

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TILMICOSIN (pigs and sheep tissues)

SUMMARY REPORT (2)

1. Tilmicosin is a macrolide antibiotic synthesized from tylosin. It has an antibacterial spectrum similar to tylosin with enhanced activity against *Pasteurella multocida* and *Pasteurella haemolytica*. Tilmicosin is recommended for the treatment of bacterial pneumonia in lambs (s.c. route) and for the treatment and prevention of bacterial pneumonia in growing/fattening pigs (oral route).
2. In the establishment of MRLs for cattle tissues the CVMP established an ADI of 240 µg/day, based on a NOAEL of 400 µg tilmicosin/kg bw in a in vivo study in HFA-rats, and the following MRLs: 1 mg/kg in bovine liver and kidney, 0.05 mg/kg in bovine muscle and fat (Commission Regulation 955/94).
3. In sheep, tilmicosin is rapidly absorbed from the injection site, reaching peak plasma levels within 8 hours after dosing. In pigs, treated orally, a plateau level of 0.22 ppm was reached at day 7 during the dosing period. Tilmicosin is distributed throughout the whole body, but highest concentrations were found in liver and kidney from pigs and sheep and in injection site from sheep.
4. In tissues and excreta of pigs and sheep, the majority of the total residues consists of the parent compound. In kidney, liver and faeces from pigs metabolite T1 was found, and in faeces also metabolite T4 was identified. In tissues and excreta from sheep, the metabolites T1 and T2 were found. T1 is N-desmethyl tilmicosin, T2 is the dimer of tilmicosin and T4 is a tilmicosin metabolite with one carbon-carbon double bond reduced and addition of SO₃H in the macrolide ring moiety.
5. After administration of a single oral dose of tilmicosin given to pigs, more than 90% of the dose was excreted within 6 days, and 96% of the dose was excreted within 13 days (about 80% in faeces and 15% in urine). Similar results were obtained from sheep treated subcutaneously with tilmicosin: 85.2% of the dose was excreted within 7 days (13.2% in urine and 71.9% in faeces).
6. In pigs treated with tilmicosin (413 ppm in the feed for 21 days), highest residue levels were found in liver and kidney (approximately 4 ppm after 6 hours, declining to <1 ppm within 7 days). Lower levels were found in muscle, fat and skin (approximately 0.3 ppm, 0.1 ppm and 0.1 ppm, declining to <0.05 ppm within 7, 7 and 14 days respectively).
7. Total residue levels in tilmicosin treated sheep (20 mg ¹⁴C-tilmicosin/kg bw) were 9.9 and 21.1 ppm in liver and kidney, 1.4 and 1.2 ppm in renal and omental fat, and 1.3 and 43.2 ppm in muscle and injection site at 3 days after injection. These levels declined slowly. After 28 days, only the level in kidney was below the proposed MRL of 1 ppm. Levels in all other commodities were still above the proposed MRLs. Parent tilmicosin levels in treated sheep (30 mg tilmicosin/kg bw) were lower: 1.55 ppm in liver, 0.48 ppm in kidney, 0.05 ppm in fat and muscle, and 0.51 ppm in injection site at 14 days, declining to below the proposed MRLs at 28 days in all commodities except injection site. At 56 days after treatment, the concentration of parent tilmicosin in the injection site (0.08 ppm) was still above the proposed MRL for muscle tissue.
8. In milk from treated sheep (10 mg/kg bw) tilmicosin declined from approximately 10 ppm at 8 hrs after treatment to below 50 ppb at 12 days after treatment.
9. The following MRLs can be established for pigs and sheep tissues : 1 ppm in liver and kidney and 0.05 ppm in muscle, fat expressed as the parent compound. These MRLs are acceptable regarding the ADI.

10. The proposed analytical methods (HPLC/UV) for the determination of tilmicosin in pig tissues (quantification limit 48 µg/kg, detection limit 5 µg/kg) and in sheep tissues (quantification limit 50 µg/kg, detection limit 1 µg/kg in kidney, muscle and fat and 7 µg/kg in liver) can be used in monitoring the established MRLs.