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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXFENDAZOLE, FENBENDAZOLE, FEBANTEL

SUMMARY REPORT (1)

1. Oxfendazole is a benzimidazole anthelmintic which is administered orally to cattle, sheep and horses for treatment and control of gastrointestinal roundworms, lung worms and tapeworms. Fenbendazole is also a benzimidazole anthelmintic which is metabolised in mammals to a series of other benzimidazoles including oxfendazole; it has a similar spectrum of activity and may also be administered to pigs and goats. Febantel is not a benzimidazole but it is metabolised to fenbendazole (and hence oxfendazole); its uses are the same as those of fenbendazole.

   None of the three compounds is used in human medicine.

2. Oxfendazole, fenbendazole and febantel are all of low acute toxicity; at high doses effects on the gastrointestinal tract and bone marrow are observed.

   Hepatotoxic effects have been observed on repeated administration to rats and mice; this was apparent in some elevated clinical chemistry values, hepatic enlargement associated with hypertrophy and vacuolation. Higher doses caused effects on the haematopoietic system are tested.

   Many benzimidazole compounds are known to mitotic spindle poisons. The microtubules of exposed cells are affected in such a way as to impair normal cell division and cause mis-segregation of chromosomes into the daughter cells resulting in aneyploidy.

   Reassuringly, there was no evidence of carcinogenicity in adequately conducted chronic toxicity studies with any of the three compounds in rats and mice.

   The majority of numerous tests for mutagenicity also gave reassuringly negative results. No evidence of mutagenicity was obtained with fenbendazole or febantel in the 'Ames' test, *in vivo* cytogenetics assays and micronucleus tests. An unscheduled DNA repair test with febantel was also negative. However, two daily oral doses of 2000 mg/kg bw febantel caused reduced fertility in male mice and increased the numbers of pre- and postimplantation losses in a dominant lethal assay.

   The effects of the benzimidazoles on reproductive parameters present the greatest cause for concern. Reduced pregnancy rate at the top dose (of 100 ppm in the diet) was observed in a 2-generation study with oxfendazole but not in a 3-generation study with doses of up to 135 mg/kg bw fenbendazole where reduced pup weights and hepatotoxicity were the main adverse effects. Oxfenfazole, fenbendazole and febantel were all teratogenic in various species and a metabolite of febantel (febantel sulphoxide) was also teratogenic.

3. None of the three compounds has any significant antimicrobial activity.

4. An ADI of 0-2.5 µg/kg bw per day for oxfendazole has been estimated by applying a safety factor of 3000 to the NOEL of 7.5 mg/kg bw per day for teratogenicity established in a sheep study. An initial safety factor of 1000 was used because of the nature of the teratogenic effect and a further factor of 3 was added because of the poor quality of the study. The Committee for Veterinary Medicinal Products agreed that there was no need to estimate separate ADIs for febantel or fenbendazole since both compounds are metabolised to oxfendazole and oxfendazole appeared to be the more toxic.

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5. The MRLs are provisional as further residues studies are considered necessary. Studies in both sheep and cattle indicate that the liver contains the highest residue concentration and that this is the tissue from which residues deplete most slowly. The MRLs for oxfendazole are intended to cover the use of the compound itself, fenbendazole and febantel and the main metabolites detected following the use of these substances, namely : oxfendazole, its sulphone and fenbendazole. The provisional MRLs consequently refer to the sum of oxfendazole, oxfendazole sulphone and fenbendazole and are 1000 µg/kg for liver and 10 µg/kg for milk, muscle, kidney and fat.

   The estimated total intake of residues for a 60 kg adult consuming 1.5 litres milk and 500 g meat at the MRLs is within the ADI. Daily consumption of 1.5 litres milk by a 10 kg child would also be well within the ADI.

6. High performance liquid chromatography can be used to determine residues of oxfendazole and its metabolites in animal tissues and in milk. Using UV detection, limits of detection are 50 µg/kg and 5-10 µg/l respectively. Using fluroimetric detection, total residues of fenbendazole, oxfendazole and its sulphone can be determined in liver at levels of 2 µg/kg; in this method all residues are converted to oxfendazole sulphone by oxidation with peracetic acid. A more recent method will detect residues in liver of oxfendazole, its sulphone and fenbendazole at levels of 5 µg/kg. A radioimmuno-assay with a limit of detection of 2 µg/kg has also been developed.

7. Further residues data are required; these should include further residues data for milk from animals treated at the maximum recommended dose, further residues data for meat using more animals per time point and further information on the nature of extractable residues.