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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TILMICOSIN
(Extension to rabbits)

SUMMARY REPORT (5)

1. Tilmicosin is a macrolide antibiotic synthesised from tylosin. It has an antibacterial spectrum similar to tylosin with enhanced activity against *Pasteurella multocida* and *Pasteurella haemolytica*.

   Tilmicosin has been evaluated by CVMP for its use in chicken, cattle, pigs and sheep. A microbiological ADI of 0.004 mg/kg bw was established (240 µg/day for a 60 kg person), based on a NOEL of 0.4 mg/kg bw in an *in vivo* study with HFA rats, and a safety factor of 100.

   Tilmicosin is entered into Annex I of Council Regulation (EEC) No 2377/90 for cattle, pigs, chicken and sheep in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Tilmicosin	Tilmicosin	Bovine, ovine, porcine	50 µg/kg 50 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	
		Ovine	50 µg/kg	Milk	
		Chicken	75 µg/kg 75 µg/kg 1000 µg/kg 250 µg/kg	Muscle Skin + fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption

   and has been recommended by the CVMP for entry 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
Tilmicosin	Tilmicosin	Bovine	40 µg/kg	Milk	Provisional MRL expires on 1.1.2001

   An application has now been submitted for an extension of the MRL to rabbits according to the general strategy reported in the 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 cattle as a major species. In rabbits, tilmicosin is indicated for the treatment of respiratory disease, and is given as a single subcutaneous injection at a dose of 10 mg/kg bw.

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3. After a single subcutaneous injection of 25 mg/kg bw to rabbits, the mean tilmicosin serum levels reached a maximum of 1.9 mg/ml after 2 hours and declined rapidly with a terminal half-life of 6 hours. Lung and uterus levels were maximal after 2 hours, declined slowly and were substantially higher than serum levels.

4. After a single subcutaneous injection at the recommended dose of 10 mg/kg bw to rabbits, tilmicosin residues were detected in all sampled tissues except non-injection site muscle. At day 7 after the administration, the tilmicosin levels ranged from 292 to 996 μg/kg, from 46 to 295 μg/kg, from 12.1 to 31.8 μg/kg and from below the limit of detection to 30.2 μg/kg in kidney, liver, fat and injection site muscle. At day 14, the tilmicosin levels were decreased and ranged from 109 to 262 μg/kg, from 15 to 31 μg/kg, from below the limit of detection to 13.6 μg/kg and from below the limit of detection to 8.9 μg/kg in kidney, liver, fat and injection site muscle. Residue levels decreased further over time and were below the limits of detection (3.5 μg/kg in muscle, 3.2 μg/kg in fat, 2.4 μg/kg in liver, 0.78 μg/kg in kidney) in all tissues except one kidney sample at day 35.

5. No data were provided on the ratio between tilmicosin and the total residues in rabbits, but this is acceptable for a minor species. According to the Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, tilmicosin was retained as marker residue and the ratio tilmicosin to microbiologically active residues was assumed to be equal to 1, as for bovine.

6. The applicant provided the same HPLC/UV-method for the determination of tilmicosin residues in rabbit tissues as already accepted for cattle. The method is described in an acceptable format and is shown valid for the determination of tilmicosin residues in rabbit tissues. The limits of quantification in rabbit tissues are 25.1 μg/kg in muscle and fat and 502 μg/kg in liver and kidney.

Conclusions and recommendation

Having considered that:

- the microbiological ADI is 4 μg/kg bw (i.e. 240 μg per 60 kg person),
- the marker residue (tilmicosin) established for cattle also exist in the rabbit and can be used in practice for the purpose of monitoring programmes of residues,
- the same MRLs are proposed for rabbit as established for cattle,
- the proposed routine analytical method for the determination of tilmicosin in rabbit tissues is well described, correctly validated for the determination of tilmicosin in tissues of cattle and shown to be also valid for the determination of tilmicosin in rabbit tissues;

the Committee for Veterinary Medicinal Products recommends the inclusion of MRLs for tilmicosin in rabbit tissues 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
Tilmicosin	Tilmicosin	Rabbit	50 μg/kg 50 μg/kg 1000 μg/kg 1000 μg/kg	Muscle Fat Liver Kidney	

Based on these MRL values, including the MRL for ovine milk, the daily intake will represent about 100% of the ADI.