COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TILMICOSIN

SUMMARY REPORT (1)

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 haemolitica*. Tilmicosin is recommended for the treatment of bacterial pneumonia in young cattle by a single subcutaneous injection of 10 mg/kg.

2. Administered orally, tilmicosin has low acute toxicity. In rodents, the LD50 exceeds 0.8 g/kg bw. A sub-acute toxicity test in rats confirms this low oral toxicity.

3. From acute toxicity studies it appears that tilmicosin administered parenterally is more toxic than tilmicosin administered orally. Intramuscular and intravenous injections of 7.5-30 mg/kg bw in various species have been fatal. Care must be taken to avoid self-injection.

4. Semi-chronic toxicity tests carried out on rats and dogs revealed effects on heart (tachycardia and dilatation) and kidneys (nephrosis), and on the relative weights of particularly heart, liver and kidney. The lowest dose giving no effect, 4 mg/kg bw daily, was observed in a 1-year dog study.

5. In teratogenicity studies with rats and rabbits, and in studies on the effect of tilmicosin on reproduction with rats, tilmicosin was not teratogenic or embryotoxic.

6. Mutagenicity tests (in vitro bacterial and in vitro and in vivo mammalian) showed that tilmicosin has no mutagenic effects. Since there is no structural resemblance of tilmicosin with known carcinogenic compounds, the absence of proliferative lesions in the toxicity studies and the absence of mutagenic effects, there was no reason for performing carcinogenicity studies.

7. With respect to the antimicrobial activity of tilmicosin in vivo and in vitro information is available. In an in vivo study with human gut flora associated (HFA) germ-free rats, the highest tested dose of 400 µg tilmicosin/kg bw can be considered to be the no observed adverse effect level. In vitro studies revealed that from the microorganisms most relevant for the human gut flora, *Bifidobacterium* and *Peptostreptococci* species are more sensitive to tilmicosin than *Bacteroides fragilis*, *Clostridium perfringens* and *Escherichia coli*. For the most sensitive species (*Bifidobacterium*) a geometric mean MIC-value of 0.01 µg/ml could be established. T2 a metabolite which is considered to be an impurity (see 11), is less antimicrobially active than tilmicosin.

8. Using the NOAEL of 400 µg tilmicosin/kg bw in the in vivo study with HFA-rats as basis for the microbiological risk evaluation, and a safety factor of 100, a microbiological ADI of 0.004 mg/kg bw/day (equivalent to 240 µg/day for a 60 kg person) can be established.

9. Following oral administration of 14C-tilmicosin to pigs approximately 80% of the administered radioactivity was excreted via faeces. About half of the faecal radioactivity appeared to be the parent compound. Hence, about 40% of an oral dose will be available as tilmicosin to gut microorganisms.

10. Administered subcutaneously, tilmicosin is quickly absorbed from the injection site. In cattle, the maximum plasma concentration is reached in one hour. Elimination of tilmicosin from blood serum is relatively slow. Approximately 70 % of the administered dose is excreted via faeces and +/- 20% via urine.

11. The available metabolic studies did not indicate extensive metabolism of the parent compound. Besides the parent compound, in excreta and liver of cattle two major (T1 and T2) and one minor metabolite (T3; not in liver) were present. T1 is N-desmethyl tilmicosin, and T3 is tilmicosin of which -N(CH2) on the mycaminose group is replaced by -OH. T2 is considered to be an impurity,

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since it has the same HPLC and TLC characteristics as the dimer of tilmicosin, which is a minor component of technical tilmicosin. In faeces and urine of cattle, approximately 20 and 65 % of the total residue respectively, was parent tilmicosin. However, due to a low recovery the percentage parent compound in faeces is probably higher than 20 %.

12. Kinetic studies on residues in cattle show that tilmicosin is distributed throughout the whole body, but with highest concentrations in liver, kidney and injection site. After 14 days withdrawal the amount of parent compound in liver and kidney is comparable and about 20 times higher than the concentration in muscle and fat. In radiolabel studies with 14C-tilmicosin the amount of total residues in liver and kidney at 3 days withdrawal was comparable and about 40-80 times the concentration in muscle and fat. The parent compound and T2 (primarily in liver) were the most abundant residues, with a contribution of parent tilmicosin to the total liver residue declining from 37% (at 3 days withdrawal) via 17 % (at 14 days withdrawal) to 7 % (at 28 days withdrawal).

13. The following maximum residue limits are established for the parent drug as marker residue :

liver and kidney	1 mg/kg
muscle and fat	0.05 mg/kg.

14. The determinative HPLC-method (detection limit 4.71 µg/kg) and the confirmative thermospray LC-MS method can be used in monitoring the proposed maximum residue limits.