



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TIAMULIN

SUMMARY REPORT (3)

1. Tiamulin is a diterpene antimicrobial with a pleuromutilin chemical structure similar to that of valnemulin. The activity of tiamulin is largely confined to gram-positive micro-organisms and *mycoplasma*. Tiamulin acts by inhibiting protein synthesis at the ribosomal level. In veterinary medicine, tiamulin is used for treatment and prophylaxis of dysentery, pneumonia and mycoplasmal infections in pigs and poultry. Tiamulin is available as a 2, 10 or 20% premix for pigs and poultry, a 12.5% solution or 45% water soluble powder for addition to drinking water for pigs and poultry, or a 10% injectable formulation for pigs. Dietary doses are 100 to 200 mg/kg feed for 5 to 10 days, and up to 6 weeks at 50 mg/kg feed for pigs, and 160 to 320 mg/kg feed for poultry. In drinking water, doses of 4 to 25 mg/kg bw for up to 1 week are used for pigs, and doses of 30 to 60 mg/kg bw for 3 to 5 days in poultry. Intramuscular doses of 10 to 20 mg/kg bw may be given daily for up to 5 days.

Tiamulin is not used in human medicine.

A toxicological ADI of 0.03 mg/kg bw, i.e. 1.8 mg per person, was established by applying a safety factor of 100 to the NOEL of 3 mg/kg bw/day, using 26 and 54-week studies in dogs, based on electrocardiogram changes and raised serum alanine aminotransferase and lactate dehydrogenase concentrations at higher doses.

Currently, tiamulin is included in Annex I of Council Regulation (EEC) No. 2377/90 for porcine and chicken:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Tiamulin	Sum of metabolites that may be hydrolysed to 8- α -hydroxytiamulin	Porcine	100 μ g/kg 500 μ g/kg	Muscle Liver	
		Chicken	100 μ g/kg 100 μ g/kg 1000 μ g/kg	Muscle Skin+Fat Liver	
	Tiamulin		1000 μ g/kg	Eggs	

and in Annex III of Council Regulation (EEC) No. 2377/90 for turkey as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Tiamulin	Sum of metabolites that may be hydrolysed to 8- α -hydroxytiamulin	Turkey	100 μ g/kg 100 μ g/kg 300 μ g/kg	Muscle Skin+Fat Liver	Provisional MRLs expire on 1.7.2001

Further to the receipt of an application to the extension of MRLs for tiamulin to rabbits, the CVMP recently recommended the establishment MRLs for tiamulin in rabbits in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Tiamulin	Sum of metabolites that may be hydrolysed to 8- α -hydroxymutilin	Rabbit	100 $\mu\text{g}/\text{kg}$ 500 $\mu\text{g}/\text{kg}$	Muscle Liver	

Further data were provided to support an entry of tiamulin in Annex I of Council Regulation (EEC) No 2377/90 for turkeys.

- In turkeys (6 per sex per time point), given *ad libitum* access to drinking water containing 0.025% w/v for 5 consecutive days, the concentrations of metabolites that could be hydrolysed to form 8- α -hydroxymutilin, as detected by gas chromatography with electrochemical detection, were less than 50 $\mu\text{g}/\text{kg}$ in muscle. In 1 out of 6 skin + fat samples 8- α -hydroxymutilin concentrations of 72, 90 and 71 $\mu\text{g}/\text{kg}$ were detected at 0 hours, 8 hours, and 1 day after treatment, respectively. Two days after treatment all skin + fat samples contained a concentration of residues that can be hydrolysed to 8- α -hydroxymutilin of less than 50 $\mu\text{g}/\text{kg}$. The average 8- α -hydroxymutilin concentrations in liver, 6 combined samples from 6 pairs of birds per time point, were 905, 518, 527, 253 and 228 $\mu\text{g}/\text{kg}$ at 0 hours, 8 hours, 1 day, 2 days and 3 days after treatment, respectively.
- In a study in which turkeys were given 50 mg ^3H -tiamulin/kg bw/day for 5 consecutive days, the total residue concentrations, as determined by liquid scintillation counting, in liver, muscle and skin + fat were 87 000, 3150, and 4600 μg equivalents/kg, respectively, 2 hours after dosing. At the same time point, mean residues of 8- α -hydroxymutilin were 8300, 110 and 120 $\mu\text{g}/\text{kg}$ in liver, muscle and skin + fat, respectively. It was concluded that 8- α -hydroxymutilin was an appropriate marker residue for turkeys and represented approximately 10, 4 and 3% of the total residues in liver, muscle and skin + fat, respectively.
- A routine analytical method for monitoring the use of tiamulin, based on gas chromatography with electrochemical detection, was provided. Metabolites in turkey tissues were extracted in organic solvent, hydrolysed to a common α -hydroxymutilin derivative and measured as 8- α -hydroxymutilin equivalents. Data were presented for the analyses of blank tissues fortified with tiamulin at 20, 200 and 2000 $\mu\text{g}/\text{kg}$ 5 times in a single batch analysis. The absence of data pertaining to the reproducibility of analyses and stability of residues in tissues was noted, however, the validation data were considered sufficient to meet with the requirements of the CVMP Note for Guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/153a/97-FINAL). The limits of quantification were 20 $\mu\text{g}/\text{kg}$ in all relevant turkey tissues.

Conclusions and recommendation

Having considered that:

- an ADI of 0.03 mg/kg bw, i.e. 1.8 mg per person, was established,
- the sum of the residues that may be hydrolysed to form 8- α -hydroxymutilin were identified as the marker residue in tissues of turkeys,
- total residue concentrations in the liver of turkeys were more than ten times higher than those found in kidney, muscle or skin + fat (skin and fat in natural proportions),
- the marker residues represent approximately 10, 4, and 3% of the total residues in turkey liver, muscle and skin + fat 2 hours after treatment,
- A validated analytical method for monitoring 8- α -hydroxymutilin in turkey liver, muscle, skin + fat, with a limit of quantification of 20 μ g/kg in these tissues is available,

the Committee for Veterinary Medicinal Products recommends the inclusion of tiamulin 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
Tiamulin	Sum of metabolites that may be Hydrolysed to 8- α -hydroxymutilin	Turkey	100 μ g/kg 100 μ g/kg 300 μ g/kg	Muscle Skin + fat Liver	

Based on these MRLs values and that for eggs, the daily intake will represent about 90% of the ADI.