The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TIAMULIN
(Extension to rabbits)

SUMMARY REPORT (2)

1. Tiamulin is a diterpene antimicrobial with a pleuromutilin chemical structure. The uses of tiamulin in pigs, chickens and turkeys were evaluated by the Committee for Veterinary Medicinal Products (CVMP). A toxicological ADI of 30 µg/kg bw (1800 µg per 60 kg person) was derived, based on a NOEL of 3 mg/kg bw/day established in the 26-week and 54-week studies in dogs and a safety factor of 100.

   Tiamulin is currently included 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	Porcine	100 µg/kg 500 µg/kg	Muscle Liver	
		Chicken	100 µg/kg 100 µg/kg 1000 µg/kg	Muscle Skin + fat Liver	
	Tiamulin	Chicken	1000 µg/kg	Eggs	

   and 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
Tiamulin	Sum of metabolites that may be hydrolysed to 8-α-hydroxymutilin	Turkey	100 µg/kg 100 µg/kg 300 µg/kg	Muscle Skin + fat Liver	Provisional MRLs expire on 1.7.2001

   An application has now been received for the extension of the MRLs to rabbits, according to the general strategy described in the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL) and based on the MRLs in pig as a major species. Tiamulin would be administered to rabbits in the feed, at a dose equivalent to 11 mg/kg bw/day for 21 days.

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2. Rabbits were administered tiamulin in the diet, at a target dose of 11 mg/kg bw/day of tiamulin for 21 days. The mean achieved dose was 13 mg/kg bw/day. Groups of rabbits were killed (6 per time point) at 0 and 8 hours and 1, 2 and 3 days after the end of treatment. Concentrations of the proposed marker residue, the sum of metabolites hydrolysed to 8-α-hydroxymutilin, in edible tissues, were determined using the proposed routine analytical method based on gas liquid chromatography (GLC) with electon capture detection. For all tissues, the limit of quantification was 20 µg/kg. The mean residues of 8-α-hydroxymutilin in rabbit kidney were 35 µg/kg, immediately after the end of treatment and were below the limit of quantification at all later time points. In liver, mean residues immediately after the end of treatment were 529 µg/kg and depleted to 283 µg/kg at 8 hours and 127 µg/kg at 1 day, 63 µg/kg at 2 days and 37 µg/kg at 3 days after the end of treatment. Residues in all samples of muscle and fat, at all time points, were below the limit of quantification.

3. No data were provided on the ratio between the marker residue and the total residues in edible tissues of rabbits, but this was considered acceptable for a minor species. The marker residue previously established for pigs (the sum of the residues that can be hydrolysed to form 8-α-hydroxymutilin) was quantifiable in the edible tissues of rabbits. Therefore, the same marker residue was retained for rabbit tissues, in accordance with EMEA/CVMP/153a/97-FINAL. The values of the MRL already established for porcine liver and muscle were also retained for rabbit liver and muscle.

4. The proposed routine analytical method for the determination of residues in the edible tissues of rabbits was essentially the same as that previously accepted for the determination of residues in porcine and chicken tissues and was based on GLC with electron capture detection. The metabolites in tissues were hydrolysed to a common α-hydroxymutilin derivative and measured as 8-α-hydroxymutilin equivalents. The method was validated for the edible tissues of rabbits; the limit of quantification for rabbit liver, kidney, muscle and fat was 20 µg/kg.

Conclusions and recommendation

Having considered that:

- an ADI of 30 µg/kg bw (1800 µg per 60 kg person) was established for tiamulin,
- the marker residue already established for pigs (the sum of the residues that can be hydrolysed to form 8-α-hydroxymutilin) was quantifiable in the edible tissues of rabbits and was therefore retained as the marker residue,
- the value of the MRLs already established for porcine muscle and liver were also retained for rabbit muscle and liver,
- a validated analytical method for the determination of the marker residue in the edible tissues of rabbits was available;

the Committee for Veterinary Medicinal Products recommends the inclusion of MRLs for tiamulin in rabbit tissues 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	Rabbit	100 µg/kg 500 µg/kg	Muscle Liver	

Based on these MRLs values, the daily intake from the consumption of rabbit tissues and hens' eggs will represent about 90% of the ADI.