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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TYLOSIN (2)

SUMMARY REPORT

1. Tylosin had previously been assessed by the Committee for Veterinary Medicinal Products and a provisional MRLs of 100 µg/kg had been established for liver, kidney and muscle for bovine, porcine and poultry and 50 µg/kg for milk of bovine (Commission Regulation Nº 3093/92).

2. 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. Most of the microbiological activity resides with tylosin factor A. Tylosin is used in pigs, cattle and poultry for the treatment of conditions caused by sensitive organisms. It may be administered by oral or parenteral routes. Tylosin is not used in human medicine.

3. The oral bioavailability of tylosin in rats, dogs and cattle was low. In pigs, oral bioavailability was greater - around 22.5%. In most species peak plasma concentrations were attained 1-2 hours after administration. Tylosin was extensively metabolised in both laboratory animals and in the target species.

4. Tylosin base and its salts were shown to be 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 NOEL was 100 mg/kg bw per day.

5. 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 in the treated groups in comparison with the controls.

6. A recent published paper described the effect of tylosin on the pituitary-gonadal axis of male Wistar rats. Statistically-significant changes were observed in some hormone levels and in pituitary weights. The toxicological significance of these findings required clarification.

7. Tylosin was not mutagenic in an *in vitro* chromosomal aberration assay in CHO cells nor in an *in vivo* micronucleus test. Weak positive results were obtained at cytotoxic dose levels in an *in vitro* mouse lymphoma assay for gene mutation. However an *in vitro* gene mutation assay in CHO cells gave negative results though the assay was not independently replicated. Overall, it was concluded that tylosin was not mutagenic.

8. Studies on reproductive toxicity were not carried out to modern standards and were rather poorly reported but gave no indication of teratogenicity nor any adverse effects on reproductive parameters such as fertility.

9. In a human volunteer study, a dose of 20 mg of tylosin administered over a period of 6 months had only a marginal effect on the numbers of resistant streptococci. A provisional ADI of 0-0.015 mg/kg bw per day was calculated by applying a safety factor of 20 to this marginal NOEL.

10. *In vitro* MIC values were provided for a range of human enteric bacteria. However it was agreed that a microbiological ADI based on these data could not be calculated at present, because there were no data on tylosin to substantiate the Appliant's choice of CF2 correction factor.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

11. Following administration to pigs in the feed, 12.3% and 7.6% of the total residues in liver and kidney of pigs slaughtered 4 hours after the last dose consisted of tylosin A. Smaller amounts of tylosin D, dihydrodesmycosin and cysteinyl-tylosin A (which readily converts to tylosin A) were also present. 94% of the administered radioactivity was excreted in the faeces. Faeces from 2 animals contained 43% of tylosin D and 44% dihydrodesmycosin.

12. Following 3 daily intramuscular injections to cattle, 34%, 20% and 34% of the total residues in liver, kidney and muscle, respectively, consisted of tylosin A, 4 hours after the last dose. The majority of the administered radioactivity was excreted in the faeces with tylosin A accounting for approximately 30% of the material present.

13. Residues of tylosin A in milk were detectable for up to 3 days after the last intramuscular injection to treated cows.

14. Non-specific microbiological assay methods were available for the determination of residues in tissues, eggs and milk. These methods measured both residues of tylosin A and residues of metabolites such as tylosin D which also had antimicrobial activity. In addition a specific HPLC method was available for the determination of residues of tylosin A; this method needed to be described in an internationally recognised standard layout (e.g. ISO 78/2).

15. In order to allow for the completion of scientific studies in progress the validity of the provisional MRLs should be extended for a further period of two years until 1 July 1997. The outstanding information shall be submitted before 1 January 1997 :

    · an explanation of the significance of the effects reported in the published paper on the effects on the pituitary-gonadal axis to be obtained;

    · the data to justify the CF2 correction factor to be generated;

    · the routine analytical method to be described according to an internationally recognised standard layout (e.g. ISO 78/2).