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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FLUBENDAZOLE

SUMMARY REPORT (1)

1. Flubendazole is a benzimidazole anthelmintic which is administered for therapeutic applications in pigs, chickens, turkeys and game birds. The preparations available include tablets, pastes, pellets and premixes. In some countries it is also available as an antheimintic for human use.

2. Flubendazole was shown to be poorly absorbed from the gastro-intestinal tract with most of the administered drug excreted unchanged in the faeces. It was of low acute toxicity.

   Daily oral doses of up to 40 mg/kg bw per day of flubendazole were given to dogs for 3 months. Some slight histological changes, which were difficult to interpret, were seen in both the male and female genital tracts. The changes in females were considered to be within age-range normal limits and not related to treatment. It was also considered that the changes in males (prostatic fibrosis) were probably not treatment-related. However, as a precautionary measure, and due to the absence of conclusive evidence regarding the aetiology of the findings, it was agreed that the dose level of 2.5 mg/kg bw per day should be regarded as a NOEL for the study. No adverse effects were observed in a 3-month feeding study in which rats were given up to 1600 mg/kg flubendazole in the diet, equivalent to 117-147 mg/kg bw per day.

   Flubendazole was tested for mutagenicity in a wide range of *in vitro* and *in vivo* assays, all of which gave negative results. In carcinogenicity studies, rats and mice were fed dietary concentrations of flubendazole intended to provide up to 40 mg/kg bw flubendazole per day; no increase in tumour incidence was observed and there were no other treatment-related effects.

   The reproductive toxicity of flubendazole was investigated in a range of species. No effects on fertility were observed in rats or dogs. In some studies in rats and rabbits, evidence of foetotoxicity (increased incidences of abortions and resorptions and reduced foetal weights) was observed at very high dose levels. There was also evidence of teratogenicity in the rat. The results of a published study, in rats, in which the apparent NOEL for teratogenicity, was 10 mg/kg bw per day were discounted because the flubendazole used had been extracted from a commercial formulation and was of doubtful purity. Instead, it was concluded that a more reliable NOEL for teratogenicity of 40 mg/kg bw per day had been established in a better-documented unpublished study, in rats.

3. Flubendazole had no significant antimicrobial activity.

4. It was noted that the JECFA had estimated an ADI of 0-12 µg/kg bw per day by applying a safety factor of 200 to the NOEL of 2.5 mg/kg bw per day in the 3-month dog study.

   The safety factor of 200 was used to take into account the fact that the doses were administered 6 days per week only.

   It was agreed that the JECFA evaluation was not significantly different from the CVMP Working Group on Safety of Residues interpretation of the data and it was therefore agreed that the JECFA ADI should be adopted.

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5. Carbamate hydrolysis and ketone reduction were the main biotransformation pathways in pigs and the (2-amino-1H-benzimidazol-5-yl)-4-fluorophenyl-methanone metabolite was the major drug-related component in pig kidney. However, there was no validated analytical method for the routine determination of this metabolite in tissues and it was therefore agreed that the flubendazole parent compound should be considered the marker residue.

   The following provisional MLRs were elaborated :

   Chicken: liver 0.5 mg/kg; muscle 0.2 mg/kg; eggs 0.4 mg/kg;

   Porcine: edible tissues (muscle, liver, kidney, fat) 0.01 mg/kg.

   It was calculated that the intake of total extractable flubendazole-derived residues, arising from consumption of animal products containing residues which did not exceed these MRLs, would not exceed the ADI proposed above.

6. An analytical method was available for the determination of the parent flubendazole using HPLC with UV detection at 312 nm. The limit of detection of the method was 0.01 mg/kg for all tissues. Validation data for this analytical method was provided only for pheasant tissues.

7. The following data are required before 31 December 1994:

   7.1 Further information on the relationship between extractable flubendazole-related residues and total (extractable & bound) residues in swine tissues;

   7.2 Information on whether M7 is the appropriate marker residue in pigs and other species; if it is, a satisfactory analytical method for determination of this metabolite should be developed and fully validated;

   7.3 Further information on the relative distributions of parent flubendazole and its metabolites in edible tissues in the chicken after treatment with 60 ppm flubendazole in the feed (the higher recommended dose);

   7.4 Data for residues in individual animals and for analytical method validation for all pharmacokinetic, metabolism, depletion and distribution studies presented for swine and poultry;

   7.5 Data on quantitative similarities between pharmacokinetic. metabolism, depletion and distribution of flubendazole in chicken and turkey (to allow MRLs to be set for turkey);

   7.6 The sensitivity of the analytical methods for the determination of residues should be improved and the methods should be validated for food-producing species (other than pheasants).