



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SPECTINOMYCIN (Sheep and chicken eggs)

SUMMARY REPORT (2)

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 chicken, 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 III 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, poultry	300 µg/kg 500 µg/kg 2000 µg/kg 5000 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1 July 2000
		Bovine	200 µg/kg	Milk	

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

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 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively. After intramuscular administration the C_{max} was 23 $\mu\text{g}/\text{ml}$ and the t_{max} was 0.8 hours with all of the dose being bioavailable.
4. No pharmacokinetic data were presented for chicken.
5. 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 $\mu\text{g}/\text{kg}$, 1 day after the last dose. These residue concentrations depleted as follows: 3 179, 47 419, 253, and less than 250 $\mu\text{g}/\text{kg}$, at 3 days; 1 242, 10 314, less than 65 and less than 119 $\mu\text{g}/\text{kg}$, at 7 days; 903, 3 890, less than 65 and less than 119 $\mu\text{g}/\text{kg}$ at day 10; 834, 1 754, less than 65 and 461 $\mu\text{g}/\text{kg}$ at day 14 and less than 500, 781, less than 65 and less than 119 $\mu\text{g}/\text{kg}$, 18 days after the last dose. Over the same withdrawal period injection site (5th) muscle tissue spectinomycin concentrations depleted from 16 300 to 168 $\mu\text{g}/\text{kg}$. 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 $\mu\text{g}/\text{kg}$, respectively). The spectinomycin concentrations in kidney, liver, muscle and fat were 514, 104, less than 40 and less than 40 $\mu\text{g}/\text{kg}$ at 7 days; 96, 72, less than 40 and less than 40 $\mu\text{g}/\text{kg}$ at 14 days and less than 40 $\mu\text{g}/\text{kg}$ in all tissues at 21 days.

6. When laying hens were treated with spectinomycin at 220, 330, and 440 mg/kg feed or 500 mg/l in drinking water all of the eggs produced contained total residue with antimicrobial activity at concentrations below 2 000 $\mu\text{g}/\text{kg}$ (limit of quantification of a microbiological plate assay).
7. There was no information concerning the ratio of marker to residues with antimicrobial activity in sheep and chicken eggs.
8. An analytical method based on HPLC with residue derivatisation and UV detection to determine spectinomycin in ovine tissues and milk and chicken's eggs 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 1000 $\mu\text{g}/\text{kg}$ in liver, 1000 $\mu\text{g}/\text{kg}$ in kidney, 100 $\mu\text{g}/\text{kg}$ in muscle, 100 $\mu\text{g}/\text{kg}$ in fat, 100 $\mu\text{g}/\text{kg}$ in eggs and 100 $\mu\text{g}/\text{kg}$ in sheep milk.

Conclusions and recommendation

Having considered that:

- an microbiological ADI of 40 µg/kg bw (i.e. 2 400 µg/kg bw/person) has previously been established,
- spectinomycin is proposed as the marker residue for ovine tissues and chicken's eggs but the proportion of the total residue with antimicrobial activity that this represents in the target tissues had not been established,
- as the disposition of spectinomycin in ovine tissues is similar to that found in bovine, porcine and chicken tissues, provisional MRLs for ovine tissues can be proposed in line with the Annex III entry for these other species,
- provisional MRLs for eggs can be set at twice the limit of quantification of the routine analytical method,
- a validated routine analytical methods for determining the presence of spectinomycin in the relevant tissues of sheep and chickens eggs species is available;

the Committee for Veterinary Medicinal Products recommends the inclusion of spectinomycin in Annex III 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 2000 µg/kg 5000 µg/kg	Muscle Fat Liver Kidney	No for use in animals from which milk is produced for human consumption. Provisional MRLs expire on 1.1.2002
		Chicken	200 µg/kg	Eggs	Provisional MRLs expire on 1.1.2002

Based on these MRLs values, the daily maximum intake of marker residue will represent approximately 37% of the ADI; this allows for the total residue correction.

Before the Committee can consider the inclusion of spectinomycin for ovine species and chicken eggs in Annex I to Council Regulation (EEC) No 2377/90, the points included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The applicant should determine the ratio of marker residue to that of total residue with antimicrobial activity in the target tissues in sheep and in chicken eggs.
2. Residue depletion studies should be presented, monitoring the depletion of marker residue, in chicken eggs.