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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXYTETRACYCLINE, TETRACYCLINE, CHLORTETRACYCLINE

SUMMARY REPORT (1)

1. Oxytetracycline is a broad spectrum antibiotic with a long history in veterinary medicine for the treatment and control of a wide variety of bacterial infections.

2. Following absorption by various routes of administration, oxytetracycline is widely distributed in the body and sequestered particularly in liver, kidney, bone and dentine. Available evidence suggests minimal, if any, metabolism for tetracyclines in man and animals. Although the data for oxytetracycline are limited, they indicate the elimination of systemically available oxytetracycline as unchanged drug, mostly in the urine.

3. The acute toxicity is low. LD_{50} values in mice vary between 3600 and 7200 mg/kg bw. In short-term toxicity tests with dogs degeneration of germinal epithelium was observed (no-effect level 125 mg/kg bw). In rats there was some evidence for a hepatotoxic effect. No effects on reproductive performance were observed. In rats, mice and rabbits no evidence was found for a teratogenic activity of oxytetracycline, but dogs showed skeletal malformations. Due to the poor quality of the latter study, oxytetracycline is considered to be not teratogenic.

4. From the results of carcinogenicity studies in rats and mice it is concluded that there is no evidence for a carcinogenic potential of oxytetracycline. Negative results with respect to mutagenicity were observed in a variety of test systems. Positive results were only found in a mouse lymphoma assay, at cytotoxic concentrations, and in the in vivo micronucleous assay with mice, however without any dose relationship.

5. With respect to the safety evaluation of oxytetracycline, microbiological effects are most relevant. In a study with human volunteers no induction of resistant enterobacteriacea was observed at a dose of 2 mg per person per day. Using this no-effect level and applying a safety factor of 10 an ADI can be established of 0 - 0.003 mg/kg bodyweight.

6. Based on this ADI and taking into account the typical residue distribution of oxytetracycline in tissues, the 36th Joint WHO/FAO Expert Committee on Food Additives established the following MRLs : kidney, 600 µg/kg; liver, 300 µg/kg; eggs, 200 µg/kg; muscle, 100 µg/kg; milk, 100 µg/kg and fat 10 µg/kg.

7. Residues of oxytetracycline can be routinely monitored by a microbiological agar diffusion assay with a detection limit of 100 µg/kg for milk and meat, and 200 µg/kg for eggs. It appeared to the Committee that the monitoring methods for residues in fat were not reliable and no MRL was therefore established.

8. The Committee decided to apply the values for oxytetracycline on a provisional basis to other compounds of the tetracycline group.

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