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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXIBENDAZOLE

SUMMARY REPORT (1)

1. Oxibendazole is a broad-spectrum anthelmintic belonging to the benzimidazole family and is used in the treatment of adult and larval forms of intestinal nematodes in various animal species including pigs, cattle, sheep and horses. It is administered orally in suspension at a dosage of 15 mg/kg.

2. Administered orally, this compound has low acute toxicity. In rodents, the LD_{50} generally exceeds 10 g/kg bodyweight. In livestock species, tolerance exceeds 300 mg/kg. Subacute toxicity tests carried out over periods of one to three weeks confirm this low toxicity in livestock.

3. Of the 98-day subchronic toxicity tests carried out on rats and dogs, only the rodent study showed any effects on the blood. The observed variations, though small, are well-attested and statistically significant even at the lowest dose tested (3 mg/kg daily).

4. Many tests for the possible effects of oxibendazole on reproduction were carried out on various animal species: rats, mice, sheep, cattle and horses. None of these studies showed the product to have any teratogenic or embryotoxic properties.

5. Micronucleus and Ames tests on oxibendazole showed no mutagenic effect. However, in addition to this very limited range of tests, studies on mammalian cells regarding chromosome aberration and genetic mutation should be carried out on a compound belonging to a group of products known to inhibit the polymerisation of tubulin into microtubules. Since no mutagenic effect was detected, no study was carried out on carcinogenesis.

6. A provisional acceptable daily dose of 0-0.003 mg/kg is proposed on the following grounds:

   - Although the dose of 3 mg/kg/day derived from the 98-day subchronic toxicity study in the rat cannot be considered as a NOEL, this value could nevertheless be adopted for the establishment of a provisional ADI since the observed variation in haematological parameters gives little cause for concern and is moreover, transitory;
   - A safety factor of 1000 would increase the usual factor of 100 by a further factor of ten to allow for the effect observed at a daily dose of 3 mg/kg and for the fact that the toxicity studies used were not recent.

7. Administered orally, oxibendazole is readily absorbed. In sheep, the maximum plasma content is reached in six hours. Much of the dose administered (up to 42% in calves) is eliminated in the urine.

   The available metabolic studies, though incomplete, indicate that oxibendazole is readily metabolised in the liver and that a significant proportion of the radioactivity measurable in the liver and kidneys during isotopic studies no longer bears any structural relation to oxibendazole - which would nevertheless still be the appropriate market residue in tissue.

8. Kinetic studies on residues in various animal species (cattle, sheep, pigs and horses) show a rapid decrease in residue levels in tissue. Total residue levels are generally lower than 0.1 mg/kg in muscle and fat four days after treatment. They are higher in the liver and kidneys. Levels of free, extractable residues are also lower than 0.1 mg/kg seven days after treatment.

   Kinetic studies on residues in the milk of treated cows suggest that these residues are rapidly eliminated and are detectable only by isotopic methods.

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9. On the basis of the available information, the following provisional maximum residue limits are proposed:

   - 0.1 mg/kg in muscle, fat, liver and kidneys;
   - 0.05 mg/l in milk.

   These provisional maximum residue limits are expressed as oxibendazole. The recommended target tissues for monitoring are liver and muscle. Compliance with these provisional maxima means limiting the daily intake to 125 µg, which is compatible with the figure of 180 µg derived from the proposed provisional acceptable daily intake of 0-0.003 mg/kg.

10. These maximum residue limits can be monitored using High-Resolution Liquid Chromatography, which has a sensitivity of 25 µg/kg in the case of liver and 30 µg/l in the case of milk.

11. To enable a definitive evaluation of oxibendazole residues, the following studies and other information should be available by 31 December 1994 :

    - A 90-day study on rats, to determine a NOEL;
    - *In vitro* and, where appropriate, *in vivo* metaphase analysis, to verify that no chromosome damage is caused;
    - An *in vitro* gene mutation assay on mammalian cells;
    - An isotopic study to determine the concentration of extractable residues;
    - Information on the concentration and toxicity of metabolites. and more specifically of 2-amino-4-propoxyaniline.