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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TILMICOSIN
(Extension to turkey)

SUMMARY REPORT (6)

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

   Tilmicosin has been previously evaluated by CVMP for its use in chicken, cattle, pigs, sheep, and rabbits. 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.

   Currently tilmicosin is included in 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, porcine, ovine, rabbits	50 µg/kg 50 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	
		Bovine, 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

   An application for the extension of the MRLs to turkey has now been submitted, according to the general strategy laid down 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 chicken as a major species. In turkeys, tilmicosin is indicated for the treatment of respiratory disease, and is given orally via the drinking water at a maximum concentration of 75 mg/l for not more than 3 consecutive days.

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2. In a GLP study turkeys were treated for 3 days with drinking water containing 75 mg tilmicosin per litre. The mean tilmicosin levels in tissues were highest after 2 days withdrawal, the first time point of slaughter, and declined to non-quantifiable levels at 18 days withdrawal (limits of quantification 25 µg/kg in muscle and skin + fat, and 60 µg/kg in liver and kidney). At day 2, the highest mean tilmicosin concentrations were observed in liver (2260 µg/kg) and kidney (1480 µg/kg), while lower level were found in skin + fat (210 µg/kg) and muscle (120 µg/kg). At day 10 after withdrawal, these levels were 250 µg/kg, 160 µg/kg, 50 µg/kg and below 30 µg/kg, respectively. The residue distribution in turkeys as observed resembles that of the relevant major species chicken, as well as that of the other target animals.

3. In a non-GLP compliant pilot metabolism study using unlabelled tilmicosin, livers of turkeys which had been exposed to drinking water containing 330 mg tilmicosin per litre were analysed for tilmicosin and for the presence of any of the known metabolites found in other target species. The parent tilmicosin appeared to be the main residue of the compounds investigated. Besides the parent, the metabolite T-1 (N-desmethyl tilmicosin) was also found in small amounts, while no other metabolite was detected. These data support the choice of tilmicosin as the most appropriate marker residue also in turkeys, as it is in chickens and all of the other target species, i.e. bovine, porcine, ovine and rabbits.

4. No data were provided on the ratio between tilmicosin and the total residues in turkeys, but this is acceptable for a minor species. In accordance with the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL), tilmicosin was retained as marker residue, and the ratio tilmicosin to microbiologically active residues was assumed to be equal to 1 in muscle and skin + fat, 0.9 in liver and 0.15 in kidney, as for chicken.

5. The same HPLC/UV-method for the determination of tilmicosin residues in turkey tissues was proposed as already accepted for chicken. The method is described in an acceptable format and is shown valid for the determination of tilmicosin residues in turkey tissues. The limit of quantification in turkey tissues are 25 µg/kg for muscle and skin + fat and 60 µg/kg for liver and kidney.

Conclusions and recommendation

Having considered that:

- an microbiological ADI of 4 µg/kg bw (i.e. 240 µg per 60 kg person) was established,
- the marker residue (tilmicosin) established for chicken also exist in the turkey and can be used in practice for the purpose of monitoring residues,
- turkey represents a minor species and, following the Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL), the same MRLs are proposed for turkey as established for chicken,
- the proposed routine analytical method for the determination of tilmicosin in turkey tissues is well described, fully validated for the determination of tilmicosin in tissues of chicken and shown to be also valid for the determination of tilmicosin in turkey tissues,

the Committee for Veterinary Medicinal Products recommends the inclusion of tilmicosin 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
Tilmicosin	Tilmicosin	Turkey	75 µg/kg 75 µg/kg 1000 µg/kg 250 µg/kg	Muscle Skin + fat Liver Kidney	

These MRL values, together with the MRL for milk, may result in a maximum daily intake representing approximately 97% of the ADI.