.

Conclusions and recommendation

Having considered that:

- an microbiological ADI of 40 µg/kg bw (i.e. 2 400 µg/person) has previously been established,
- spectinomycin was identified as the marker residue and represents about 80% of the total residue with antimicrobial activity in ovine kidney for up to 5 days after treatment; residues in liver, muscle and fat were too low for the percentage in these tissues to be determined,
- as the disposition of spectinomycin in ovine tissues is similar to that found in bovine, porcine and chicken tissues, full MRLs for ovine tissues can be proposed in line with the Annex I entry for these other species,
- a validated routine analytical methods for determining the presence of spectinomycin in the relevant tissues of sheep is available;

the Committee for Veterinary Medicinal Products recommends the inclusion of spectinomycin 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
Spectinomycin	Spectinomycin	Ovine	300 µg/kg 500 µg/kg 1000 µg/kg 5000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.

Based on these MRLs values, and the MR:TR ratios (i.e. 80% in ovine kidney, 20% estimated in other bovine and ovine edible tissues, and 100% in milk), the daily maximum intake of total residue will represent approximately 70% of the ADI.