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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TYLOSIN (1)

SUMMARY REPORT

1. Tylosin is a macrolide antibiotic which is active against certain Gram-positive and Gram-negative bacteria and Gram-positive mycoplasmas. It consists predominantly of tylosin (factor A), but varying amounts of desmycosin (factor B), macrocin (factor C) and relomycin (factor D) may also be present, depending on the manufacturing source.

   Tylosin is used in pigs, cattle and poultry for the treatment of conditions caused by sensitive organisms.

   Tylosin is not used in human medicine.

2. Tylosin is of low acute oral toxicity. Several repeat-dose studies were conducted in rats and dogs; most of these studies were carried out some years ago and are not to modern standards. In a 2-year study in the dog, doses of 200 mg/kg bw and above caused vomiting, diarrhoea and pyelonephritis; the no-observed-effect level was 100 mg/kg bw per day.

   Two replicate carcinogenicity studies were carried out in Wistar rats. In males but not females, there was a dose-related increase in pituitary adenomas; this was attributed to the indirect effect of tylosin in prolonging survival and increasing weight gain - further data are required to confirm this hypothesis.

   Tylosin was not mutagenic in an *in vitro* chromosome aberration assay nor in an *in vivo* micronucleus test. A weak positive response in a mouse lymphoma assay in the absence of metabolic activation needs further explanation.

   The studies on reproductive toxicity were poorly reported but gave no indication of adverse effects.

3. Tylosin has significant antimicrobial activity. In a human volunteer study, a dose of 20 mg of tylosin of 6 months had only a marginal effect on the numbers of resistant streptococci. No adequate *in vitro* data were available.

4. A provisional ADI of 0-0.015 mg/kg bw per day is proposed. This was estimated by applying a safety factor of 20 to marginal no-effect level of 20 mg/day in the human volunteer study.

5. Although tylosin is extensively metabolised, no single metabolite appears to be present in a concentration greater than the parent compound. This suggests that the parent compound could serve as a "marker" residue. There are difficulties in identifying a "target" tissue since residues of tylosin depleted most slowly from the kidney when the drug was given by oral administration and depleted most slowly from the liver when the drug was given parenterally. High residues were also encountered at the injection site following parenteral administration. Additional residues data are required including data to demonstrate the relationship between the total residues and the "marker" residue.

   Because only a provisional ADI has been estimated, and because further data are required concerning the nature of residues in tissues, it is proposed to set provisional MRLs at the limits of reliable determination as follows :

milk	0.05 mg/l
meat (liver, kidney, muscle)	0.1 mg/kg

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6. A microbiological method for the determination of residues of tylosin in milk uses *Sarcina lutea* as the test organism and has a limit of determination of 0.05 mg/l. Non-specific microbiological methods are also available for the determination of residues in meat tissues; these have a limit of determination of 0.1 mg/kg. There is also an HPLC method for the determination of tylosin in meat tissues and in milk - this has a limit of determination of 0.05 mg/kg.

7. Additional information is desired before 30 June 1994 on the following :

   further information on the hypothesis concerning the pituitary adenomas found in the rate carcinogenicity study;

   further information to explain the positive result in the mouse lymphoma assay;

   full details of the reproductive toxicity studies;

   information to enable a conclusion to be drawn regarding a NOEL for the antimicrobial risk to humans;

   further residues studies to explain the relationship between the total residues, and the residues of tylosin and its metabolites; in edible tissues of cattle and pigs; further residues data for eggs.